Disease Exposure in Infancy Affects Women's Reproductive Outcomes and Offspring Health. Evidence from Southern Sweden 1905-2000

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Disease exposure in infancy affects women's reproductive outcomes and offspring health. Evidence from southern Sweden 1905-2000

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Abstract

Early-life adversity negatively affects morbidity and survival in late life, but knowledge is limited about effects on women's reproduction and reproductive health. To deepen our understanding of the full effects of disease exposure in early life, including long-term consequences, we study women's reproductive outcomes and their offspring's health. Using the Scanian Economic Demographic Database and Swedish register data covering close to a century (1905-2000), in combination with local infant mortality rates as a measure of disease exposure in the year of birth, we follow women's reproductive careers over their life course, examining a comprehensive set of outcomes. Results show that women exposed to disease in infancy give birth to a lower proportion of boys (lower offspring sex ratio), which is in line with the notions that male fetuses are more vulnerable to their mother's adverse physical or contextual conditions and that pregnancies with male fetuses are more often miscarried. We also find that boys of exposed mothers are more likely to be born preterm and are heavier than boys born to non-exposed mothers, suggesting *in utero* out-selection of weaker male fetuses. Moreover, exposed women have a higher risk of miscarriage and of male stillbirth, but we do not find strong evidence that their overall likelihood of giving birth is affected. Taken together, our results imply that disease exposure in infancy has a continuous impact on reproduction and health across the female life course, and even affects the early-life health of the next generation.

Keywords

Early life exposures; reproduction; historical demography; life course epidemiology; intergenerational health transfers

Significance

How does disease exposure in early life affect women's reproductive outcomes and their offspring's health at the start of life? This paper shows evidence of lasting effects of exposure to peaking infant mortality rate in the year of birth on Swedish women's mid-life health in 1905-2000. Exposed women give birth to fewer boys, experience more miscarriages and male stillbirths, and frailer male fetuses appear to be out-selected *in utero.* Results point to both health scarring (mother) and health selection (fetus). These findings imply that disease exposure in infancy has lasting impact on reproduction and health across the female life course, and even affects the health of the next generation, of relevance for policy interventions in preconceptional, prenatal and infant care.

1. Introduction

An interdisciplinary literature documents that early-life exposure to adversity relates to worse later-life health (1–4) and worse adult socioeconomic status, possibly because of early-life adversity's impairing effect on health and cognitive ability (5, 6). Adverse exposures during the fetal stage and infancy, which are 'critical periods' with the most rapid development of organs and cells, have lifelong and irreversible impacts (7). Despite theoretical pathways indicating that early-life adversity can have implications for human reproduction, there is limited research on how early-life exposures to adversity, and in particular disease exposure, affects fertility and reproductive health. This study fills the gap in the literature by examining the effect of disease exposure in infancy on women's reproductive health using a comprehensive set of outcomes. Reproductive outcomes reflect women's ability to conceive and carry a pregnancy to term and are important indicators of women's health in mid-life. Studying reproductive outcomes thus provides insights into the effects of early-life conditions on health in a period of life when mortality and morbidity tend to be low. Reproductive outcomes also mirror the next generation's health at the start of life. A thorough understanding of the effects of a health shock experienced early in life on a woman's reproduction is thus key to understand if and how future generations are affected by peaking disease exposure in early life.

High level of disease exposure in infancy can result in increased morbidity and mortality across the life course through direct damages to the body, i.e. scarring (8). Reproductive outcomes, including fecundity, may be affected as non-lethal childhood infections can afflict damage to women's physiology, including impairment of the reproductive function (9), resulting in reduced fecundity and a higher rate of miscarriages and stillbirths. Mothers in worse health may also have offspring who are in worse health at the start of life (10). On the other hand, among disease-exposed and less healthy women, more robust fetuses may be selected *in utero* (11, 12). This selection could result in a lower likelihood of a (live) birth, but also increase the likelihood of relatively more robust offspring born.

At the same time, early-life adversity can select healthier women into reproduction, so that their reproductive outcomes are better compared to those of non-exposed women (13). Health selection following disease exposure in infancy implies that women with a frail health may not survive in a high mortality context, resulting in a relatively robust group of survivors (2, 6, 14, 15). Although scarring effects of early-life adversity on health commonly dominate selection effects (16), selection sometimes dominates in earlier ages and scarring at later ages so that there is a crossover with age (17). There is evidence for health selection into marriage after exposure to early-life health shocks, which may exacerbate the overall effect of health shocks on reproductive outcomes (18, 19).

There is a very limited literature on early life influences on women's reproduction. A few studies examine the relation between early-life conditions and number of births (parity) and reproductive success (surviving children) among women (19–22). Conclusions are mixed. While some studies find evidence for decreased fertility following exposure to early-life adversity, others suggest increased fertility or no association with exposure to an early-life health shock. Yet, parity and number of surviving children are relatively crude measures of reproductive outcomes, and the early-life effects on later reproduction identified may be an underestimation of the full effect of women's early life exposure to adversity on their reproductive health. Similarly, these studies do not provide evidence to whether maternal early-life adversity affects the early-life health of her

children. Women reproducing in poor health or in more difficult external conditions may experience more spontaneous abortions (miscarriages). Pregnancy loss is expected to be selective, with higher incidence among relatively weak fetuses (i.e., stronger selection *in utero*) (23) and among boys. Research suggests that male fetuses tend to be more severely affected by an unfavorable maternal physical condition and stress than female fetuses, so that fewer boys than girls are born in such conditions, resulting in a lower sex ratio at birth (12, 24). Empirical work points to sex ratio deviations following disadvantageous contextual conditions (11, 25–29), and a relation to disadvantageous maternal health conditions at the time of conception or during pregnancy (28, 30–32). Whether sex ratio also deviates in relation to maternal early life exposures is still unknown. Finally, the literature on the relationship between maternal conditions and reproductive outcomes addresses health of the mother during or in the period just preceding pregnancy rather than long-term effects shaped in her early life (see e.g. (11, 27, 28, 30–32). The field has made little progress in gaining a comprehensive understanding of how early life exposure to adversity affects reproduction and reproductive health, in part due to data limitations.

We contribute to the literature on early-life adversity and reproductive outcomes through a comprehensive examination of mechanisms of scarring and selection for both mothers and their offspring. Further, our results contribute to the emerging literature on intergenerational transmissions in health and cross-generation effects of early-life insults (33–35). We examine the effect of early-life disease exposure using unique data sources on a broad set of reproductive outcomes, including women's likelihood of giving birth, total fertility, twinning, miscarriage, stillbirth, offspring sex ratio at birth and birthweight (see Figure 1 for a schematic overview of the expected effects on reproductive outcomes of exposure to high infectious disease load in early life).

We use the well-established Scanian Economic-Demographic Database (SEDD, 36) linked to the Swedish national registers, consisting of longitudinal data for an area in southern Sweden, containing nearly complete records of vital events for both married and non-married women residing in the area. Information from purposively digitized obstetric records is also used. Our study sample includes women born in 1890-1950, followed 1905-2000, and a wide range of fertility and offspring health outcomes (see Figure 1). We compare women exposed to high versus low-medium level of disease in infancy. Disease exposure is measured by peaks in infant mortality rates (IMR) for the county and year of birth of each woman. It is an exogenous exposure in infancy which corresponds to relatively mild and population-shared health shocks (see methods section and details in SI Appendix).

[Figure 1: About here]

2. Results

Women's mortality

To examine whether selection or scarring mechanisms dominate prior to and during reproductive stages in relation to exposure to disease in infancy, we first analyse female mortality by age group. Cox proportional hazards models show no statistically significant differences in the hazard of death in ages 1-14 or 15-49 in relation to the level of disease exposure in the woman's year of birth

(Figure 2a; SI Appendix Table S4). The direction of the effect changes across age, from a dominance of selection in childhood and adolescence (hazard ratio 0.78, p-value 0.13), to a mild dominance of scarring in adulthood (hazard ratio 1.07, p-value 0.51), in line with previous studies (3, 17).

Fertility outcomes

Next, we study the impact of women's disease exposure in infancy on a wide range of reproductive outcomes: fertility, offspring sex ratio at birth, stillbirths, and twinning. The impact of disease exposure in infancy on the likelihood of giving birth is analysed using Cox models (Figure 2b; SI Appendix, Table S5). For first births, no statistically significant effects are observed on the full sample of women, but a marginally statistically significant lower hazard of birth is observed (hazard ratio 0.93; p-value 0.08) if the sample is restricted to women observed in SEDD areas at least from age 15. For second and higher order births, no statistically significant results are noted. We also use cure models, a type of survival model accounting for the fact that some women never have (additional) children, which similarly do not show evidence that the likelihood or timing of birth significantly associate with women's exposure to high IMR in infancy for first or higher order births (SI Appendix, Table S6).

We calculate offspring sex ratios at birth. For all births, 107.8 males were born per 100 females for women exposed to low-medium IMR in infancy, and 100.7 males per 100 females for women exposed to high IMR in infancy (p-value 0.05 in Chi-squared test for differences in means). Larger differences are observed for first births (109.5 versus 95.3; p-value 0.01). The results of logistic regressions measuring the likelihood that a child born is male (Figure 2c; SI Appendix, Table S7) show, for all births, a 7% lower odds of a male birth among live-born children of exposed mothers (p-value 0.04). We find a much stronger effect for first births (14% lower odds of a male birth, p-value 0.00), but no statistically significant effects for second and higher order births. In the model for first births, maternal exposure to disease is a stronger predictor of the likelihood of a male birth than the control variables (woman's age and year of birth).

