Exposure to disease in early life and the reproductive health of women born in Southern Sweden between 1813 and 1898

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The importance of early life conditions for health in later life has been known for many years. Recent developments in modelling techniques have given rise to a series of in-depth studies which have focused, amongst other things, on educational attainment, labour market outcomes, adult health, the incidence of particular diseases and old-age mortality. Not many studies, however, focus on the impact on health during early adulthood and, in particular, the literature that analyses the effect of early life conditions on female reproductive health by taking a life course approach is scant and often inconclusive. Using data from the Scanian Economic Demographic Database, which is based on family reconstitutions from church records on births, deaths and marriages for five rural parishes for the years 1813 to 1968, this work studies the impact of nutrition during the fetal stage and of the disease load experienced in infancy on the fertility outcomes of women by analysing the sex ratios at birth and the probability that her offspring will die perinatally. We find that exposure to disease in a female´s early life reduces her likelihood of giving birth to a boy for second and higher order parities and increases the probability that her female offspring will die in the early neonatal stage .

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Introduction

Wide attention has been given in the recent literature to the understanding of the way in which early life conditions influence later life outcomes. Associations have been found between the level of nutrition and the disease load experienced during the fetal stage and infancy and the development of chronic diseases later in life (for nutrition see for example: Barker 1994; 1995a; 1995b; 1997; 2001; for inflammation see for example: Bengtsson and Lindström 2000; 2003; Finch and Crimmins 2004; Liuba 2003), as well as with attainments in education (Almond 2006; Case and Paxson 2010; Palloni et al. 2009), height (Bozzoli et al. 2009; Chen and Zhou 2007), socioeconomic status (Almond 2006; Bengtsson and Broström 2009) and abilities to accumulate wealth (Bengtsson and Mineau 2009).

The majority of the works analysing the impact of early life conditions on later life health focus on the elderly and there is still a need for further analyses on early and mid-adulthood. Today about 15% of couples are unable to become pregnant and although current environmental factors are important determinants of subfecundity, much of these effects are product of the conditions experienced in early life and the result of early programming (Nohr et al. 2009). Besides fecundity, adverse exposures during the periods of rapid development may also impose an impact on other aspects of reproductive health more closely linked to the ability of carrying a pregnancy to term and to offspring health and survival. However, the literature measuring the effects of early life conditions on female reproductive health is both scant and inconclusive. Moreover it primarily concentrates on evaluating the impact of exposure to famines or of other situations of inadequate nutrition during the mother´s gestation. Although many scholars have demonstrated the wide effects that exposure to disease in early life impose on later life health and survival (see for example: Bengtsson and Lindström 2000; 2003; Finch and Crimmins 2004; Liuba 2003), there are no studies analysing the impacts of these same exposures on reproduction.

Using data from the Scanian Economic Demographic Database for women born between 1813 and 1898, this work attempts to contribute to the literature by analysing the effects of exposure to disease during the first year of life on the sex ratio of a woman´s offspring and on the probability that they will be stillborn or experience neonatal mortality. Early life conditions are measured by considering whether the woman was born in a year with high infant mortality as an indicator of the disease load experienced in infancy. Exposure to a high disease load is considered both generally and also specifically for the epidemics of measles, scarlet fever and whooping cough. The results show that women exposed to a high disease load in their first year of life have, for parities above the first, a reduced probability of giving birth to a boy relative to those born in a year with a low-medium

disease load. Moreover, male offspring of these women have a lower risk of being stillborn and a slightly reduced likelihood of dying in the early neonatal stage. Female offspring, on the other hand, have higher early neonatal mortality. These results are mainly driven by women born in years with epidemics of whooping cough and partly also scarlet fever. No significant effects are seen for those exposed to measles in their first year of life.

In previous studies that considered the same data and methodological approach significant effects on the probability of dying was observed for men and women exposed to epidemics in infancy. A passage from a dominance of selection in early childhood to a dominance of scarring in old age was observed, while gender differences were seen during childbearing/working ages. During these stages, in fact, women who had been exposed to a high disease load in infancy displayed a lower likelihood of dying than their peers born in more favourable periods, while the opposite was true for males. When distinctions were made by the type of disease environment experienced in early life, relative to women born in years with a low-medium disease load, during childbearing/working ages mortality was lower amongst females exposed in infancy to measles or scarlet fever, while it was higher for those exposed to whooping cough. These findings may help to understand how individuals are selected to survive until reproductive ages but at the same time the results of the current work may provide some explanations to the patterns observed for mortality during adulthood and old age. Reproductive endocrinology is, in fact, both an outcome of programming but also one of the components of the pathways that should be taken into account when analysing gender differences in the development of chronic disease in later life (Davies and Norman 2002).

Measures of reproductive health and possible causes

Sex ratio at birth

One important measure of a woman´s fitness and health during gestation is the sex ratio of her offspring. The primary sex ratio is the proportion of males to females at the time at conception, while the secondary sex ratio is the proportion at the time of birth. The average sex ratio at birth for humans is roughly about 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 and of the sex-specific fetal mortality (Tremblay et al. 2003).

Evolutionary theorists also explain that the sex ratio at birth may be altered by organisms in order to raise reproductive success as a mean of adaptation to environmental changes (Williams and Gloster 1992). According to the Trivers and Willard hypothesis (1973), natural selection favours parents that bias their investment to offspring of the sex possessing the highest reproductive success (see Brown

2001; Cronk 2007 for a review of works that test the Trivers and Willard hypothesis). These authors state that the highest number of grand-offspring is achieved when more sons are produced by parents experiencing above-average conditions and more daughters by parents who are experiencing poor conditions. Sons of mothers in good conditions can, in fact, produce more offspring than their sisters while the opposite is true for sons of mothers in poor conditions (Trivers and Willard 1973).

James (2008) argues that parental fertility may influence the sex ratio. It is claimed by this author that there is a U-shaped relationship between sex ratio and the time of conception 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 occur earlier or later. Due to this relationship, the sex ratio is also linked to the duration of gestation, with a higher proportion of boys being born following gestations shorter than or equal to 39 weeks or longer than 42 weeks, as well as to the duration of the time taken to achieve conception and to coital rate, although the latter variation is small and has not been proven by clinical evidence (James 2008).

The sex ratio at birth is also influenced by fetal mortality, which is higher for male embryos during earlier stages of gestation, in particular the phase of organogenesis (Kellokumpu-Lehtinen and Pelliniemi 1984). In fact the primary sex ratio is estimated to be at least 120:100 (McMillen 1979). The initial part of gestation is also the stage where total fetal mortality is highest, with about half of all fetal deaths occurring in the first 12 weeks (Shapiro et al. 1962). Age of mother and length of birth interval also influence fetal mortality, with the highest rates being experienced for older mothers and for short and long extremes in birth intervals (Shapiro et al. 1962). Furthermore, rates of fetal death vary by parity in relation to the week of gestation, for example within the first 12 weeks fetal mortality is lower for gravida one than for gravida two, while the opposite is true after 20 weeks (Shapiro et al. 1962). The risk of a fetal loss is double if the previous pregnancy also ended by a loss (Shapiro et al. 1962), thus indicating a clustering amongst mothers.

Evidence of adaptive changes in the sex ratio has been found across several animal groups (Clutton-Brock 1986; Clutton-Brock and Lason 1986). There are also various studies describing factors which have altered the sex ratio at birth in human populations, some of which are linked to an adaptation to environmental changes. The sex ratio at birth is lower for higher birth orders (James and Rostron 1985; James 1987; Ruder 1985) or multiple births (Bulmer 1970; James 1975), which could be related to sibling competition for resources (Williams and Gloster 1992). The proportion of male children is also lower for older fathers and, to a lesser extent, for older mothers (James and Rostron 1985; James 1987; Ruder 1985). After wars there is a lower male-male competition for mates and more males are born (James 1987; MacMahon and Pugh 1954).