Logistic regressions of the odds of a stillbirth, which is studied until 1967, (Figure 2d; SI Appendix, Table S8) show that women exposed to high IMR at birth have 28% higher odds of stillbirth compared to non-exposed women, an effect above the threshold for statistical significance (p-value 0.17). The results differ by sex of the child, showing 56% higher odds of a male stillbirth for exposed mothers (p-value 0.04) and no significant differences for females. Further, exposed mothers have a 23% lower odds of a multiparous birth event (logistic regression, reported in Figure 2e; SI Appendix, Table S9). This result is above the threshold for statistical significance (p-value 0.18), but the number of multiparous birth events in the data is small. Nevertheless, the direction of the results is in line with our previously presented findings: disease exposure in infancy affects women's fertility outcomes negatively.

We also analyze the effect of disease exposure in infancy on the total number of births and the total number of children surviving to age 5. Poisson models are used, restricting the analysis to births taking place between ages 18 and 42 and considering only women observed without gaps at least from age 18 until age 47 so we can follow-up until the last-born children turn five. For the same sample we study the likelihood of being childless, defined as not having given birth to any child between ages 18 and 42 using logistic regressions. Exposure to disease does not have a significant effect on these outcomes (SI Appendix, Tables S10 and S11).

Offspring health at birth

We next examine offspring health at birth considering indicators obtained from obstetric records. Using linear regressions, in the full sample offspring birthweight does not differ significantly between mothers exposed to high IMR in infancy, but results differ by gestational week and sex (SI Appendix, Table S12). Among offspring born pre-term (gestational weeks 30-37), birthweight of offspring of exposed mothers is on average higher (96.89 grams; p-value 0.08), while no statistically significant differences are found for offspring born in gestational weeks 38-43. Among offspring born pre-term even larger differences are seen for boys (143.52 grams; p-value 0.05), while no statistically significant differences are found for girls (Figure 3a and Appendix Table S12).

Similar patterns are observed when considering offspring ponderal index, an indicator of fetal growth status (SI Appendix, Table S13). Among offspring born preterm (gestational weeks 30-37), boys of exposed mothers have higher average ponderal index (1.02 kg/m^3; p-value 0.10), while no statistically significant differences are found for boys born in gestational weeks 38-43. No statistically significant effects were seen for girls. Furthermore, using logistic regressions, no statistically significant differences in the odds of being born small for gestational age (SGA) are seen in relation to maternal disease exposure in infancy, neither when studying boys or girls together nor separately (SI Appendix, Table S14). For boys, lower odds of being SGA are observed for those born to mothers born in a year of high IMR, but this effect is imprecisely estimated (OR 0.54, p-value 0.15).

Taken together, the analyses of offspring health indicate that boys born to mothers who were exposed to a high level of disease in infancy are less likely to be small when born preterm. This effect could originate from two factors: differences in gestational length by mother's early life disease exposure, or differences in her likelihood of experiencing miscarriages leading to out-selection of small boys. We find evidence for both mechanisms. Logistic regressions show that, among boys, the odds of being born preterm, defined as weeks 30-37 of gestation, is higher if having a mother that was adversely exposed (O.R. 1.44; p-value 0.01; Figure 3b; SI Appendix, Table S15). Logistic regressions show a higher likelihood of having experienced at least two miscarriages among exposed mothers (O.R. 1.98; p-value 0.02; Figure 3c; SI Appendix, Table S16). These results should be interpreted with caution, since the number of women who experienced two or more miscarriages is low (62 women, 1.42% of the women in the hospital obstetric records sample).

[Figure 2: About here]

[Figure 3: About here]

3. Discussion

Our findings demonstrate that adverse exposures in early life affect reproductive health and the health of the next generation. Women exposed to high levels of disease in infancy give birth to a lower proportion of boys (lower offspring sex ratio) and have a higher risk of miscarriage and male stillbirth. Moreover, boys born to exposed mothers are more likely to be born preterm and have higher birthweight and higher ponderal index, an indicator of fetal growth status. Affected women are also more likely to experience miscarriages and male stillbirths, and less likely to experience

multiparous births. These findings are in line with the notion that male fetuses are more sensitive to their mother's adverse physical or contextual conditions, and the fact that pregnancies with male fetuses more often result in a miscarriage (12, 24). Results are in line with earlier literature showing that women of low socioeconomic status exposed to whooping cough in infancy had a lower proportion of boys (3). In other words, there is out-selection of male fetuses in utero. At the same time, we do not find strong evidence that the overall likelihood of giving birth is affected by maternal disease exposure in infancy. The latter result is in line with e.g., Hayward et al. (13) who do not find robust evidence on that early-life adversity affects reproductive success measured in terms of number of children. Our work shows that parity alone may be too crude a measure of reproductive outcomes to capture the full effect of early-life disease on women's health in mid-life.

The vast literature on the long-run health effects of early-life conditions shows that pronounced gains in human life expectancy since the mid-19th century partially stem from reductions in exposure to infections in early life. A question that has received limited attention is whether these reductions in infectious exposure also have had an impact on fertility and other reproductive outcomes, including offspring health and thus, whether the effects also transfer to the next generation. Using a well-established high-quality longitudinal demographic database for southern Sweden combined with obstetric records of births, we studied the influence of the early life disease environment on reproductive outcomes for women and the health of their newborns. We study effects across birth cohorts (1890-1950) and follow these women and their offspring between 1905-2000. We avoid studying a health-selected cohort of survivors as we examine a relatively mild early-life infection exposure, indicated by peaking county-level infant mortality rates, common to cohorts before and after the demographic transition. We can also limit stayer bias, as we include women born in the whole region of Scania who lived in the research area and used their county of birth to identify their level of disease exposure in infancy. With rich data on multiple reproductive outcomes, including information on miscarriages, stillbirths, offspring birth weight, gestational age and sex ratio at birth, our setting offers a unique opportunity to extend the study of early-life adversity on women's reproduction beyond measures of parity and number of surviving children.

Our findings are in line with existing evidence showing that sex ratios at birth are lower for women reproducing in poorer health at time of conception or in more disadvantageous current contextual conditions (11, 22–24, 28–32), that birth weight for affected cohorts' boys is upwardly affected for mothers exposed to stressful events during pregnancy (12), and a downward adjustments of twinning with boys (27). We demonstrate that such negative effects not only relate to current conditions but can stem from women's existing health after early-life exposure to adversity. We also show that to fully capture the effects of exposure on reproductive health and to understand how health is transmitted across generations, including processes of scarring and selection for both mothers and offspring, it is important to focus on a range of reproductive outcomes. Measuring reproductive outcomes only using indicators such as parity and number of surviving children may underestimate the overall effect of women's health on their reproductive outcomes, especially for populations living post-demographic transition where fertility is generally lower, controlled, and supported by assisted reproductive technology. Given the comprehensive set of outcomes our results contribute to our understanding regarding disease exposure influences on female reproduction in contemporary populations.

Identifying the mechanisms through which early life disease exposure affects women's reproduction is beyond the scope of this work, but our results align with proposed theoretical mechanisms. Through processes of scarring (8), infectious disease exposure can have a non-lethal but damaging impact upon women's physiology, impairing reproduction in different ways (9). The hormonal and reproductive systems may be permanently damaged, in which pathways of inflammation may play a role. After bacterial and viral early-life infection, inflammatory immune responses (37–39) and inadequate development of vital organs and the immune system may lead to disease and reduced longevity (38, 39). Associations between adverse early life exposures and ovarian function have been noted both in clinical and experimental studies (40). A woman's likelihood of (quick) conception but also her ability to carry a pregnancy to term may therefore be affected. The link between disease exposure in infancy and reproductive and offspring health may also work through epigenetic change (41–43), or epigenetic inheritance (42, 44), but effects can also stem from offspring health selection. Women with a frail health may experience more spontaneous abortions (miscarriages) compared to women in better health.

The limitations of this study partially relate to generalizability of our findings to other settings. First, the studied population is not a natural fertility population where fertility was primarily determined by biological factors and where the role of early-life exposure to adversity was likely even more relevant for reproductive outcomes. Yet, we believe that the studied population and our findings are relevant for contemporary settings with better general health and where socioeconomic factors and cultural norms are main drivers of reproductive choices, enabled by modern medical technology. Second, while the study setting is not necessarily representative for Europe or beyond, variation in disease exposure is a common phenomenon and there is no reason to assume that the influence on reproductive outcomes should be different in other settings. Third, while an advantage of our analytical set-up is that it allows for the inclusion of women in-migrating into the study area and that disease exposure is exogenous to individual characteristics, we are unable to measure the precise timing of exposure to high levels of disease in the year of birth. We thus do not have exact precision regarding in which trimester or month of infancy that local IMR peaked.

Previous work on the effects of exposure to disease in early life show that mortality among exposed women was relatively lower during childhood and adolescence, not significantly different during the reproductive years, and relatively higher after around age 50 compared to the non-exposed (17). Other work found scarring effects resulting in increased mortality during women's reproductive years following childhood exposure to infectious disease mortality within the family (45). The current study provides evidence that effects of early-life exposure on morbidity and health possibly take off in midlife. Previous work on the effects of early-life conditions on health generally focused on mortality and have therefore not been able to capture the effects of early-life adversity in mid-life when mortality is generally low and overlooked relevant aspects of health, including morbidity and reproductive outcomes.

Our findings are important to understand the tremendous changes in population health and reproductive patterns in the past centuries. Although young-age mortality fell strongly during the 20th century with better population health, exposure to infectious disease has remained common among infants and young children. In light of changing disease environments, including the Covid-19 pandemic, it is important to understand the potential reach of long-run implications of infectious disease exposure for health. We show that reproductive outcomes, including offspring health, are

not only affected by women's health in the period leading up to and during pregnancy, but are also influenced by her stock of health shaped in early life. Maternal health stock should be considered when studying determinants of infant health (46), particularly in developing countries. Moreover, awareness about long-term ramifications of infectious disease in infancy can inform health decisions among young women, and help target interventions in preconceptional, prenatal and infant care (47). This is high on the global health agenda; the 2030 United Nation's Sustainable Development Goals include reducing neonatal and maternal mortality, ensuring access to reproductive health-care services, and increasing gender equality (48). Our work highlights the importance of interventions aiming to reduce exposure to disease, but also the need for specific screening during reproductive ages of women who were subject to adversity in early life.

4. Materials and methods

We employ a unique longitudinal dataset consisting of historical data covering a region in Southern Sweden and purposively digitized obstetric records, linked to Swedish national register data. This dataset allows us to overcome some of the limitations of previous studies regarding the number of birth cohorts studied, completeness and duration of follow-up and types and level of detail of measurements of reproductive outcomes. A more detailed description of the data and methods used in this work can be found in the Appendix Supplementary Information (SI) (Section 1). The historical sample consists of parish records for the city of Landskrona and five surrounding rural parishes for the period 1905-1967 obtained from SEDD and the linked national register data covers the period 1968-2000. See map of the study area in SI Appendix Figure S1 and (49) for a recent application using SEDD. Our study population consists of women born in the region of Scania (Malmöhus and Kristianstad counties) between 1890 and 1950, who are followed between age 15-50 in SEDD areas in the years 1905-2000. We have information on 28,254 women and 18,590 of their births.

For a subsample of women, obstetric records of midwife-assisted home births and hospital births for the period 1918-1945 were digitized and linked. They include information on infant birth weight and length, the woman's earlier miscarriages, and woman's date of last menstruation, which is used to determine gestational age. After exclusion of records with errors or missing data, this sample consist of 7,177 children (4,576 mothers).

Disease exposure in infancy is measured using year and county-level infant mortality rate (IMR) 1890-1950, detrended with a Hodrick-Prescott filter (see Appendix). Infant mortality rate is an indicator of the level of infectious disease which infants were exposed to (50). Whereas this indicator does not measure actual disease exposure for an individual, it has the advantage of being exogenous and thus not confounded by other individual- or family-level factors such as socioeconomic status, genetic characteristics, or underlying health. Given the secular decline in IMR, we calculate relative deviations from the trend, to identify infectious disease peaks. Following (3, 17) we define as years with high IMR those in the top 20^{th} percentile in the county's distribution of deviations from the trend. The empirical analyses compare women born in counties and years with high IMR to those born in years and counties below this threshold. We conduct a sensitivity analysis to address possible biases related to the years identified as having a high disease load, and the results were consistent to those of the main models (SI Appendix, Section 3 and Tables S17-S27).

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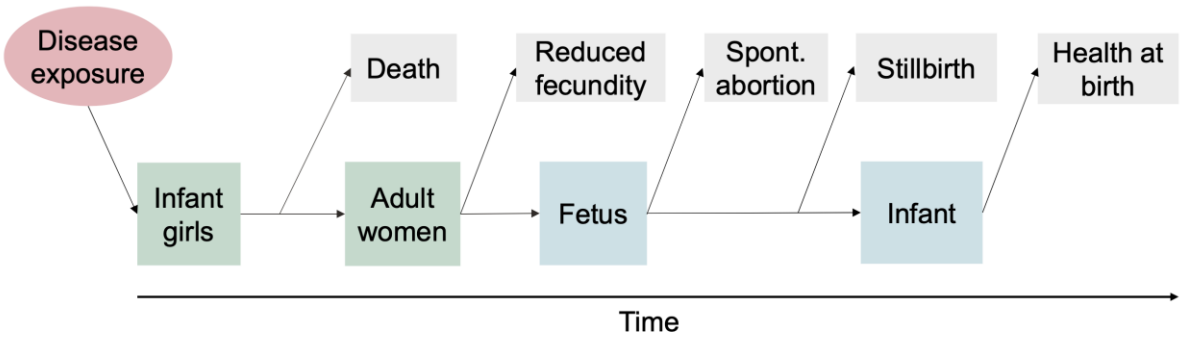
Figures and Tables

Figure 1: Theoretical model: Exposure in infancy to high levels of disease and women's reproduction and offspring health



Notes: The figure represents the relationship between disease exposure during a girl's infancy and reproductive and other life course outcomes, as well as the health of the next generation. Only a selected group of women may survive to adult ages. Their ability to conceive may be affected negatively if health scarring effects dominate those of health selection. For women who conceive, unfavorable conditions in the womb or congenital malformations of the fetus can lead to spontaneous abortion (miscarriage) and stillbirth. Male fetuses are more likely to be miscarried or stillborn. Birthweight of offspring born alive may be higher depending on the strength of selection taking place in utero and is thus likely to be sex dependent.

Figure 2. Women's disease exposure in early life and life course and fertility outcomes, southern Sweden, 1905 – 2000

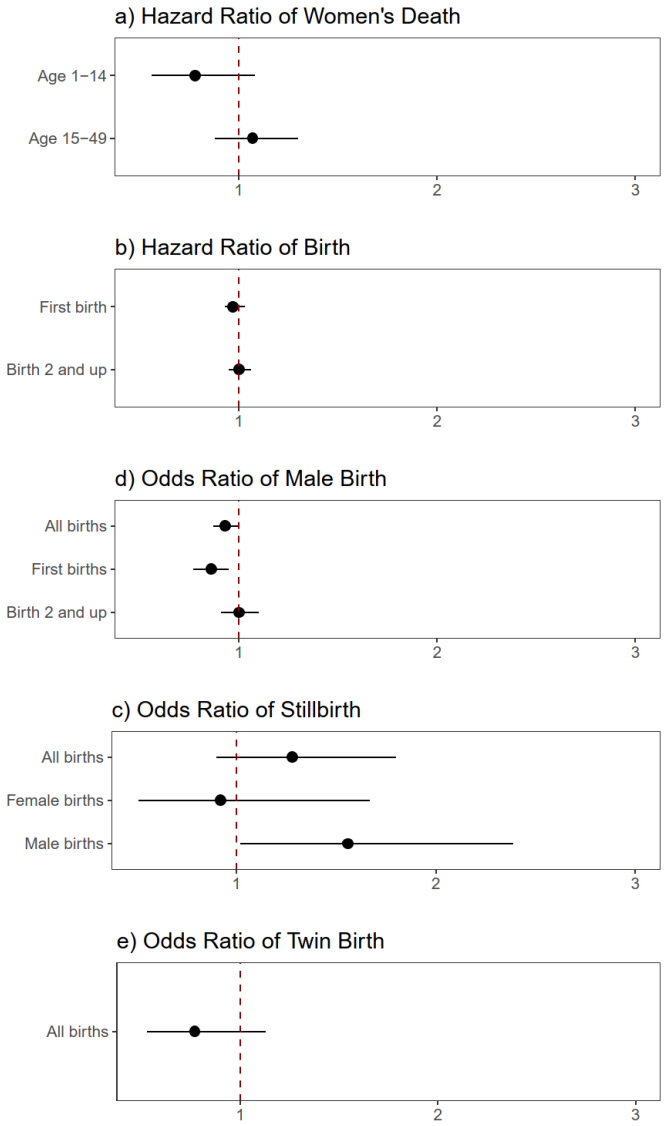


Figure notes: The results presented in this figure originate from different models. Appendix Tables S4-S9 presents the precise estimates. Data comes from SEDD (Scanian Economic Demographic Database). See Section 1 in the Supplementary Material for data description.
Panel a) is the hazard ratio of exposed women's death between age 1-14 (women=19,358, 334 deaths) and 15-49 (women=31,068, 725 deaths), estimated with Cox proportional hazard models. Panel b) is the hazard ratio of birth to exposed women, estimated with Cox proportional hazard models for first (women = 25,787; births = 9,277) and second and higher order births (women=12,256; births = 8,359). Panel c) is the odds ratio that a new-born offspring is male for exposed women, by parity, estimated using logistic regressions (women = 11,550; births = 20,361). Panel d) is the odds ratio that a new-born offspring is stillborn for exposed women by sex, estimated using logistic regressions (births = 17,668, stillbirths = 225), for 1905-1967, period during which information on stillbirths is available. Panel e) is the odds ratio that a birth event is multiparous birth for exposed women, estimated using a logistic regression (birth events = 20,597; twin births events = 236).

Figure 3. Women's disease exposure in early life and offspring health at birth, southern Sweden, 1905 – 2000

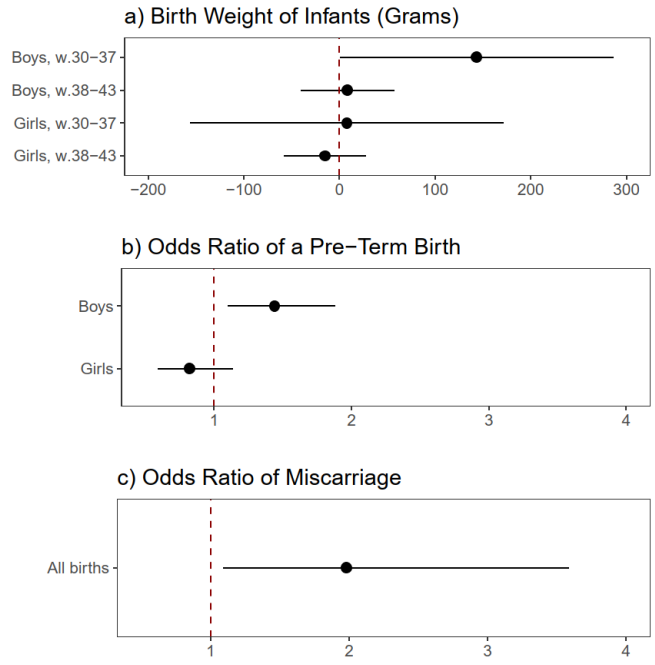


Figure notes: The results presented in this figure originate from different models. Appendix Tables S13 - S16 presents precise estimates. Data comes from SEDD (Scanian Economic Demographic Database) and digitized obstetric records. See Section 1 in supplementary appendix for data description. Panel a) is the birth weight of exposed women's sons and daughters born preterm (gestational age 30-37 weeks) and term/post-term births (gestational age 38-43 weeks), estimated with linear regression models (n=7,177). Panel b) is the odds ratio that a new-born offspring is born pre-term (gestational age 30-37 weeks) by sex, for exposed mothers, measured using logistic regressions(n=7,177). Panel c) is the odds ratio that exposed women who gave birth (and were thus in the obstetric records) had two or more miscarriages, measured using a logistic regression (women = 4,364; 62 women with two or more miscarriages).