Several studies have analysed possible associations between nutrition and sex ratio at birth. In a work that used aggregate level data from different countries, significant positive correlations were observed between food availability and the percentage of male births, and greater mortality of male embryos and fetuses was described as the possible physiological mechanism resulting in these patterns (Williams and Gloster 1992). Association between maternal nutrition and the sex ratio at birth were also found in two studies using individual level data of different African populations (Andersson and Bergstrom 1998; Gibson and Mace 2003). Another work evaluated whether exposure to the Dutch Hunger Winter of 1944-45 at the time of conception or during late gestation resulted, respectively, in lower conception and/or implantation rates for male embryos or in selective miscarriages (Stein et al. 2004). No evidence was found for either of these effects and, instead, an increase in the sex ratio at birth was observed for women who were exposed to the famine prior to conception.

Stillbirth and neonatal mortality

Further measures of a woman´s health during pregnancy are the rates of stillbirths and neonatal mortality experienced by her offspring. According to the Wold Health Organization (WHO) a stillbirth or fetal death is a "death prior to the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord or definite movement of voluntary muscles" (World Health Organization 2006). The perinatal period starts when 22 complete weeks of gestation have passed and culminates seven completed days after birth, while the neonatal period begins with births and ends 28 complete days after birth (World Health Organization 2006). Since they are often related to different causes, neonatal mortality is subdivided into early and late neonatal deaths, which occur, respectively, in days 0-6 and 7-27 of life (World Health Organization 2006). Perinatal mortality is the term used for all deaths arising from obstetric events, which lead to stillbirth or early neonatal deaths (World Health Organization 2006). Neonatal deaths and still births are often caused by poor maternal health, inappropriate care and handling of complications during pregnancy, problems during delivery and poor hygiene both during parturition and in the first hours after birth (World Health Organization 2006). The rates of neonatal deaths and stillbirths are currently falling, partly as a result of improvements in reproductive health, socioeconomic status and quality of obstetric and neonatal care (World Health Organization 2006).

Stillbirths can occur before the start of labour (intra utero) because of complications of the pregnancy or of diseases acquired by the mother, or during labour (intrapartum death) (World

Health Organization 2006). Ante partum deaths could be related to an insufficiency of the placenta, which limits the supply of oxygen and nutrients to the fetus and the removal of its metabolic waste, resulting in hindered growth (Bound et al. 1956). Other common causes of stillbirths are antepartum asphyxia, which could be due to an unexpected arrest of the supply of oxygen to the fetus, often caused by premature placental separation with antepartum haemorrhage (Bound et al. 1956). Prolonged or complicated labour may also result in intra-partum asphyxia or birth trauma (Bound et al. 1956), leading to a damage of the brain and other organs and to death during or soon after birth (World Health Organization 2006). Fetal death from asphyxia can also occur due to of obstructed labour, a problem often linked to small pelvises in women resulting from poor nutrition during their childhood and which is also an important cause of maternal deaths (Neilson et al. 2003).

Data from the Wisconsin Stillbirth Service Programme shows that identifiable causes can only be found in about 25% of stillbirths, and of these about 40% are related to multiple malformation syndromes, about 40% single fetal malformation syndromes and the remainder either fetal disruptions or dysplasias, the latter term referring to abnormal development or growth of organs, tissues or cells (Wapner and Lewis 2002). When these deaths are categorized by cause, one third are related to defined sporadic conditions, one quarter to abnormalities of the chromosomes, 12% to presumed multifactorial processes, 5 % to mendelian disorders, which are disorders of a single-gene, and less than 5% to environmental events (Wapner and Lewis 2002).

Early neonatal mortality is often related to maternal health and nutrition during gestation, other types of pregnancy complications, obstetric problems before or during birth, premature birth, low birth weight, malformations, or a lack of adaptation of the newborn child to the extrauterine environment (World Health Organization 2006). Late neonatal deaths are, instead, more frequently linked to infections and bad care after birth (World Health Organization 2006). Today about 1% of all newborn infants have a major congenital malformation and about 15% weigh less than 2500 g, and these complications are especially common in developing countries (World Health Organization 2006). Although maternal nutrition and health at conception are very important determinants of birth weight, it is often a result of preterm birth and of the complications that arise from it (World Health Organization 2006). Preterm infants are, in fact, at high risk of developing illness and of dying (World Health Organization 2006). Compared with singleton pregnancies, multiple pregnancies cause higher risks both for the mother and for the fetus, the latter partly because of preterm birth (World Health Organization 2006).

Mortality in the early neonatal period is higher for boys (World Health Organization 2006). 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 since males are usually born at younger gestational ages (Hall and Carr-Hill 1982) and for a given gestational age with less developed respiratory systems (Torday et al. 1981). These biological differences might, however, be counteracted in areas with a strong preference for boys, where girls can experience a higher neonatal mortality (World Health Organization 2006).

Mechanisms through which early life conditions can affect female reproduction

The fetal stage and infancy are the periods with the most rapid development of organs and cells and any adverse conditions perceived during these stages leave a permanent damage which lasts throughout the entire life course and which cannot be reversed by later experiences (Ben-Shlomo and Kuh 2002; Kuh and Ben-Shlomo 2004). As a reaction to a negative stimulus during these critical stages, through developmental plasticity one same genotype can give rise to different phenotypes (Bateson et al. 2004), programming disease in later life (Lucas 2007). Although a consensus has not always been reached on the aetiology (Blackwell et al. 2001), it has been shown that poor health in later life may result from malnutrition during gestation, as is stated by the fetal origins hypothesis (Barker 1994; 1995a; 1995b; 1997; 2001), or from exposure to disease in the first year of life, as is claimed by the infancy inflammation hypothesis (Bengtsson and Lindström 2000; 2003; Finch and Crimmins 2004; Liuba 2003). These two effects are not necessarily competing but may be complementary (Finch and Crimmins 2004), since during illness the body requires more nutrients for recovery, while it has less capacity to utilize for growth the energy obtained from food.

The rate of cell division, which under normal conditions is very rapid during the fetal stage, may be lowered as an adaptive mechanism to insufficient supply of nutrients or oxygen, primarily affecting the tissues which are undergoing 'critical' development when undernutrition occurs (Barker 1995a). Through these changes in the distribution and number of cells and of organ structure and the resetting of hormonal feedback and metabolic activity, the structure, physiology and metabolism of the body are permanently affected (McCance and Widdowson 1974) and gene expression is permanently altered (Lummaa and Clutton-Brock 2002). In addition, through inflammatory mechanisms short-term adaptive responses to infections or injury may become maladaptive in the long run (Finch and Crimmins 2004), causing deranged immunological balance between specific infectious agents and the human host (Fridlizius 1989) and leading to chronic disease in older ages.

The possible impact of early life conditions on female reproductive health and success could be mediated through both direct effects on organs and hormonal systems involved in reproduction and through indirect pathways connected to selection. Adverse exposures during the fetal stage and first

year of life could result in only stronger individuals surviving to reproductive ages. An impact could also be observed on the development of disease and therefore on the subsequent survival probability in adulthood, thus influencing the length of the reproductive lifespan of each woman (Lummaa and Tremblay 2003). Selection could also be inferred through educational outcomes, socioeconomic status, probability of marriage and partner selection, all aspects which have been shown to be affected by early life conditions but which, at the same time, are important determinants of the fertility of a couple.

Early life conditions can also influence females´ fecundity through effects on the hormonal systems and the organs involved in reproduction. A correct functioning of the hypothalamus-pituitary-gonadal axis is necessary in order to achieve regular ovulatory cycles (Elias et al. 2005). Two dimensions of the ovarian function which are important for female fecundity are the production and maturation of gametes and the production of the steroid hormones estradiol and progesterone (Ellison 1996). Levels of follicular estradiol are correlated with the size of the follicle (Apter et al. 1987) and the fertilizability of the oocyte (Yoshimura and Wallach 1987), while luteal progesterone has a crucial role in the success of implantation and in the maintenance of a pregnancy (Ellison 1996). A female´s ability to carry a pregnancy to term may also be hindered by malformations of the morphology of the uterus (Lumey and Stein 1997).