Disease exposure in infancy affects women's reproductive outcomes and offspring health. Evidence from southern Sweden 1905-2000

Supplementary information: Appendix

5. Data and methods

1.1 Source material and study sample

This study uses data from the Scanian Economic Demographic Database (SEDD – 1)[1], which comprises births, deaths, marriages, and migrations occurring in the town of Landskrona and five parishes in its rural hinterland for the period 1905-1967, all located in southern Sweden (see map in Figure S1). The SEDD was constructed using register-type data from catechetical examination registers and updated with information on births, marriages, and deaths from church books. The material is of high quality and considered to be complete regarding vital events (6). See (7) for a recent example of research using SEDD. For the period after 1967, individuals from the SEDD area are followed in the national register data from Statistics Sweden and the National Board of Health and Welfare. Our study population consists of women born in the region of Scania (Malmöhus and Kristianstad counties) between 1890 and 1950. These women are followed through their reproductive ages in the SEDD areas in the years 1905-2000. All women are included in the study sample during the period in which they live in the study area, regardless of marital status. We have information on 28,254 women and 18,590 births.

For a subsample of women, obstetric records were digitized and linked to SEDD (8). Obstetric records consist of midwifery records of children born at home in the five rural parishes between 1918 and 1945[2], and hospital birth records of children from Landskrona and the five rural parishes, born in the hospitals of Landskrona, Lund and Helsingborg between 1926 and 1967[3]. Sweden was one of the first countries in Europe where deliveries in hospitals replaced home deliveries. Our database of digitized and linked obstetric records covers a much longer period than similar databases, such as the Uppsala Birth Cohort Study (9).

The obstetric records include information on infant birth weight in grams and birth length in centimeters, which are here considered as additional indicators of reproductive health. The records also include a wide range of other information on the health of the mother and the child and medical details about the pregnancy and delivery, including information about women's earlier miscarriages, and the woman's date of last menstruation.

[1] The SEDD is administered by the Centre for Economic Demography, Lund University, Sweden. For a description of the structure of SEDD see (2). For a general overview of previous research using SEDD see (3). The dataset for analysis was constructed using programs developed by Quaranta (4, 5).

[2] Mothers are born between 1890 and 1922. Midwifery records for the city of Landskrona were unfortunately not preserved in the archives.

[3] Obstetric hospital birth records are available at Region Skåne archives in Lund. The hospital birth records of the hospitals of Lund and Helsingborg are sorted based on year of birth of the child, and we have digitized records for children born between 1926 and 1945. Birth records from Landskrona hospital are arranged based on year of birth of the mother, and we have digitized records of mothers born up to 1931, who gave birth starting from 1935 (the first year when the hospital had a maternity ward) until 1967.

Gestational age was calculated as the number of days between the reported first day of the last menstrual period and the date of birth, and it was afterwards converted into weeks. Twins and children with no reported date of last menstruation or with possible errors in this information (gestational weeks below 30 or above 43) or whose birth weight or birth length was missing or likely wrongly recorded were excluded from the analysis. The remaining sample consists of 7,177 children, 300 of whom were born at home assisted by qualified midwives and the remaining 6,877 were born in hospitals (121 in Helsingborg, 5,872 in Landskrona, and 882 in Lund).

1.2 Disease exposure

As an indicator of disease exposure in early life we use peaking infant mortality rates (IMR) for the county (Malmöhus or Kristianstad) and year of birth of each woman. Yearly data on the number of births and number of infant deaths was collected for each county from official sources (10) and we calculated county-level IMR for the years 1890-1950. Each county's IMR series was de-trended by applying a Hodrick-Prescott filter (11) with a filtering factor of 6.25, the recommended value to remove the trend from yearly series (12). Given the large decline in IMR in 1890-1950, we calculated relative deviations from the trend in IMR for each county. We consider short-term variations in IMR as indicator of high diseases exposure, since years when IMR was higher than its trend are likely to have been epidemic years (6, 13–16). Women born in such years are likely to have been exposed to the same diseases that killed a larger than normal number of infants. Whereas this indicator cannot measure actual exposure of the woman to disease, it has the advantage of being exogenous and thus not confounded by other individual- or family-level factors such as socioeconomic status, genetic characteristics, or underlying health. Moreover, peaks in IMR are relatively mild and population-shared health shocks, which can be more informative than focusing on the long-term effects on individuals surviving very harsh single events such as the Spanish flu or famines, who are likely to be strongly health-selected. Following (14, 15), years with high IMR have a relative deviation from the county trend in the top 20th percentile in the distribution of deviations from the trend for that county.[4] All analyses compare women born in counties and years with high IMR to those born in years and counties with low-medium IMR. From here onwards these groups are defined, respectively, as exposed and non-exposed women. Figure S2 shows the IMR, deviations from the trend and relative deviations from the trend for Malmöhus and Kristianstad counties.

All statistical models control for year of birth as a continuous variable, to account for the declining trend in IMR and other general changes related to fertility and overall health and medical conditions. To address possible biases related to the years identified as having a high disease load, particularly the fact that years with peaking IMR are not evenly spread across the studied cohorts and that the two counties exhibited different patterns of high disease years, a sensitivity analysis was conducted in section 3 of the Supplementary information.

[4] For Malmöhus, such years were 1892, 1899, 1908, 1914, 1916, 1931, 1940, 1941, 1944, 1945, 1948 and 1949, while for Kristianstad they were 1892, 1899, 1902, 1907, 1911, 1919, 1922, 1929, 1931, 1936, 1937, 1940, 1949. By considering years with high relative deviations from the trend rather than years with high deviations, we avoid possible biases related to the fact that, given the large decline across cohorts in the IMR values, larger deviations from the trend are observed in years with high IMR than in years with lower IMR.

1.3 Outcome variables

We follow women residing in SEDD areas across their lives and study a comprehensive set of reproductive outcomes (see Figure 1 in the main text). Prior to analyzing reproductive health, we consider as outcome variables female mortality in ages 1-14 and 15-49. This allows us to gain a better overall understanding of whether selection or scarring mechanisms dominate during childhood and adolescence, and during reproductive stages, in relation to exposure to disease in early life.

A wide range of reproductive outcomes is considered in the empirical analysis. Fertility is measured by studying the likelihood of giving birth, analyzing first and second and higher order births separately. Furthermore, sex ratio at birth, stillbirths[5] and twinning are considered. We also study total number of births and total number of children surviving to age 5. For the last two outcomes, we restrict the analysis to births taking place between age 18 and 42 (which accounts for 97% of all births) and consider only women who were observed without gaps at least from age 18 until age 47 (to observe all possible child deaths occurring before age 5). Throughout the paper we refer to these women as women observed for their full reproductive period. For the same sample of women, we study the likelihood of being childless, defined as not having given birth to any child between ages 18 and 42.

In a final step we focus on offspring health at birth, and use information from obstetric records to examine as outcomes offspring birthweight, ponderal index, likelihood of being small for gestational age (SGA), likelihood of being born preterm, as well as the number of miscarriages experienced by women.[6] Ponderal index is used as an indicator of fetal growth status, and it is calculated as weight (kg) / length^3 (m). Infants are defined SGA when weighing less than two standard deviations below the expected birth weight for gestational age and gender. The standard deviation is calculated from the study sample distribution of weight deviations from expected weights, taking the Swedish intrauterine growth curves as the point of reference (17). Infants are defined as being born preterm if they were born in weeks 30-37 of gestation.

1.4 Empirical specification

In all models, the main explanatory variable is the level of IMR in the woman's year and county of birth. The impact of exposure to disease in early life on women's mortality is studied using Cox proportional hazard models[7]. Two models are estimated, one for ages 1-14, and one for ages 15-49, to study separately the impact on the life stage preceding reproduction, and during reproductive ages. We include a control for the woman's year of birth.

Cox proportional hazard models are also used to analyze the impact of disease exposure in early life on women's likelihood of giving birth, studying separately first and second and higher order births. Through the use of Cox models, the analysis considers both whether a birth event happens and the time until such an event. Age is considered as the time variable when studying first births. Second and higher order births are studied using the interval between births as the time

[5] Information on stillbirths is only available until 1967.

[6] Information about miscarriages is available in obstetric records from hospitals, but not in records of home births assisted by midwives.

[7] Throughout the paper, when using Cox proportional hazard models, the proportional hazards assumption was tested using tests based on Schoenfeld residuals. No violation in the assumption was observed in any of the models for the variable measuring the disease exposure in the woman's year of birth.

variable, and clustering standard errors on the mother to account for her shared characteristics between her births. Intervals are truncated eight years from the previous birth, since only a small fraction of births takes place after such time. We include a control for the woman's year of birth. The model for higher order births also controls for the woman's age (categorical: 15-24, 25-34 and 35-49)[8]. Cure models (split population models), a variant of Cox proportional hazard models that account for part of the sample never experiencing an event of interest, are used to address stopping and birth spacing. Such models estimate separately factors that contribute to the likelihood to experience the event (the birth of the first child / additional child) and factors contributing to the time until the event (age at birth in the case of first births, and birth interval in the case of second and higher order births).

Poisson models are used to analyze the impact of disease exposure in early life on women's total fertility and on the number of offspring surviving to age 5, throughout women's reproductive careers. The models also control for the year of birth of the woman. The likelihood of being childless is modelled using a logistic regression, also controlling for women's year of birth.

Offspring sex ratios at birth are calculated for women exposed to high and low-medium IMR at birth, considering only live singleton births. We conduct likelihood ratio tests (Chi-squared) to measure whether the differences between the two groups are statistically significant. For all singleton birth events, logistic regressions are estimated to study the likelihood that the child born is a male. Three separate estimations are made: all births, first births, and second and higher order births. In addition to the level of IMR in the woman's year and county of birth, the models control for maternal year of birth and age (categorical: 15-24, 25-34 and 35-49). To account for shared characteristics of the mother across her births, a random effects component is included in the models.

We analyze the likelihood that a birth is a stillborn child using logistic regressions. Only singleton births are considered in this analysis and we here limit the study to births taking place until 1967. We study all births as well as male and female births separately. Models control for maternal year of birth and age (categorical: 15-24, 25-34 and 35-49) and include a random effects component to account for shared characteristics of the mother across her births.

Further, we analyze the likelihood that a birth event is multiparous birth using logistic regressions. The outcome variable is a dependent variable assuming value 1 for multiple births and 0 for singleton births. Models control for maternal year of birth and age and include a random effects component to account for shared characteristics of the mother across her births.

To analyze offspring birthweight and ponderal index, we estimate separate linear regressions, each considering one of these two outcomes. We include controls for the woman's year of birth and age. Models are estimated for the full sample, and separately by sex and by gestational week. Two distinct gestational age groups are considered: preterm (gestational weeks 30-37) and term/post-term (gestational weeks 38-43). To analyze the likelihood of being SGA, logistic regressions are used, also controlling for the mother's year of birth and age. The analysis is conducted for the full sample as well as separately by sex. We study the likelihood of being born preterm using logistic regressions that also control for the mother's year of birth and age.

To study the impact of disease exposure in early life on miscarriages experienced by women, we estimate logistic regressions considering as outcome a binary variable measuring whether the

[8] Models for first birth do not control for mother's age, since age is the time variable.

woman experienced two or more miscarriages. The models control for the woman's year of birth and total number of births. The results of this model should be interpreted with caution, since the number of women who experienced two or more miscarriages is low (62 women, 1.42% of the women in the hospital obstetric records sample) and is subject to recall bias. At the same time, a majority of miscarriages take place in early pregnancy, before women are aware of their pregnancy, so that the total (unobserved) differences in the number of miscarriages between exposed and non-exposed women is likely to be larger than reported.

6. Descriptive statistics

Table S1 provides descriptive statistics for the full sample, showing values separated into all births, first births, and second and higher order births, respectively. The total sample comprises 28,254 women, who had 18,590 birth events within the period they were included in the sample. About 20% of the women were exposed to high IMR in their year and county of birth. The sample includes women who were born in Scania, 92% of whom were born in Malmöhus county. The sex ratio at birth for the full sample is 106.10 males per 100 females. The sex ratio among first born children (106.39) is slightly higher than for later born children (105.81).

In Table S2 descriptive statistics are shown for women observed during their full reproductive period, which is a total of 3,304 women. Of these women, 19% were exposed to a high disease load in their year of birth, and 97% of them were born in Malmöhus county. On average such women had 1.46 children in ages 18-42, and 72% of them gave birth to at least one child in such age range.

Table S3 presents descriptive statistics of the sample of 7,177 children for whom obstetric records are available. Average birth weight for children in the sample is 3,497 grams, while average ponderal index is 27 kg/m^3. Of the analyzed sample, 2% were born SGA. The sample comprises a slightly higher share of boys than girls. When it comes to maternal characteristics, 15% of children were born to a mother who was exposed to high IMR at birth. More than half of the sample of mother's were aged 25-34 at birth. The average birth year of mothers is slightly lower in this sub-sample than in the full sample, which follows from the availability of the obstetric records (children born between 1918 and 1967), while in the full sample women are followed between 1905 and 2000.

7. Sensitivity analysis

This work considers infant mortality rates (IMR) for the county and year of birth of each women as indicators of disease exposure. The IMR series for Malmöhus and Kristianstad counties were detrended using Hodrick-Prescott filter. Years with high IMR have a relative deviation from the county trend in the top 20^{th} percentile in the distribution of deviations from the trend for that county. For Malmöhus, such years were 1892, 1899, 1908, 1914, 1916, 1931, 1940, 1941, 1944, 1945, 1948 and 1949, while for Kristianstad they were 1892, 1899, 1902, 1907, 1911, 1919, 1922, 1929, 1931, 1936, 1937, 1940, 1949. By considering years with high relative deviations from the trend rather than years with high deviations, we avoid possible biases related to the fact that, given the large decline across cohorts in the IMR values, larger deviations from the trend are observed in years with high IMR than in years with lower IMR.

To address possible biases related to the years identified as having a high disease load, for each outcome four additional model specifications were made: sample of women born before 1940; full sample, controlling for a categorical variable for birth decade instead of the birthyear

trend; full sample, adding a control for county of birth; full sample, adding an interaction between county of birth and the birth year trend. The reason why in one of these models the sample is limited to women born before 1940 is that in Malmöhus county half of the years identified as peak IMR years fall after such period.

As can be seen in tables S17-S27 below, for all outcomes the results of the four additional model specifications remain consistent to the results of the main models. More specifically, with regards to female mortality we see a dominance of selection in ages 1-14 (not statistically significant) and a very slight dominance of scarring in ages 15-50. With regards to reproductive outcomes, we find that women exposed to a high disease load in infancy have a lower odd of giving birth to a male among first born offspring, and a higher odd of stillbirth among male offspring. We also see some indication that exposed women have a lower odd of giving birth to twins, even if such result is slightly above the threshold of statistical significance. We do not find any clear effects of a woman's disease exposure in early life on her likelihood of giving birth, although when controlling for the woman's birth decade instead of birth year a lower hazard of second or higher order birth is observed (p-value 0.05). No statistically significant effects are found in any of the model specifications for total number of births, nor the likelihood of being childless. Focusing on offspring health at birth, the sensitivity analysis confirms that boys born pre-term (weeks 30-37 of gestation) whose mothers were exposed to a high disease load in early life have higher average birthweight (statistically significant) and higher ponderal index (at the border of the threshold for statistical significance). Moreover, boys of exposed mothers have a lower odd of being born small for gestational age (slightly above the threshold for statistical significance) and a higher odd of being born pre-term (statistically significant).

Given that the results of the sensitivity analysis estimations are well in line with the main results of this work, we conclude that the findings of this study are not biased by which years were selected as high disease years.

Tables

Table S1: Descriptive statistics, all women, Scania 1905-2000

	All births	First births	Second and higher order births
IMR			
Low-medium	80.26	81.35	79.21
High	19.74	18.65	20.79
Woman's age			
15-24	33.73	59.32	8.92
25-34	28.83	22.64	34.82
35-49	37.45	18.04	56.26
Woman's birth year (mean)	1919.22	1916.63	1921.73
Woman's birth county (%)			
Kristianstads	8.00	7.01	8.95
Malmöhus	92.00	92.99	91.05
Number of women	28254	25787	12557
Number of live birth events	18590	9277	9313
Sex ratio at birth (singleton live births)	106.10	106.39	105.81

Note: values are weighted by person years. Source: own elaborations from SEDD.

Table S2: Descriptive statistics, women observed during their full reproductive period, Scania 1905-2000

	Mean / %
IMR (%)	
Low-medium	80.93
High	19.07
Woman's birth year (mean)	1918.662
Woman's birth county (%)	
Kristianstads	2.91
Malmöhus	97.09
Number of children (mean)	1.46
Births in ages 18-42 (%)	
0	27.63
1 or more	72.37
Number of women	3304

Source: own elaborations from SEDD.

Table S3: Descriptive statistics, sample with available obstetric records, Scania 1918-1967

	Mean / %
Birth weight (mean)	3497.38
Ponderal index (mean)	27.13
Small for gestational age (%)	2.01
IMR at mother's birth (%)	
Low-medium	85.22
High	14.78
Woman's birth year (mean)	1916.23
Woman's age (%)	
15-24	26.65
25-34	57.6
35-49	15.74
Child's sex (%)	
Girls	48.73
Boys	51.27
Number of children	7177

Source: own elaborations from SEDD

Table S4: Cox models estimating the hazard of death of women in ages 1-14 and 15-49, Scania 1905-2000

	Ages 1-14				Ages 15-49			
Variable	H.R.	Lower C.I.	Upper C.I.	p-value	H.R.	Lower C.I.	Upper C.I.	p-value
IMR at woman's birth								
Low-medium	1.00			ref.	1.00			ref.
High	0.78	0.56	1.08	0.13	1.07	0.88	1.30	0.51
Woman's birth year	0.94	0.93	0.95	0.00	0.97	0.96	0.97	0.00
Number of women	19358				31068			
Number of deaths	334				725			

Source: own elaborations from SEDD

Table S5: Cox models estimating the likelihood of giving birth, Scania 1905-2000

	First births								Second and higher order births			
	Model 1				Model 2				Model 3			
Variable	H.R.	Lower C.I.	Upper C.I.	p-value	H.R.	Lower C.I.	Upper C.I.	p-value	H.R.	Lower C.I.	Upper C.I.	p-value
IMR at woman's birth												
Low-medium	1.00			ref.	1.00			ref.	1.00			ref.
High	0.97	0.93	1.03	0.32	0.93	0.86	1.01	0.08	1.00	0.95	1.06	0.90
Woman's birth year	1.02	1.02	1.02	0.00	1.02	1.02	1.02	0.00	0.99	0.99	0.99	0.00
Woman's age												
15-24									1.58	1.50	1.67	0.00
25-34									1.00			ref.
35-49									0.37	0.35	0.40	0.00
Number of women	25787				12282				12256			
Number of births	9277				3727				8359			