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). Following birth the hypothalamus-pituitary-gonadal axis continues its maturation until menarche and the first years of menstruation (Elias et al. 2005). Oocytes are formed during the fetal stage and their number declines rapidly after birth and more moderately following puberty and therefore adverse exposures both prior to and after birth may have a negative impact on reproduction (Lemasters et al. 2000). A lack of adequate growth of specific organs at critical stages of gestation and early childhood can also lead to hormonal deregulation (Barker 1995b). A woman´s endogenous hormonal environment is not only an important factor for the correct functioning of the menstrual cycle but has also been shown to influence the long-term risk of development of chronic diseases such as cancer, cardiovascular diseases and osteoporosis (Harlow and Ephross 1995).

Survival and reproduction are two processes which are closely interconnected. In fact, according to the theory of life history regulation fertility and maintenance of the body 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). Through natural selection adult ovarian hormonal function is linked to the rate

of growth in childhood and to maturation in adolescence, therefore shaping the reproductive system of women (Ellison 1996). The effects of the processes of adaptation are not only limited to the female´s chances of survival and reproductive success, but may also affect the health and survival of her offspring. Moreover, alterations in gene expressions occurring in reaction to conditions of stress during a woman´s cell development are also passed to the next generation (Lummaa and Clutton-Brock 2002).

The effects of the different mechanisms described above have been observed in studies that use historical or contemporary data. Higher age at first birth and reductions in the probability of experiencing a birth were observed for women born with very low birthweight (Ekholm et al. 2005) or preterm (Swamy et al. 2008). For couples planning a pregnancy, associations were also found between high or low birthweight and increased time to achieve a pregnancy, another commonly used measure of fecundity (Nohr et al. 2009). These effects are largely mediated through gynecological disorders, some of which relate to malformations of reproductive organs. For example, girls born small for gestational age have smaller uterus and reduced ovarian volumes (Ibanez et al. 2000). Others are linked to malfunctioning in the hormonal system, to some extent in connection to body fat, which has a regulatory role in reproduction (Frisch 1988). Increased probabilities of experiencing menstrual problems have been demonstrated for underweight or overweight females (Lake et al. 1997), or in the higher/lower age at menarche for underweight/overweight women (Frisch 1994). An earlier cessation of menstruation has also been shown for females who experienced a reduced weight gain during their first year of life or who were short at birth (Cresswell et al. 1997). Obese women also present greater risk of hypertension during pregnancy, which is a well-known reproductive risk (Lake et al. 1997). Maternal birthweight, weight gain during pregnancy and length of gestation were found to be associated with a baby´s birthweight and need for neonatal intensive care (Hackman et al. 1983).

Studies that measure associations between measurements at birth and later life reproductive success might not be able to determine causal relationships since confounding factors could be the cause of both of these characteristics. In fact the same genotype can be the underlying cause of both low birthweight and health problems in adulthood (Hattersley and Tooke 1999). Other works have, instead, used exposure to famines or to years of low crop yield as indicators of early life nutrition. Women exposed to the severe famine of the Dutch Hunger winter gave birth to offspring of low weight and who experienced higher perinatal mortality (Lumey and Stein 1997). Concerning fecundity, discordant results have been shown, with one study pointing to no effects on age at menarche, proportion remaining childless, age at first birth, total number of children and inter-birth intervals (Lumey and Stein 1997) while when adopting a slightly different definition of the sample in

another work exposed women presented a greater reproductive success (Painter et al. 2008). A yet different work which considered women exposed to this famine during childhood and adolescence showed a decreased probability of experiencing a birth, and these females also presented greater likelihood of not achieving their desired number of children due to medical reasons (Elias et al. 2005). In a study using data from 18th Century Finland associations were found between crop yield during the year of birth and the probability of marrying, giving birth to at least one child and offspring viability for men and women born into landless families but not for the landed (Rickard et al. 2010). Moreover, while the survival of these individuals to adulthood was not significantly affected by crop yield, that of their offspring was.

Season of birth, another indicator which is free of confounders, has also been shown to be associated with reproduction. Month of birth has an influence on the probability of experiencing menstrual disorders, earlier menarche and early or late menopause (Jongbloet et al. 1994) as well as on fecundability (Nonaka et al. 1990). In a study based on the Canadian rural parish of Saguenay on the nineteenth century, women born in the best month of the year had seven more grandchildren than those born in the worse month as a result of longer reproductive lifespans, a higher total number of live births and a more likely survival of offspring to adulthood (Lummaa and Tremblay 2003). In another historical analysis using a population-based French Canadian database, the sex ratio at birth was associated with the season of birth of the child itself and even more significantly with the that of his/her mother (Nonaka et al. 1999). Furthermore, work conducted in Gambia has shown that individuals born during the hungry season were more likely to die from infection and pregnancy complications (Moore et al. 1997; Moore et al. 1999).

Data and methods

Source material

The source material used for this work is the Scanian Economic Demographic Database (SEDD)[1], 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 southernmost part of Sweden in the region of Scania. The quality of the parish register material is high and the gaps for births, deaths and marriages are limited[2]. The five parishes were located near one another and they

[1] The SEDD was created in a collaborative project between the Regional Archives in Lund and the Centre for Economic Demography at Lund University (Bengtsson et al. 2012) and it is currently structured following the format suggested by the Intermediate Data Structure (Alter et al. 2009). The data used in this work was extracted on February 6, 2012, using the applications developed by Andersson (2012) and Quaranta (2012).

[2] Calculations showed that for all occupational groups at least 40% of all infant deaths occurred within the first month of the life of babies.

present variations that were common in peasant societies with regards to topography, size, and socio-economic conditions. The entire area was open farmland, except the northern part, which was more wooded. The southern localities became industrialized and urbanized in the last decades of the nineteenth century. The individuals considered are women born between 1813 and 1898, giving birth in the period 1828 to 1948.

Occupational information from poll-tax and census registers is also employed. All occupations were coded into HISCO (van Leeuwen et al. 2002) and, following a condensed version of HISCLASS, categorized into five groups: higher occupations, skilled, farmers, lower skilled and unskilled. Furthermore, when constructing the SEDD immigrants were traced in registers of their previous residences in order to determine the occupation of the head of each individual´s family of origin.

Measures of early life condition

To identify years with a high disease load, local infant mortality rates were calculated from the data and decomposed into trend and cycle components using the Hodrick Prescott filter with a filtering factor of 6.25. High disease years were defined as those having a relative deviation from the trend in IMR that exceeded 20%. For each of these years the major cause of death was specified. Due to small numbers 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 years with a low relative deviation from the trend in IMR were considered as having a low-medium disease load. Although the threshold level to indicate high IMR were not exceeded in 1862 and 1877, they were considered as epidemic years since more than 50% of all deaths of children resulted, respectively, from measles and scarlet fever. Instead, even if IMR was high in 1832, 1881 and 1886, the main causes of death could not be determined due to indications of symptomatic conditions (dropsy, pain, etc.) rather than specific pathologies or to missing data, reason for which these years were excluded from the study. The single smallpox epidemic was also removed because of small numbers.

Methods

In this work the reproductive health of women is evaluated by measuring the probability that a newborn child is a male as well as the likelihood that her offspring are born alive and survive the early and late neonatal stages. Early neonatal mortality is considered as a death occurring between day 0 and 6 of life of a child who was born alive, while late neonatal mortality concerns children who survived the first 6 days but die between day 7 and 27. Each of these outcomes is modelled by using

a logistic regression and separate analyses are conducted for boys and girls, with the exception of the probability of giving birth to a boy, which in itself has a gender dimension. Twins are excluded from the studies and all analyses besides that of stillbirths consider only live births.

The main explanatory variable introduced is the disease environment experienced by each woman in her year of birth. At a first stage this is considered through an indicator variable signalling high or low-medium disease load. The models later include a categorical variable distinguishing the specific type of disease environment that was observed in the year of birth of each women, in particular low-medium disease load, or epidemics of measles, scarlet fever or whooping cough. Control variables are also added to the model, more specifically the birth period of the child (1830-1849, 1850-1869, 1870-1889, 1890-1909, 1910-1929 and 1930-1941), the SES of the mother´s family of origin (higher occupations, skilled, farmers, lower skilled, unskilled or unknown occupation) and the age of the mother at birth (15-24, 25-34, 35-50). Current SES is not considered since it can be correlated with the woman´s early life conditions. However, as a sensitivity analysis the same estimations are run by using current SES instead of SES of the woman´s family of origin. The study on the probability of giving birth to a boy is conducted separately for the first and successive parities, while in the other models a control for parity is introduced (first, second-fourth, fifth and above).

Results

Sex ratio at birth

Women experiencing a high disease load in infancy have a lower tendency to give birth to boys for second and higher order births. More specifically, as can be seen in Table 2 they experience a 14% lower and statistically significant odd that their new-born child is a boy (0.86, p-value = 0.025). This result remains constant when considering both live and still births and also when including a control for parity (results not shown). When distinguishing the specific types of disease environments, it is mainly those who were born in a year with scarlet fever or whooping cough epidemics that show lower probabilities of bearing boys, although neither of these results is statistically significant. Women exposed to measles do not display any significant differences in the sex ratio of their offspring. The probability that the first born child was a boy is constant across all disease environments.

Still births

Women who were born in a year with a high disease load have a lower risk that their offspring will be stillborn. This pattern was constant for both gender groups, although, as can be seen in Table 3, statistically significance was only observed for boys (girls OR 0.60, p-value 0.168; OR 0.55, p-value

0.076). The results are constant when current SES is considered instead of SES of the mother´s family of origin (not shown). For boys the results were stronger both in term of magnitude and statistical significance when only second and higher order parities are considered, (OR of 0.29 and a p-value of 0.037; results not shown). Similarly to what was seen for the sex ratio at birth, also in the case of stillbirths the results described are mainly driven by women who were exposed to scarlet fever or whooping cough, although these results lack statistical significance. Women who were exposed to measles in infancy, instead, evidence a higher risk of bearing a dead child, again lacking statistical significance.

Early neonatal mortality

Female offspring of women who were exposed to a high disease load in their first year of life have a higher risk of experiencing early neonatal mortality (OR 1.70, p-value 0.030), as can be seen in Table 4. For males the ratio is slightly under one and not statistically significant. These results are constant when considering current SES rather than SES of the woman´s family of origin and the magnitude of these effects is particularly important for the first parity (girls OR 2.32, p-value 0.014; boys OR 0.83, p-value 0.673). Interesting patterns can also be observed when considering all children in the same model and introducing an interaction between maternal early life conditions and offspring´s sex. Whereas boys generally experience higher neonatal mortality than girls (OR is 1.54, p-value 0.006), the opposite is true amongst offspring of mothers born in a year with a high disease load. The interaction term is, in fact, statistically significant even if only slightly (OR 0.55 and p-value 0.083). When studying neonatal mortality according to the specific type of disease environment experienced by mothers in their infancy, significantly higher risks of dying are observed for daughters of females who were born in a year with whooping cough epidemics, and when studying all children in the same model the interaction between male and whooping cough is statistically significant. In the model for boys even if no statistically significant results are observed, in relation to mothers born in a year with a low-medium disease load the risk of dying in the early neonatal stage is slightly higher for offspring of mother´s born in a year with whooping cough epidemic and lower for offspring of mothers born in years with measles or scarlet fever epidemics. These patterns remain constant when controlling for current SES instead of SES of the mother´s family of origin (results not shown).

Late neonatal mortality

Children born from mothers who experienced different types of disease environments in infancy do not exhibit statistically significant differences on their likelihood of dying in the late neonatal stage. In relation to offspring of mothers born in a year with a low-medium disease load, daughters of mothers born in a year with high infant mortality have slightly higher odds of dying between day 7

and 27 of their lives, while the odd is slightly reduced for sons. These patterns remain constant when controlling for current SES instead of SES of the mother´s family of origin (results not shown).

Discussion

This work was aimed at measuring the impact of exposure to disease in early life on the reproductive health of women by analysing as outcome variables their offspring sex ratio at birth and rates of stillbirth and neonatal mortality. Women born in a year with a high infant mortality rate were compared to those born in other years and subsequently the effect of experiencing specific types of epidemics in infancy, in particular measles, scarlet fever, and whooping cough, were confronted.

Females exposed to epidemics in early life presented worse reproductive health. For parities above the first those born in a year with a high disease load showed a lower risk of giving birth to boys. Moreover boys had a reduced likelihood of being stillborn and a slightly decreased probability of dying in the early neonatal stage. For girls, on the other hand, higher rates of early neonatal mortality were observed amongst those born to mothers who were exposed to a high disease load during their infancy. When the specific types of epidemics experienced by the woman were studied separately, it became evident that these results were primarily driven by females exposed to whooping cough. The patterns were also rather similar, although slightly weaker, for those exposed to scarlet fever, while no evident impacts on reproductive health were observed for those born in a year with measles. In the models that analysed late neonatal mortality as outcome no statistically significant results were observed, although the direction of the effects were similar to those of early neonatal mortality.

These results could partly be explained by a greater propensity of women exposed to epidemics in early life to be affected by problems linked to hormonal regulation and to organs that are involved in reproduction. The lower sex ratio at birth observed for women exposed to a high disease load during infancy is supported by the Trivers and Willard hypothesis, which states that less fit mothers are more likely to give birth to girls in order to increase their reproductive success. This could be mediated through ovulatory problems affecting the timing of conception and therefore the primary sex ratio or through complications in pregnancy increasing the rate of early fetal loss. As was said earlier, fetal mortality is particularly high during the initial parts of gestation, particularly for males. Moreover, it was stated that in the first part of gestation fetal mortality is lower for first parities, something that could perhaps explain why reduced sex ratios are only observed for offspring of women who had already given birth to one child.

The significantly higher rates of neonatal mortality observed for offspring of women exposed to a high disease load during their first year of life also provides evidence of worse reproductive health.

The fact that when making gender distinctions these patterns are only observed for girls could be an artefact of selection of only healthier women being able to conceive males and to carry these pregnancies to term, and of only stronger male fetuses being born alive. These same selective mechanisms could be the reason for males also having lower probabilities of being stillborn. Why female offspring of women exposed to a high disease load in infancy also show reduced stillbirth rates but increased neonatal mortality is somewhat puzzling. On the other hand, the lack of significant effects when considering late neonatal mortality as the outcome variable is not unexpected given that these types of deaths are believed to be more strongly related to infections and maternal care rather than to maternal health and nutrition during gestation.

Concerning the impacts of exposure to different types of disease environments, compromised reproductive health is primarily seen for women who were born in a year with whooping cough. In another work strong evidence of poor health was also found for these females; more specifically they experienced higher rates of mortality from the mid-twenties until old age than those born in a year with low-medium disease load (Quaranta, unpublished results). In the same study females exposed to measles and scarlet fever in infancy presented reduced probabilities of dying during childbearing/working ages, while the opposite was true for males. The reduced mortality of females exposed to measles as well as the lack of any adverse impacts on their reproductive health that was shown here could both be an artefact of selection, with only the healthier women surviving to reproductive ages. On the other hand the results for females exposed to scarlet fever are somewhat discordant since increased survival as well as worsened reproductive health were observed. Extending this study to also analyse other aspects more closely related to fecundity and reproductive success may provide a better understanding of these patterns.

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References

Almond, D. 2006. "Is the 1918 Influenza Pandemic Over? Long-Term Effects of In Utero Influenza Exposure in the Post-1940 U.S. Population." *Journal of Political Economy* 114(4):672-712.

Alter, G., K. Mandemakers, and M. Gutmann. 2009. "Defining and Distributing Longitudinal Historical Data in a General Way Through an Intermediate Structure." *Historical Social Research* 34(3):78-114.

Andersson, R. and S. Bergstrom. 1998. "Is maternal malnutrition associated with a low sex ratio at birth?" *Human Biology* 70(6):1101-1106.

Apter, D., I. Raisanen, P. Ylostalo, and R. Vihko. 1987. "Follicular growth in relation to serum hormonal patterns in adolescent compared with adult menstrual cycles." *Fertility and Sterility* 47(1):82-88.

Barker, D.J.P. 2001. "Fetal and Infant Origins of Adult Disease." *Monatsschrift Kinderheilkunde* 149(Supplement 1):S2-S6.