Note: Model 1 and model 3 include all women. Model 2 only includes women who were observed in SEDD areas at least from age 15, and excludes women from their first outmigration, so that there are no periods of absence from SEDD areas between age 15 and their last inclusion (i.e. only women for whom we can measure parity with full precision are considered). In model 3 intervals are truncated 8 years from the previous birth. The sample size in model 3 is therefore different than shown in table S1. Source: own elaborations from SEDD

Table S6. Cure models estimating the likelihood and time-to-birth, Scania 1905-2000

	Model 1		**Model 2**		**Model 3**	
	Coeff.	p	Coeff.	p	Coeff.	p
Stopping (cure fraction)	Log odds		Log odds		Log odds	
IMR at woman's birth						
Low-medium	*ref*		*ref*		*ref*	
High IMR	0.009	0.882	0.105	0.283	0.013	0.842
Woman's birth year	-0.494	0.000	-0.988	0.000	0.318	0.000
Woman's age						
15-24					-1.269	0.000
25-34					*ref*	
35-49					1.518	0.000
Constant	-1.250	0.000	-1.196	0.000	-0.634	0.000
Spacing (transition/scale)	Hazard Rate	p	Hazard Rate	p	Hazard Rate	p
IMR at woman's birth						
Low-medium	*ref*		*ref*		*ref*	
High IMR	0.001	0.815	0.001	0.925	-0.001	0.950
Woman's birth year	0.033	0.000	0.053	0.000	-0.195	0.000
Woman's age						
15-24					0.075	0.003
25-34					*ref*	
35-49					0.042	0.189
Constant	-3.218	0.000	-3.22	0.000	-1.411	0.000
Shape	1.669	0.000	1.640	0.000	.323	0.000
Log likelihood	-33050		-14760		-27035	
Number of subjects	25,594		12,199		12,256	
Number of births	9,227		3,727		8,359	
Time at risk	177,576		108,429		101,276	

Notes: In the cure panel, the log odds of stopping is reported. In the spacing panel, the scale refers to the proportional hazard of having another bird so that a positive coefficient is an increased hazard of another birth (a shorter birth interval) and a negative coefficient a decreased hazard of another birth (a longer birth interval). Model 1 and 2 concern first births. Model 3 concerns second and higher order births. All models contain a control for birth year (standardized). Model 2 only includes women who are observed in the research region at age 15 and until their first absence from the research region, so that they remain under continuous observation. Source: own elaborations from SEDD

Table S7: Odds ratio that a live-born child is male, Scania 1905-2000

	All births				First births				Second and higher order births			
Variable	O.R.	Lower C.I.	Upper C.I.	p-value	O.R.	Lower C.I.	Upper C.I.	p-value	O.R.	Lower C.I.	Upper C.I.	p-value
IMR at woman's birth												
Low-medium	1.00			ref.	1.00			ref.	1.00			ref.
High	0.93	0.87	1.00	0.04	0.86	0.77	0.95	0.00	1.00	0.91	1.10	0.94
Woman's age												
15-24	1.01	0.95	1.07	0.83	1.01	0.92	1.10	0.90	1.01	0.92	1.10	0.91
25-34	1.00			ref.	1.00			ref.	1.00			ref.
35-49	1.00	0.91	1.09	0.94	0.96	0.77	1.21	0.74	1.00	0.90	1.11	0.98
Woman's birth year	1.00	1.00	1.00	0.60	1.00	1.00	1.00	0.19	1.00	1.00	1.00	0.66
Number of women	11550				9166				7169			
Number of births	20361				9172				11189			

Note: Only singleton births are considered. Source: own elaborations from SEDD

Table S8: Odds ratio that a child is stillborn, Scania 1905-1967

	All births				Female births				Male births			
Variable	O.R.	Lower C.I.	Upper C.I.	p-value	O.R.	Lower C.I.	Upper C.I.	p-value	O.R.	Lower C.I.	Upper C.I.	p-value
IMR at woman's birth												
Low-medium	1.00			ref.	1.00			ref.	1.00			ref.
High	1.28	0.90	1.80	0.17	0.92	0.51	1.67	0.78	1.56	1.02	2.39	0.04
Woman's age												
15-24	0.77	0.56	1.05	0.10	0.91	0.56	1.50	0.72	0.69	0.46	1.03	0.07
25-34	1.00			ref.	1.00			ref.	1.00			ref.
35-49	1.76	1.22	2.52	0.00	2.01	1.16	3.49	0.01	1.60	1.00	2.58	0.05
Woman's birth year	0.99	0.98	1.00	0.08	0.99	0.97	1.00	0.12	0.99	0.98	1.01	0.33
Number of women	10093				6363				6664			
Number of births	17668				8559				9109			
Number of still birth events	225				87				138			

Source: own elaborations from SEDD

Table S9: Odds ratio of a multiparous birth event, Scania 1905-2000

Variable	O.R.	Lower C.I.	Upper C.I.	p-value
IMR at woman's birth				
Low-medium	1.00			ref.
High	0.77	0.53	1.13	0.18
Woman's age				
15-24	0.70	0.51	0.95	0.02
25-34	1.00			ref.
35-49	1.22	0.81	1.84	0.35
Woman's birth year	1.00	0.99	1.01	0.77
Number of women	11630			
Number of births	20597			
Number of twin births	236			

Source: own elaborations from SEDD

Table S10: Linear regressions measuring the total number of children born in ages 18-42 and the total number of children surviving to age 5, for women who were observed during their full reproductive period, Scania 1905-2000

	Number of children born				Number of children surviving to age 5			
	Coef.	Lower C.I.	Upper C.I.	p-value	Coef.	Lower C.I.	Upper C.I.	p-value
IMR at woman's birth								
Low-medium	1.00			ref.	1.00			ref.
High	0.01	-0.06	0.08	0.74	0.00	-0.07	0.08	0.95
Woman's birth year	0.00	0.00	0.01	0.00	0.01	0.00	0.01	0.00
Number of women	3304				3304			

Source: own elaborations from SEDD

Table S11: Logistic regressions measuring the likelihood of not giving birth to any children in ages 18-42 for women who were observed during their full reproductive period, Scania 1905-2000

	O.R.	Lower C.I.	Upper C.I.	p-value
IMR at woman's birth				
Low-medium	1.00			ref.
High	1.10	0.89	1.35	0.37
Woman's birth year	0.97	0.97	0.98	0.00
Number of women	3304			

Source: own elaborations from SEDD

Table S12: Linear regressions of offspring birthweight by gestational week and sex, Scania 1918-1967

ALL CHILDREN												
	Week 30-43				Week 30-37				Week 38-43			
Variable	Coef.	Lower C.I.	Upper C.I.	p-value	Coef.	Lower C.I.	Upper C.I.	p-value	Coef.	Lower C.I.	Upper C.I.	p-value
IMR at woman's birth												
Low-medium	0.00			ref.	0.00			ref.	0.00			ref.
High	-4.82	-38.02	28.39	0.78	96.89	-10.69	204.48	0.08	-13.06	-45.81	19.69	0.43
Woman's age												
15-24	-90.11	-118.49	-61.72	0.00	-3.14	-94.95	88.67	0.95	-80.87	-108.91	-52.83	0.00
25-34	0.00			ref.	0.00			ref.	0.00			ref.
35-49	32.01	-3.00	67.02	0.07	-93.88	-206.38	18.62	0.10	62.26	27.67	96.85	0.00
Woman's birth year	-2.47	-3.93	-1.02	0.00	-5.98	-10.77	-1.20	0.01	-2.14	-3.58	-0.71	0.00
Constant	8256.04	5464.88	11047.19	0.00	14490.70	5324.34	23657.06	0.00	7675.91	4927.09	10424.74	0.00
Number of children	7177				768				6409			
BOYS												
	Week 30-43				Week 30-37				Week 38-43			
Variable	Coef.	Lower C.I.	Upper C.I.	p-value	Coef.	Lower C.I.	Upper C.I.	p-value	Coef.	Lower C.I.	Upper C.I.	p-value
IMR at woman's birth												
Low-medium	0.00			ref.	0.00			ref.	0.00			ref.
High	5.82	-43.81	55.45	0.82	143.52	0.67	286.36	0.05	8.40	-40.74	57.55	0.74
Woman's age												
15-24	-93.70	-134.36	-53.05	0.00	48.82	-78.05	175.69	0.45	-91.41	-131.19	-51.64	0.00
25-34	0.00			ref.	0.00			ref.	0.00			ref.
35-49	26.38	-24.88	77.65	0.31	-101.50	-259.88	56.88	0.21	62.01	11.84	112.18	0.02
Woman's birth year	-2.90	-5.04	-0.77	0.01	-9.23	-16.12	-2.35	0.01	-1.79	-3.87	0.28	0.09
Constant	9134.76	5041.39	13228.12	0.00	20736.77	7552.54	33921.01	0.00	7069.48	3087.80	11051.15	0.00
Number of children	3680				443				3237			
GIRLS												
	Week 30-43				Week 30-37				Week 38-43			
Variable	Coef.	Lower C.I.	Upper C.I.	p-value	Coef.	Lower C.I.	Upper C.I.	p-value	Coef.	Lower C.I.	Upper C.I.	p-value
IMR at woman's birth												
Low-medium	0.00			ref.	0.00			ref.	0.00			ref.
High	-4.17	-48.03	39.69	0.85	7.80	-156.27	171.87	0.93	-14.86	-57.92	28.21	0.50
Woman's age												
15-24	-87.15	-126.17	-48.13	0.00	-55.93	-187.83	75.96	0.40	-71.22	-109.98	-32.47	0.00
25-34	0.00			ref.	0.00			ref.	0.00			ref.
35-49	39.00	-8.08	86.09	0.10	-85.74	-242.96	71.48	0.28	65.13	18.35	111.92	0.01
Woman's birth year	-2.23	-4.19	-0.27	0.03	-3.12	-9.68	3.44	0.35	-2.58	-4.53	-0.64	0.01
Constant	7726.73	3975.62	11477.85	0.00	8984.61	-3571.24	21540.47	0.16	8449.71	4724.55	12174.87	0.00
Number of children	3497				325				3172			