-. 1997. "Maternal Nutrition, Fetal Nutrition, and Disease in Later Life." *Nutrition* 13(9):807-813.

-. 1995a. "The Fetal and Infant Origins of Disease." *European Journal of Clinical Investigation* 25(7):457-463.

-. 1995b. "Fetal Origins of Coronary Heart Disease." *British Medical Journal* 311(6998):171-174.

-. 1994. *Mothers, Babies, and Disease in Later Life*. London: British Medical Journal Publishing Group.

Bateson, P., D. Barker, T. Clutton-Brock, D. Deb, B. D'Udine, R.A. Foley, P. Gluckman, K. Godfrey, T. Kirkwood, M.M. Lahr, J. McNamara, N.B. Metcalfe, P. Monaghan, H.G. Spencer, and S.E. Sultan. 2004. "Developmental plasticity and human health." *Nature* 430(6998):419-421.

Bengtsson, T. and G.P. Mineau. 2009. "Early-Life Effects on Socio-Economic Performance and Mortality in Later Life: A Full Life-Course Approach Using Contemporary and Historical Sources." *Social Science & Medicine* 68(9):1561-1564.

Bengtsson, T. and G. Broström. 2009. "Do Conditions in Early Life Affect Old-Age Mortality Directly and Indirectly? Evidence from 19th-Century Rural Sweden." *Social Science & Medicine* 68(9):1583-1590.

Bengtsson, T. and M. Lindström. 2000. "Childhood Misery and Disease in Later Life: The Effects on Mortality in Old Age of Hazards Experienced in Early Life, Southern Sweden, 1760-1894." *Population Studies* 54(3):263-277.

Bengtsson, T., M. Dribe, and P. Svensson. 2012. *The Scanian Economic Demographic Database. Version 2.0 (Machine-readable database)*. Lund: Lund University, Centre for Economic Demography.

Bengtsson, T. and M. Lindström. 2003. "Airborne Infectious Diseases During Infancy and Mortality in Later Life in Southern Sweden, 1766-1894." *International Journal of Epidemiology* 32(2):286-294.

Ben-Shlomo, Y. and D. Kuh. 2002. "A Life Course Approach to Chronic Disease Epidemiology: Conceptual Models, Empirical Challenges and Interdisciplinary Perspectives." *International Journal of Epidemiology* 31(2):285-293.

Blackwell, D.L., M.D. Hayward, and E.M. Crimmins. 2001. "Does Childhood Health Affect Chronic Morbidity in Later Life?" *Social Science & Medicine* 52(8):1269-1284.

Bound, J.P., N.R. Butler, and W.G. Spector. 1956. "Classification and causes of perinatal mortality." *British Medical Journal* 2(5003):1191-6; contd.

Bozzoli, C., A. Deaton, and C. Quintana-Domeque. 2009. "Adult Height and Childhood Disease." *Demography* 46(4):647-669.

Brown, G.R. 2001. "Sex-biased investment in nonhuman primates: can Trivers & Willard's theory be tested?" *Animal Behaviour* 61(4):683-694.

Bulmer, M.G. 1970. *The biology of twinning in man*. London: Clarendon.

Case, A. and C. Paxson. 2010. "Causes and Consequences of Early-Life Health." *Demography* 47 Suppl:S65-85.

Chen, Y. and L. Zhou. 2007. "The Long-Term Health and Economic Consequences of the 1959–1961 Famine in China." *Journal of Health Economics* 26(4):659-681.

Clutton-Brock, T.H. 1986. "Sex ratio variation in birds." *Ibis* 128(3):317-329.

Clutton-Brock, T.H. and G.R. Lason. 1986. "Sex ratio variation in mammals." *The Quarterly Review of Biology* 61(3):339-374.

Cresswell, J.L., P. Egger, C.H. Fall, C. Osmond, R.B. Fraser, and D.J. Barker. 1997. "Is the age of menopause determined in-utero?" *Early Human Development* 49(2):143-148.

Cronk, L. 2007. "Boy or girl: gender preferences from a Darwinian point of view." *Reproductive Biomedicine Online* 15 Suppl 2:23-32.

Davies, M.J. and R.J. Norman. 2002. "Programming and reproductive functioning." *Trends in Endocrinology & Metabolism* 13(9):386-392.

Ekholm, K., J. Carstensen, O. Finnström, and G. Sydsjö. 2005. "The Probability of Giving Birth among Women Who Were Born Preterm or with Impaired Fetal Growth: A Swedish Population-based Registry Study." *American Journal of Epidemiology* 161(8):725-733.

Elias, S.G., P.A.H. van Noord, P.H.M. Peeters, I. den Tonkelaar, and D.E. Grobbee. 2005. "Childhood exposure to the 1944–1945 Dutch famine and subsequent female reproductive function." *Human Reproduction* 20(9):2483-2488.

Ellison, P.T. 1996. "Developmental influences on adult ovarian hormonal function." *American Journal of Human Biology* 8(6):725-734.

Finch, C.E. and E.M. Crimmins. 2004. "Inflammatory Exposure and Historical Changes in Human Life-Spans." *Science* 305(5691):1736-1739.

Fridlizius, G. 1989. "The Deformation of Cohorts: Nineteenth-Century Decline in a Generational Perspective." *Scandinavian Economic History Review* 37(3):3-17.

Frisch, R.E. 1994. "The right weight: body fat, menarche and fertility." *The Proceedings of the Nutrition Society* 53(1):113-129.

-. 1988. "Fatness and fertility." *Scientific American* 258(3):88-95.

Gibson, M.A. and R. Mace. 2003. "Strong mothers bear more sons in rural Ethiopia." *Proceedings.Biological Sciences / the Royal Society* 270(Suppl 1):S108-S109.

Hackman, E., I. Emanuel, G. van Belle, and J. Daling. 1983. "Maternal birth weight and subsequent pregnancy outcome." *JAMA : The Journal of the American Medical Association* 250(15):2016-2019.

Hall, M.H. and R. Carr-Hill. 1982. "Impact of Sex Ratio on Onset and Management of Labour." *BMJ* 285(6339):401-403.

Harlow, S.D. and S.A. Ephross. 1995. "Epidemiology of menstruation and its relevance to women's health." *Epidemiologic Reviews* 17(2):265-286.

Hattersley, A.T. and J.E. Tooke. 1999. "The Fetal Insulin Hypothesis: an Alternative Explanation of the Association of Low Birthweight with Diabetes and Vascular Disease." *Lancet* 353(9166):1789-1792.

Ibanez, L., N. Potau, G. Enriquez, and F. de Zegher. 2000. "Reduced uterine and ovarian size in adolescent girls born small for gestational age." *Pediatric Research* 47(5):575-577.

James, W.H. 1987. "The human sex ratio. Part 1: A review of the literature." *Human Biology* 59(5):721-752.

-. 1975. "Sex-ratio in twin births." *Annals of Human Biology* 2(4):365-378.

James, W.H. and J. Rostron. 1985. "Parental age, parity and sex ratio in births in England and Wales, 1968-77." *Journal of Biosocial Science* 17(1):47-56.

James, W.H. 2008. "The variations of human sex ratio at birth with time of conception within the cycle, coital rate around the time of conception, duration of time taken to achieve conception, and duration of gestation: A synthesis." *Journal of Theoretical Biology* 255(2):199-204.

Jongbloet, P.H., W.M. Kersemaekers, G.A. Zielhuis, and A.L. Verbeek. 1994. "Menstrual disorders and month of birth." *Annals of Human Biology* 21(6):511-518.

Kellokumpu-Lehtinen, P. and L.J. Pelliniemi. 1984. "Sex ratio of human conceptuses." *Obstetrics and Gynecology* 64(2):220-222.

Kuh, D. and Y. Ben-Shlomo. 2004. *A Life Course Approach to Chronic Disease Epidemiology*. 2nd ed. Oxford ; New York: Oxford University Press.

Lake, J.K., C. Power, and T.J. Cole. 1997. "Women's reproductive health: the role of body mass index in early and adult life." *International Journal of Obesity and Related Metabolic Disorders : Journal of the International Association for the Study of Obesity* 21(6):432-438.

Lemasters, G.K., S.D. Perreault, B.F. Hales, M. Hatch, A.N. Hirshfield, C.L. Hughes, G.L. Kimmel, J.C. Lamb, J.L. Pryor, C. Rubin, and J.G. Seed. 2000. "Workshop to identify critical windows of exposure for children's health: reproductive health in children and adolescents work group summary." *Envoronmental Health Perspective* 108(3):505-509.

Liuba, P. 2003. "Arterial Injury due to Infections in Early Life-A Possible Link in Coronary Heart Disease." *Doctoral Dissertation, Scripta Academia Lundensia* .

Lucas, A. 2007. "Programming by Early Nutrition in Man." Pp. 38-55 in *Ciba Foundation Symposium 156 - The Childhood Environment and Adult Disease*Anonymous : John Wiley & Sons, Ltd.

Lumey, L.H. and A.D. Stein. 1997. "In utero exposure to famine and subsequent fertility: The Dutch Famine Birth Cohort Study." *American Journal of Public Health* 87(12):1962-1966.

Lummaa, V. and M. Tremblay. 2003. "Month of birth predicted reproductive success and fitness in pre-modern Canadian women." *Proceedings.Biological Sciences / the Royal Society* 270(1531):2355-2361.

Lummaa, V. and T. Clutton-Brock. 2002. "Early development, survival and reproduction in humans." *Trends in Ecology & Evolution* 17(3):141-147.

MacMahon, B. and T.F. Pugh. 1954. "Sex ratio of white births in the United States during the Second World War." *American Journal of Human Genetics* 6(2):284-292.

McCance, R.A. and E.M. Widdowson. 1974. "The determinants of growth and form." *Proceedings of the Royal Society of London.Series B, Containing Papers of a Biological Character.Royal Society (Great Britain)* 185(78):1-17.

McMillen, M.M. 1979. "Differential Mortality by Sex in Fetal and Neonatal Deaths." *Science* 204(4388):pp. 89-91.

Moore, S.E., T.J. Cole, A.C. Collinson, E.M. Poskitt, I.A. McGregor, and A.M. Prentice. 1999. "Prenatal or early postnatal events predict infectious deaths in young adulthood in rural Africa." *International Journal of Epidemiology* 28(6):1088-1095.

Moore, S.E., T.J. Cole, E.M. Poskitt, B.J. Sonko, R.G. Whitehead, I.A. McGregor, and A.M. Prentice. 1997. "Season of birth predicts mortality in rural Gambia." *Nature* 388(6641):434.

Neilson, J., T. Lavender, S. Quenby, and S. Wray. 2003. "Obstructed labour." *British Medical Bulletin* 67(1):191-204.

Nohr, E.A., M. Vaeth, S. Rasmussen, C.H. Ramlau-Hansen, and J. Olsen. 2009. "Waiting time to pregnancy according to maternal birthweight and prepregnancy BMI." *Human Reproduction* 24(1):226-232.

Nonaka, K., B. Desjardins, H. Charbonneau, J. Legare, and T. Miura. 1999. "Human sex ratio at birth and mother's birth season: multivariate analysis." *Human Biology* 71(5):875-884.

Nonaka, K., B. Desjardins, J. Legare, H. Charbonneau, and T. Miura. 1990. "Effects of maternal birth season on birth seasonality in the Canadian population during the seventeenth and eighteenth centuries." *Human Biology* 62(5):701-717.

Painter, R.C., R.G.J. Westendorp, S.R. de Rooij, C. Osmond, D.J.P. Barker, and T.J. Roseboom. 2008. "Increased reproductive success of women after prenatal undernutrition." *Human Reproduction* 23(11):2591-2595.

Palloni, A., C. Milesi, R.G. White, and A. Turner. 2009. "Early Childhood Health, Reproduction of Economic Inequalities and the Persistence of Health and Mortality Differentials." *Social Science & Medicine* 68(9):1574-1582.

Rickard, I.J., J. Holopainen, S. Helama, S. Helle, A.F. Russell, and V. Lummaa. 2010. "Food availability at birth limited reproductive success in historical humans." *Ecology* 91(12):3515-3525.

Ruder, A. 1985. "Paternal-age and birth-order effect on the human secondary sex ratio." *American Journal of Human Genetics* 37(2):362-372.

Shapiro, S., E.W. Jones, and P.M. Densen. 1962. "A Life Table of Pregnancy Terminations and Correlates of Fetal Loss." *The Milbank Memorial Fund Quarterly* 40(1):pp. 7-45.

Sieff, D.F., L. Betzig, L. Cronk, A.G. Fix, M. Flinn, L. Sattenspiel, K. Gibson, D.A. Herring, N. Howell, S.R. Johansson, Z. Pavlík, J.W. Sheets, E.A. Smith, E. Voland, and E. Siegelkow. 1990. "Explaining Biased Sex Ratios in Human Populations: A Critique of Recent Studies [and Comments and Reply]." *Current Anthropology* 31(1):pp. 25-48.

Stearns, S.C.,. 1992. *The evolution of life histories*. Oxford: Oxford Univ. Press.

Stein, A.D., P.A. Zybert, and L.H. Lumey. 2004. "Acute Undernutrition is not Associated With Excess of Females at Birth in Humans: the Dutch Hunger Winter." *Proceedings of the Royal Society B Biological Sciences* 271 Suppl 4:S138-S141.

Swamy, G.K., T. Ostbye, and R. Skjaerven. 2008. "Association of preterm birth with long-term survival, reproduction, and next-generation preterm birth." *JAMA : The Journal of the American Medical Association* 299(12):1429-1436.

Torday, J.S., H.C. Nielsen, M. Fencl Mde, and M.E. Avery. 1981. "Sex Differences in Fetal Lung Maturation." *The American Review of Respiratory Disease* 123(2):205-208.

Tremblay, M., H. Vézina, L. Houde, and R. Chung. 2003. "Demographic Determinants of the Sex Ratio at Birth in the Saguenay Population, Quebec." *Population (English Edition, 2002-)* 58(3):pp. 383-394.

Trivers, R.L. and D.E. Willard. 1973. "Natural Selection of Parental Ability to Vary the Sex Ratio of Offspring." *Science* 179(4068):90-92.

van Leeuwen, M., I. Maas, and A. Miles. 2002. *HISCO. Historical International Standard Classification of Occupations*. Leuven: Leuven University Press.

Waldron, I. 1983. "Sex differences in human mortality: the role of genetic factors." *Social Science & Medicine (1982)* 17(6):321-333.

Wapner, R.J. and D. Lewis. 2002. "Genetics and metabolic causes of stillbirth." *Seminars in Perinatology* 26(1):70-74.

Williams, R.J. and S.P. Gloster. 1992. "Human sex ratio as it relates to caloric availability." *Social Biology* 39(3-4):285-291.

World Health Organization. 2006. "Neonatal and perinatal mortality : country, regional and global estimates." *WHO Press* .

Yoshimura, Y. and E.E. Wallach. 1987. "Studies of the mechanism(s) of mammalian ovulation." *Fertility and Sterility* 47(1):22-34.

Tables and figures

Table 1: Aggregate sex ratio at birth and rates of stillbirth and neonatal mortality

	Low-med disease load	High disease load	Measles	Scarlet fever	Whooping cough
Sex ratio at birth	109.43	102.25	115.00	101.00	103.85
Stillbirth rate - females	13.78	10.96	20.41	4.48	12.53
Stillbirth rate - males	17.48	9.90	17.48	4.52	10.37
Neonatal mortality rate - females	32.01	43.30	20.83	58.56	48.63
Neonatal mortality rate - males	43.56	38.00	56.94	27.27	39.83
Early neonatal mortality rate - females	16.01	25.18	12.50	27.03	31.71
Early neonatal mortality rate - males	25.56	23.00	24.91	18.18	27.25

Table 2: Odds ratio that a birth will be a male.