Source: own elaborations from SEDD

Table S13: Linear regressions of offspring ponderal index by gestational week and sex, Scania 1918-1967

ALL CHILDREN												
	Week 30-43				Week 30-37				Week 38-43			
Variable	Coef.	Lower C.I.	Upper C.I.	p.value	Coef.	Lower C.I.	Upper C.I.	p.value	Coef.	Lower C.I.	Upper C.I.	p.value
IMR at woman's birth												
Low-medium	0			ref.	0			ref.	0			ref.
High	0.12	-0.10	0.33	0.29	0.50	-0.29	1.30	0.21	0.08	-0.14	0.30	0.50
Woman's age												
15-24	-0.38	-0.56	-0.19	0.00	-0.68	-1.36	0.00	0.05	-0.29	-0.48	-0.11	0.00
25-34	0			ref.	0			ref.	0			ref.
35-49	0.13	-0.10	0.36	0.26	0.01	-0.82	0.84	0.98	0.17	-0.07	0.40	0.16
Woman's birth year	0.00	-0.01	0.01	0.89	0.01	-0.02	0.05	0.53	0.00	-0.01	0.01	0.87
Constant	25.85	7.67	44.04	0.01	4.39	-63.30	72.08	0.90	28.81	10.24	47.38	0.00
Number of children	7177				768				6409			
BOYS												
	Week 30-43				Week 30-37				Week 38-43			
Variable	Coef.	Lower C.I.	Upper C.I.	p.value	Coef.	Lower C.I.	Upper C.I.	p.value	Coef.	Lower C.I.	Upper C.I.	p.value
IMR at woman's birth												
Low-medium	0			ref.	0			ref.	0			ref.
High	0.23	-0.12	0.57	0.20	1.02	-0.19	2.24	0.10	0.13	-0.23	0.48	0.48
Woman's age												
15-24	-0.42	-0.70	-0.14	0.00	-1.15	-2.22	-0.07	0.04	-0.28	-0.56	0.01	0.06
25-34	0			ref.	0			ref.	0			ref.
35-49	-0.05	-0.40	0.31	0.80	-0.14	-1.48	1.20	0.84	-0.01	-0.37	0.35	0.95
Woman's birth year	0.00	-0.01	0.02	0.82	0.03	-0.03	0.09	0.35	0.00	-0.02	0.01	0.90
Constant	24.00	-4.43	52.43	0.10	-27.02	-138.74	84.71	0.63	29.21	0.74	57.68	0.04
Number of children	3680				443				3237			
GIRLS												
	Week 30-43				Week 30-37				Week 38-43			
Variable	Coef.	Lower C.I.	Upper C.I.	p.value	Coef.	Lower C.I.	Upper C.I.	p.value	Coef.	Lower C.I.	Upper C.I.	p.value
IMR at woman's birth												
Low-medium	0			ref.	0			ref.	0			ref.
High	0.02	-0.25	0.28	0.90	-0.47	-1.30	0.36	0.27	0.04	-0.24	0.31	0.79
Woman's age												
15-24	-0.33	-0.56	-0.09	0.01	0.00	-0.66	0.67	0.99	-0.31	-0.56	-0.06	0.01
25-34	0			ref.	0			ref.	0			ref.
35-49	0.31	0.03	0.59	0.03	0.28	-0.51	1.08	0.49	0.34	0.04	0.64	0.03
Woman's birth year	0.00	-0.01	0.01	0.95	-0.01	-0.04	0.03	0.64	0.00	-0.01	0.01	0.89
Constant	27.94	5.28	50.60	0.02	40.84	-22.60	104.28	0.21	29.02	5.05	53.00	0.02
Number of children	3497				325				3172			

Source: own elaborations from SEDD

Table S14: Odds ratio that a newborn offspring is small for gestational age, Scania 1918-1967

	All births				Boys				Girls			
Variable	O.R.	Lower C.I.	Upper C.I.	p-value	O.R.	Lower C.I.	Upper C.I.	p-value	O.R.	Lower C.I.	Upper C.I.	p-value
IMR at woman's birth												
Low-medium	1.00			ref.	1.00			ref.	1.00			ref.
High	0.93	0.58	1.51	0.78	0.54	0.23	1.26	0.15	1.40	0.77	2.55	0.27
Woman's age												
15-24	1.26	0.87	1.82	0.23	1.54	0.94	2.53	0.09	0.96	0.55	1.70	0.90
25-34	1.00			ref.	1.00			ref.	1.00			ref.
35-49	0.67	0.37	1.21	0.19	0.78	0.35	1.72	0.53	0.56	0.23	1.36	0.20
Woman's birth year	1.01	0.99	1.03	0.35	1.01	0.98	1.04	0.67	1.01	0.98	1.04	0.41
Number of children	7177				3680				3497			

Source: own elaborations from SEDD

Table S15: Odds ratio that a newborn offspring is born pre-term (gestational weeks 30-37), Scania 1918-1967

	All births				Boys				Girls			
Variable	O.R.	Lower C.I.	Upper C.I.	p-value	O.R.	Lower C.I.	Upper C.I.	p-value	O.R.	Lower C.I.	Upper C.I.	p-value
IMR at woman's birth												
Low-medium	1.00			ref.	1.00			ref.	1.00			ref.
High	1.11	0.90	1.36	0.33	1.44	1.10	1.88	0.01	0.82	0.59	1.14	0.25
Woman's age												
15-24	1.44	1.20	1.71	0.00	1.38	1.09	1.73	0.01	1.53	1.17	2.00	0.00
25-34	1.00			ref.	1.00			ref.	1.00			ref.
35-49	1.23	0.99	1.53	0.06	1.22	0.91	1.65	0.18	1.26	0.91	1.75	0.16
Woman's birth year	1.00	0.99	1.01	0.51	1.00	0.99	1.02	0.59	0.99	0.98	1.00	0.12
Number of children	7177				3680				3497			

Source: own elaborations from SEDD

Table S16: Odds ratio of experiencing at least two miscarriages, Scania 1918-1967

Variable	O.R.	Lower C.I.	Upper C.I.	p-value
IMR at woman's birth				
Low-medium	1.00			ref.
High	1.98	1.09	3.59	0.02
Woman's birth year	1.00	0.97	1.03	0.98
Total number of births	1.41	1.26	1.57	0.00
N. women	4364			
N. women with two+ miscarriages	62			

Source: own elaborations from SEDD

Table S17: Sensitivity analysis - Cox models estimating the hazard of death of women in ages 1-14 and 15-49, Scania 1905-2000

Age 1-14						
Model	H.R.	Lower C.I.	Upper C.I.	p-value	N. women	N. deaths
Main model	0.78	0.56	1.08	0.13	19358	334
Mother's birth before 1940	0.89	0.63	1.24	0.48	15428	324
Mother's birth decade	0.79	0.57	1.11	0.18	19358	334
Mother's birth county	0.78	0.56	1.08	0.13	19358	334
Mother's birth county # birth year	0.78	0.56	1.08	0.13	19358	334
Age 15-50						
Model	H.R.	Lower C.I.	Upper C.I.	p-value	N. women	N. deaths
Main model	1.07	0.88	1.30	0.51	31068	725
Mother's birth before 1940	1.03	0.83	1.28	0.77	25630	666
Mother's birth decade	0.97	0.80	1.19	0.80	31068	725
Mother's birth county	1.07	0.88	1.30	0.48	31068	725
Mother's birth county # birth year	1.08	0.89	1.31	0.46	31068	725

Note: each row shows results of a different model specification. Source: own elaborations from SEDD

Table S18: Sensitivity analysis - Cox models estimating the likelihood of giving birth, Scania 1905-2000

First birth						
Model	H.R.	Lower C.I.	Upper C.I.	p-value	N. women	N. births
Main model	0.97	0.93	1.03	0.32	25787	9277
Mother's birth before 1940	1.04	0.97	1.12	0.23	21523	7356
Mother's birth decade	1.03	0.97	1.08	0.37	25787	9277
Mother's birth county	0.98	0.93	1.03	0.39	25787	9277
Mother's birth county # birth year	0.98	0.93	1.03	0.38	25787	9277
Second and higher order births						
Model	H.R.	Lower C.I.	Upper C.I.	p-value	N. women	N. births
Main model	1.00	0.95	1.06	0.90	12256	8359
Mother's birth before 1940	0.96	0.89	1.05	0.39	9375	6744
Mother's birth decade	0.94	0.89	1.00	0.05	12256	8359
Mother's birth county	1.00	0.95	1.06	0.92	12256	8359
Mother's birth county # birth year	1.00	0.95	1.06	0.89	12256	8359

Note: each row shows results of a different model specification. Source: own elaborations from SEDD

Table S19: Sensitivity analysis - odds ratio that a live-born child is male, Scania 1905-2000