	Parity 1	Parity > 1	Parity 1	Parity > 1
Disease load in mother´s year of birth				
Low-medium disease load	1.00	1.00	(--)	(--)
	[ref.]	[ref.]		
High disease load	1.07	0.86**	(--)	(--)
	[0.90,1.27]	[0.76,0.98]		
Type of disease environment in mother´s year of birth				
Low-medium disease load	(--)	(--)	1.00	1.00
			[ref.]	[ref.]
Measles	(--)	(--)	1.1	1.01
			[0.80,1.51]	[0.80,1.27]
Scarlet fever	(--)	(--)	1.05	0.83
			[0.76,1.44]	[0.63,1.09]
Whooping cough	(--)	(--)	1.12	0.88
			[0.88,1.43]	[0.74,1.05]
Child´s birth period				
1830-1849	1.11	1.12	1.1	1.11
	[0.82,1.50]	[0.86,1.44]	[0.81,1.48]	[0.86,1.44]
1850-1869	1.00	1.00	1.00	1.00
	[ref.]	[ref.]	[ref.]	[ref.]
1870-1889	1.20*	0.91	1.19	0.91
	[0.98,1.48]	[0.79,1.04]	[0.96,1.46]	[0.79,1.04]
1890-1909	1.03	1.03	1.04	1.05
	[0.84,1.28]	[0.89,1.20]	[0.83,1.29]	[0.90,1.22]
1910-1929	1.11	0.98	1.07	1.01
	[0.88,1.40]	[0.82,1.17]	[0.85,1.36]	[0.84,1.21]
1930-1941	1.23	0.93	1.22	0.94
	[0.68,2.22]	[0.62,1.40]	[0.68,2.21]	[0.63,1.42]
SES of mother´s family of origin				
Higher Occupations	1.46	1.23	1.48	1.16
	[0.91,2.36]	[0.89,1.70]	[0.90,2.42]	[0.83,1.62]
Skilled	1.03	0.83	1.05	0.82
	[0.71,1.50]	[0.65,1.05]	[0.72,1.53]	[0.64,1.05]
Farmers	1.00	1.00	1.00	1.00
	[ref.]	[ref.]	[ref.]	[ref.]
Lower skilled	1.03	0.96	1.02	0.93
	[0.83,1.27]	[0.84,1.11]	[0.82,1.27]	[0.81,1.07]
Unskilled	0.86	1.06	0.84	1.04
	[0.62,1.19]	[0.84,1.33]	[0.61,1.16]	[0.83,1.31]
Unknown occupation	0.98	0.95	0.99	0.94
	[0.80,1.21]	[0.82,1.10]	[0.80,1.23]	[0.81,1.09]
Age of mother at birth				
15-24	0.93	0.81**	0.98	0.81**
	[0.80,1.08]	[0.66,0.99]	[0.84,1.13]	[0.66,1.00]
25-34	1.00	1.00	1.00	1.00
	[ref.]	[ref.]	[ref.]	[ref.]
35-50	0.96	0.94	0.97	0.93
	[0.80,1.14]	[0.85,1.04]	[0.81,1.16]	[0.83,1.03]
Observations	3799	6420	3664	6230
Number of male births	2008	3301	1935	3215

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

Table 3: Odds ratio of a still birth

	Girls	Boys	Girls	Boys
Disease load in mother´s year of birth				
Low-medium disease load	1.00	1.00	(--)	(--)
	[ref.]	[ref.]		
High disease load	0.61	0.55*	(--)	(--)
	[0.30,1.23]	[0.28,1.06]		
Type of disease environment in mother´s year of birth				
Low-medium disease load	(--)	(--)	1.00	1.00
			[ref.]	[ref.]
Measles	(--)	(--)	1.42	1.09
			[0.56,3.62]	[0.43,2.73]
Scarlet fever	(--)	(--)	0.51	0.46
			[0.07,3.84]	[0.06,3.47]
Whooping cough	(--)	(--)	0.61	0.49
			[0.24,1.56]	[0.20,1.23]
Child´s birth order				
Birth order 1	2.31***	1.58**	2.28***	1.55*
	[1.34,3.96]	[1.00,2.51]	[1.33,3.92]	[0.97,2.46]
Birth order 2-4	1.00	1.00	1.00	1.00
	[ref.]	[ref.]	[ref.]	[ref.]
Birth order 5+	0.84	0.39**	0.78	0.40**
	[0.40,1.79]	[0.19,0.81]	[0.36,1.69]	[0.19,0.83]
Child´s birth period				
1830-1849	0.6	1.21	0.57	1.14
	[0.18,2.03]	[0.51,2.89]	[0.17,1.93]	[0.48,2.74]
1850-1869	1.00	1.00	1.00	1.00
	[ref.]	[ref.]	[ref.]	[ref.]
1870-1889	0.66	0.98	0.62	0.97
	[0.36,1.22]	[0.59,1.63]	[0.33,1.15]	[0.58,1.61]
1890-1909	0.31***	0.33***	0.31***	0.34***
	[0.14,0.67]	[0.16,0.68]	[0.14,0.68]	[0.17,0.70]
1910-1941	0.35**	0.25***	0.37**	0.26***
	[0.15,0.81]	[0.10,0.61]	[0.16,0.86]	[0.11,0.64]
SES of mother´s family of origin				
Higher Occupations	1.09	1.7	1.22	1.87
	[0.14,8.54]	[0.63,4.56]	[0.15,9.67]	[0.69,5.05]
Skilled	2.71*	0.95	2.92*	0.98
	[0.92,7.92]	[0.32,2.78]	[0.98,8.71]	[0.33,2.89]
Farmers	1.00	1.00	1.00	1.00
	[ref.]	[ref.]	[ref.]	[ref.]
Lower skilled	2.33**	1.12	2.50**	1.18
	[1.13,4.80]	[0.64,1.96]	[1.18,5.29]	[0.67,2.06]
Unskilled	1.29	0.81	1.38	0.83
	[0.35,4.72]	[0.28,2.37]	[0.37,5.12]	[0.28,2.43]
Unknown occupation	1.75	0.96	1.87	0.99
	[0.78,3.91]	[0.51,1.81]	[0.82,4.28]	[0.52,1.88]
Age of mother at birth				
15-24	0.30**	1	0.31**	1.01
	[0.10,0.85]	[0.51,1.98]	[0.11,0.87]	[0.51,1.99]
25-34	1.00	1.00	1.00	1.00
	[ref.]	[ref.]	[ref.]	[ref.]
35-50	1.47	2.89***	1.41	2.79***
	[0.86,2.53]	[1.79,4.66]	[0.82,2.44]	[1.72,4.51]
Observations	4975	5399	4808	5239
Number of stillbirths	69	91	68	90

Notes: Exponentiated coefficients; 95% confidence intervals in brackets; * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. The child birth periods 1910-1929 and 1930-1941 were merged together because no stillbirths occurred in 1830-41 therefore predicting failure perfectly.

Table 4: Odds ratio that a child will die in the early neonatal stage

	All children	Girls	Boys	All children	Girls	Boys
Disease load in mother´s year of birth						
Low-medium disease load	1.00	1.00	1.00	(--)	(--)	(--)
	[ref.]	[ref.]	[ref.]			
High disease load	1.65**	1.70**	0.92	(--)	(--)	(--)
	[1.03,2.65]	[1.05,2.73]	[0.57,1.49]			
Type of disease environment in mother´s year of birth						
Low-medium disease load	(--)	(--)	(--)	1.00	1.00	1.00
				[ref.]	[ref.]	[ref.]
Measles	(--)	(--)	(--)	0.82	0.82	0.86
				[0.25,2.63]	[0.26,2.66]	[0.37,1.99]
Scarlet fever	(--)	(--)	(--)	1.64	1.85	0.63
				[0.69,3.89]	[0.76,4.49]	[0.22,1.75]
Whooping cough	(--)	(--)	(--)	2.25***	2.23***	1.12
				[1.24,4.08]	[1.22,4.08]	[0.59,2.13]
Child´s gender & disease load in mother´s year of birth						
Female	1.00	(--)	(--)	1.00	(--)	(--)
	[ref.]			[ref.]		
Male	1.54***	(--)	(--)	1.56***	(--)	(--)
	[1.13,2.09]			[1.14,2.14]		
High disease load & male	0.55*	(--)	(--)	(--)	(--)	(--)
	[0.28,1.08]					
Measles & male	(--)	(--)	(--)	1.09	(--)	(--)
				[0.26,4.59]		
Scarlet fever & male	(--)	(--)	(--)	0.42	(--)	(--)
				[0.11,1.55]		
Whooping cough & male	(--)	(--)	(--)	0.48*	(--)	(--)
				[0.20,1.13]		
Child´s birth order						
Birth order 1	1.13	1.82**	0.8	1.08	1.61*	0.82
	[0.83,1.55]	[1.12,2.97]	[0.52,1.22]	[0.79,1.49]	[0.98,2.65]	[0.54,1.26]
Birth order 2-4	1.00	1.00	1.00	1.00	1.00	1.00
	[ref.]	[ref.]	[ref.]	[ref.]	[ref.]	[ref.]
Birth order 5+	1.27	1.02	1.46	1.24	1.08	1.35
	[0.87,1.84]	[0.55,1.92]	[0.91,2.34]	[0.84,1.82]	[0.57,2.02]	[0.83,2.19]
Child´s birth period						
1830-1849	1.17	1.16	1.19	1.12	1.11	1.16
	[0.58,2.36]	[0.38,3.53]	[0.48,2.97]	[0.55,2.28]	[0.37,3.38]	[0.46,2.89]
1850-1869	1.00	1.00	1.00	1.00	1.00	1.00
	[ref.]	[ref.]	[ref.]	[ref.]	[ref.]	[ref.]
1870-1889	1.02	1.09	0.98	1.02	1.13	0.93
	[0.68,1.55]	[0.58,2.04]	[0.56,1.72]	[0.67,1.55]	[0.60,2.12]	[0.52,1.64]
1890-1909	1.41*	0.91	1.87**	1.45*	0.88	1.98**
	[0.94,2.13]	[0.47,1.74]	[1.11,3.15]	[0.96,2.20]	[0.45,1.74]	[1.16,3.39]
1910-1929	1.22	0.84	1.58	1.16	0.75	1.57
	[0.75,1.98]	[0.40,1.78]	[0.83,2.98]	[0.70,1.92]	[0.34,1.65]	[0.82,3.02]
1930-1941	2.22*	2.1	2.14	2.20*	2.03	2.15
	[0.93,5.29]	[0.63,6.97]	[0.59,7.73]	[0.92,5.27]	[0.61,6.74]	[0.59,7.78]
SES of mother´s family of origin						
Higher Occupations	1.28	0.57	1.69	1.36	0.6	1.79
	[0.58,2.87]	[0.08,4.32]	[0.69,4.13]	[0.61,3.04]	[0.08,4.53]	[0.73,4.38]
Skilled	0.5	0.51	0.48	0.48	0.49	0.47
	[0.20,1.25]	[0.12,2.22]	[0.14,1.59]	[0.19,1.21]	[0.11,2.14]	[0.14,1.55]
Farmers	1.00	1.00	1.00	1.00	1.00	1.00
	[ref.]	[ref.]	[ref.]	[ref.]	[ref.]	[ref.]
Lower skilled	0.89	0.77	0.97	0.84	0.79	0.88
	[0.59,1.33]	[0.39,1.53]	[0.58,1.62]	[0.55,1.28]	[0.39,1.56]	[0.52,1.49]
Unskilled	1.2	1.62	0.89	1.2	1.67	0.87
	[0.67,2.13]	[0.70,3.76]	[0.40,1.98]	[0.67,2.14]	[0.71,3.91]	[0.39,1.94]
Unknown occupation	0.89	1.15	0.76	0.89	1.23	0.72
	[0.60,1.33]	[0.61,2.16]	[0.45,1.28]	[0.60,1.34]	[0.65,2.33]	[0.43,1.23]
Age of mother at birth						
15-24	1.05	1.24	0.97	1.11	1.37	0.97
	[0.69,1.60]	[0.66,2.32]	[0.55,1.73]	[0.73,1.69]	[0.73,2.58]	[0.55,1.72]
25-34	1.00	1.00	1.00	1.00	1.00	1.00
	[ref.]	[ref.]	[ref.]	[ref.]	[ref.]	[ref.]
35-50	1.38**	2.07***	1.05	1.3	1.88**	1.02
	[1.01,1.89]	[1.26,3.41]	[0.69,1.59]	[0.94,1.79]	[1.13,3.14]	[0.67,1.55]
Observations	10214	4906	5308	9889	4740	5149
Number of early neonatal deaths	224	91	133	216	87	129

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

Table 5: Odds ratio that a child will die in the late neonatal stage

	Girl	Boy	Girl	Boy
Disease load in mother´s year of birth				
Low-medium disease load	1.00	1.00	(--)	(--)
	[ref.]	[ref.]		
High disease load	1.21	0.86	(--)	(--)
	[0.69,2.11]	[0.49,1.50]		
Type of disease environment in mother´s year of birth				
Low-medium disease load	(--)	(--)	1.00	1.00
			[ref.]	[ref.]
Measles	(--)	(--)	0.59	1.59
			[0.14,2.47]	[0.75,3.36]
Scarlet fever	(--)	(--)	1.63	0.65
			[0.62,4.29]	[0.15,2.74]
Whooping cough	(--)	(--)	1.44	0.68
			[0.67,3.08]	[0.29,1.58]
Child´s birth order				
Birth order 1	0.92	1.47*	0.92	1.57*
	[0.56,1.52]	[0.94,2.31]	[0.55,1.54]	[1.00,2.49]
Birth order 2-4	1.00	1.00	1.00	1.00
	[ref.]	[ref.]	[ref.]	[ref.]
Birth order 5+	0.86	0.9	0.87	0.95
	[0.42,1.77]	[0.48,1.72]	[0.41,1.84]	[0.50,1.81]
Child´s birth period				
1830-1849	2.18*	2.87***	2.15*	2.85***
	[0.91,5.22]	[1.39,5.91]	[0.89,5.15]	[1.37,5.92]
1850-1869	1.00	1.00	1.00	1.00
	[ref.]	[ref.]	[ref.]	[ref.]
1870-1889	1.03	1.21	0.86	1.23
	[0.52,2.04]	[0.68,2.15]	[0.42,1.76]	[0.69,2.22]
1890-1909	1.33	1.19	1.25	1.16
	[0.67,2.63]	[0.63,2.23]	[0.61,2.56]	[0.60,2.23]
1910-1941	1.03	1.09	1.07	1.2
	[0.45,2.32]	[0.50,2.41]	[0.47,2.45]	[0.54,2.66]
SES of mother´s family of origin				
Higher Occupations	0.79	0.5	0.39	0.54
	[0.18,3.38]	[0.12,2.09]	[0.05,2.88]	[0.13,2.28]
Skilled	0.55	0.66	0.51	0.68
	[0.17,1.85]	[0.23,1.88]	[0.15,1.71]	[0.24,1.95]
Farmers	1.00	1.00	1.00	1.00
	[ref.]	[ref.]	[ref.]	[ref.]
Lower skilled	0.42**	0.71	0.33***	0.74
	[0.21,0.85]	[0.42,1.20]	[0.15,0.71]	[0.43,1.26]
Unskilled	0.62	0.48	0.62	0.49
	[0.21,1.81]	[0.17,1.37]	[0.21,1.80]	[0.17,1.41]
Unknown occupation	0.63	0.43***	0.58*	0.43***
	[0.34,1.17]	[0.23,0.79]	[0.31,1.10]	[0.23,0.79]
Age of mother at birth				
15-24	1.02	0.62	0.99	0.63
	[0.56,1.89]	[0.33,1.19]	[0.53,1.85]	[0.33,1.21]
25-34	1.00	1.00	1.00	1.00
	[ref.]	[ref.]	[ref.]	[ref.]
35-50	0.63	0.97	0.56*	1.00
	[0.35,1.15]	[0.59,1.61]	[0.30,1.05]	[0.60,1.66]
Observations	4815	5175	4653	5020
Number of late neonatal deaths	80	98	76	96

Notes: Exponentiated coefficients; 95% confidence intervals in brackets; * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. The child birth periods 1910-1929 and 1930-1941 were merged together because no late neonatal deaths occurred in 1830-41 therefore predicting failure perfectly.