All births						
Model	O.R.	Lower C.I.	Upper C.I.	p-value	N. women	N. births
Main model	0.93	0.87	1.00	0.04	11550	20361
Mother's birth before 1940	0.92	0.84	1.00	0.06	9152	16457
Mother's birth decade	0.91	0.85	0.99	0.02	11550	20361
Mother's birth county	0.93	0.87	1.00	0.04	11550	20361
Mother's birth county # birth year	0.93	0.86	0.99	0.04	11550	20361
First birth						
Model	O.R.	Lower C.I.	Upper C.I.	p-value	N. women	N. births
Main model	0.86	0.77	0.95	0.00	9166	9172
Mother's birth before 1940	0.84	0.74	0.97	0.02	7268	7273
Mother's birth decade	0.84	0.75	0.94	0.00	9166	9172
Mother's birth county	0.86	0.77	0.95	0.00	9166	9172
Mother's birth county # birth year	0.86	0.77	0.95	0.00	9166	9172
Second and higher order births						
Model	O.R.	Lower C.I.	Upper C.I.	p-value	N. women	N. births
Main model	1.00	0.91	1.10	0.94	7169	11189
Mother's birth before 1940	0.98	0.86	1.10	0.70	5622	9184
Mother's birth decade	0.98	0.89	1.09	0.72	7169	11189
Mother's birth county	0.99	0.90	1.09	0.92	7169	11189
Mother's birth county # birth year	0.99	0.90	1.09	0.84	7169	11189

Note: Only singleton births are considered. Each row shows results of a different model specification. Source: own elaborations from SEDD

Table S20: Sensitivity analysis - odds ratio that a child is stillborn, Scania 1905-1967

All births						
Model	O.R.	Lower C.I.	Upper C.I.	p-value	N. women	N. births
Main model	1.28	0.90	1.80	0.17	10093	17668
Mother's birth before 1940	1.39	0.96	2.01	0.08	9105	16352
Mother's birth decade	1.29	0.89	1.86	0.18	10093	17668
Mother's birth county	1.28	0.90	1.81	0.16	10093	17668
Mother's birth county # birth year	1.28	0.90	1.81	0.16	10093	17668
Female births						
Model	O.R.	Lower C.I.	Upper C.I.	p-value	N. women	N. births
Main model	0.92	0.51	1.67	0.78	6363	8559
Mother's birth before 1940	1.17	0.64	2.12	0.62	5804	7923
Mother's birth decade	0.85	0.45	1.60	0.62	6363	8559
Mother's birth county	0.90	0.50	1.63	0.73	6363	8559
Mother's birth county # birth year	0.90	0.50	1.64	0.73	6363	8559
Male births						
Model	O.R.	Lower C.I.	Upper C.I.	p-value	N. women	N. births
Main model	1.56	1.02	2.39	0.04	6664	9109
Mother's birth before 1940	1.58	0.99	2.52	0.05	6071	8429
Mother's birth decade	1.68	1.06	2.65	0.03	6664	9109
Mother's birth county	1.58	1.03	2.43	0.04	6664	9109
Mother's birth county # birth year	1.59	1.03	2.43	0.03	6664	9109

Note: Each row shows results of a different model specification. Source: own elaborations from SEDD

Table S21: Sensitivity analysis - odds ratio of a multiparous birth event, Scania 1905-2000

Model	O.R.	Lower C.I.	Upper C.I.	p-value	N. women	N. births
Main model	0.77	0.53	1.13	0.18	11630	20597
Mother's birth before 1940	0.86	0.53	1.41	0.55	9219	16651
Mother's birth decade	0.81	0.54	1.23	0.33	11429	20255
Mother's birth county	0.77	0.53	1.13	0.18	11630	20597
Mother's birth county # birth year	0.77	0.53	1.13	0.19	11630	20597

Note: Each row shows results of a different model. Source: own elaborations from SEDD

Table S22: Sensitivity analysis - linear regressions measuring the total number of children born in ages 18-42 and the total number of children surviving to age 5, for women who were observed during their full reproductive period, Scania 1905-2000

Total children born					
Model	Coef.	Lower C.I.	Upper C.I.	p-value	N. women
Main model	0.01	-0.06	0.08	0.74	3304
Mother's birth before 1940	0.02	-0.08	0.11	0.75	2769
Mother's birth decade	0.00	-0.08	0.08	1.00	3304
Mother's birth county	0.01	-0.06	0.08	0.77	3304
Mother's birth county # birth year	0.01	-0.06	0.08	0.77	3304
Total children surviving to age 5					
Model	Coef.	Lower C.I.	Upper C.I.	p-value	N. women
Main model	0.00	-0.07	0.08	0.95	3304
Mother's birth before 1940	0.01	-0.08	0.11	0.78	2769
Mother's birth decade	-0.01	-0.08	0.07	0.89	3304
Mother's birth county	0.00	-0.07	0.07	0.98	3304
Mother's birth county # birth year	0.00	-0.07	0.08	0.98	3304

Note: Each row shows results of a different model. Source: own elaborations from SEDD

Table S23: Sensitivity analysis - logistic regressions measuring the likelihood of not giving birth to any children in ages 18-42 for women who were observed during their full reproductive period, Scania 1905-2000

Model	O.R.	Lower C.I.	Upper C.I.	p-value	N. women
Main model	1.10	0.89	1.35	0.37	3304
Mother's birth before 1940	1.00	0.78	1.28	0.98	2769
Mother's birth decade	1.04	0.83	1.29	0.74	3304
Mother's birth county	1.10	0.89	1.35	0.37	3304
Mother's birth county # birth year	1.10	0.89	1.35	0.36	3304

Note: Each row shows results of a different model. Source: own elaborations from SEDD

Table S24: Sensitivity analysis – linear regressions of offspring birthweight, boys born in weeks 30-37, Scania 1918-1967

Model	Coef.	Lower C.I.	Upper C.I.	p-value	N. boys
Main model	143.52	0.67	286.36	0.05	443
Mother's birth before 1940	143.52	0.67	286.36	0.05	443
Mother's birth decade	112.69	-42.28	267.66	0.15	443
Mother's birth county	142.82	-0.25	285.89	0.05	443
Mother's birth county # birth year	142.25	-1.21	285.70	0.05	443

Source: own elaborations from SEDD

Table S25: Sensitivity analysis – linear regressions of offspring ponderal index, boys born in weeks 30-37, Scania 1918-1967

Model	Coef.	Lower C.I.	Upper C.I.	p-value	N. boys
Main model	1.02	-0.19	2.24	0.10	443
Mother's birth before 1940	1.02	-0.19	2.24	0.10	443
Mother's birth decade	0.72	-0.59	2.03	0.28	443
Mother's birth county	1.03	-0.18	2.24	0.10	443
Mother's birth county # birth year	1.04	-0.17	2.26	0.09	443

Source: own elaborations from SEDD

Table S26: Odds ratio that a newborn boy is small for gestational age, Scania 1918-1967

Model	O.R.	Lower C.I.	Upper C.I.	p-value	N. boys
Main model	0.54	0.23	1.26	0.15	3680
Mother's birth before 1940	0.54	0.23	1.26	0.15	3680
Mother's birth decade	0.50	0.21	1.20	0.12	3680
Mother's birth county	0.54	0.23	1.25	0.15	3680
Mother's birth county # birth year	0.54	0.23	1.25	0.15	3680

Source: own elaborations from SEDD

Table S27: Odds ratio that a newborn boy is born pre-term (gestational weeks 30-37), Scania 1918-1967

Model	O.R.	Lower C.I.	Upper C.I.	p-value	N. boys
Main model	1.44	1.10	1.88	0.01	3680
Mother's birth before 1940	1.44	1.10	1.88	0.01	3680
Mother's birth decade	1.43	1.07	1.90	0.01	3680
Mother's birth county	1.47	1.12	1.92	0.01	3680
Mother's birth county # birth year	1.47	1.12	1.92	0.01	3680

Source: own elaborations from SEDD

Figures

Figure S1: Map of the study area: city of Landskrona and five rural parishes located in Scania (Sweden)

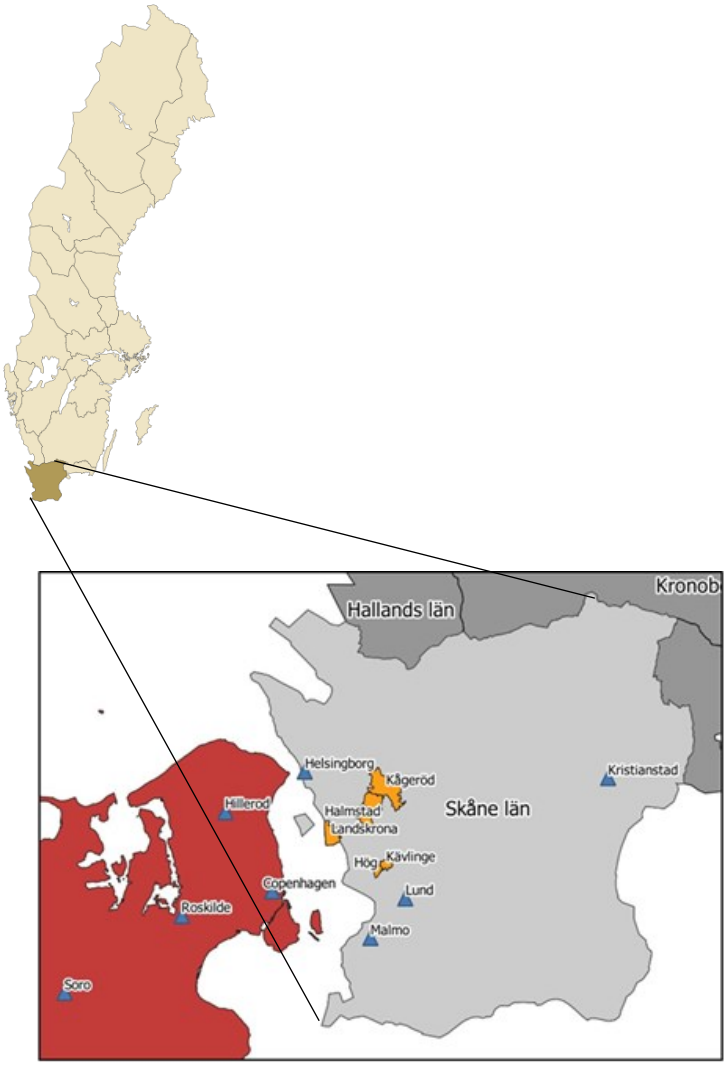
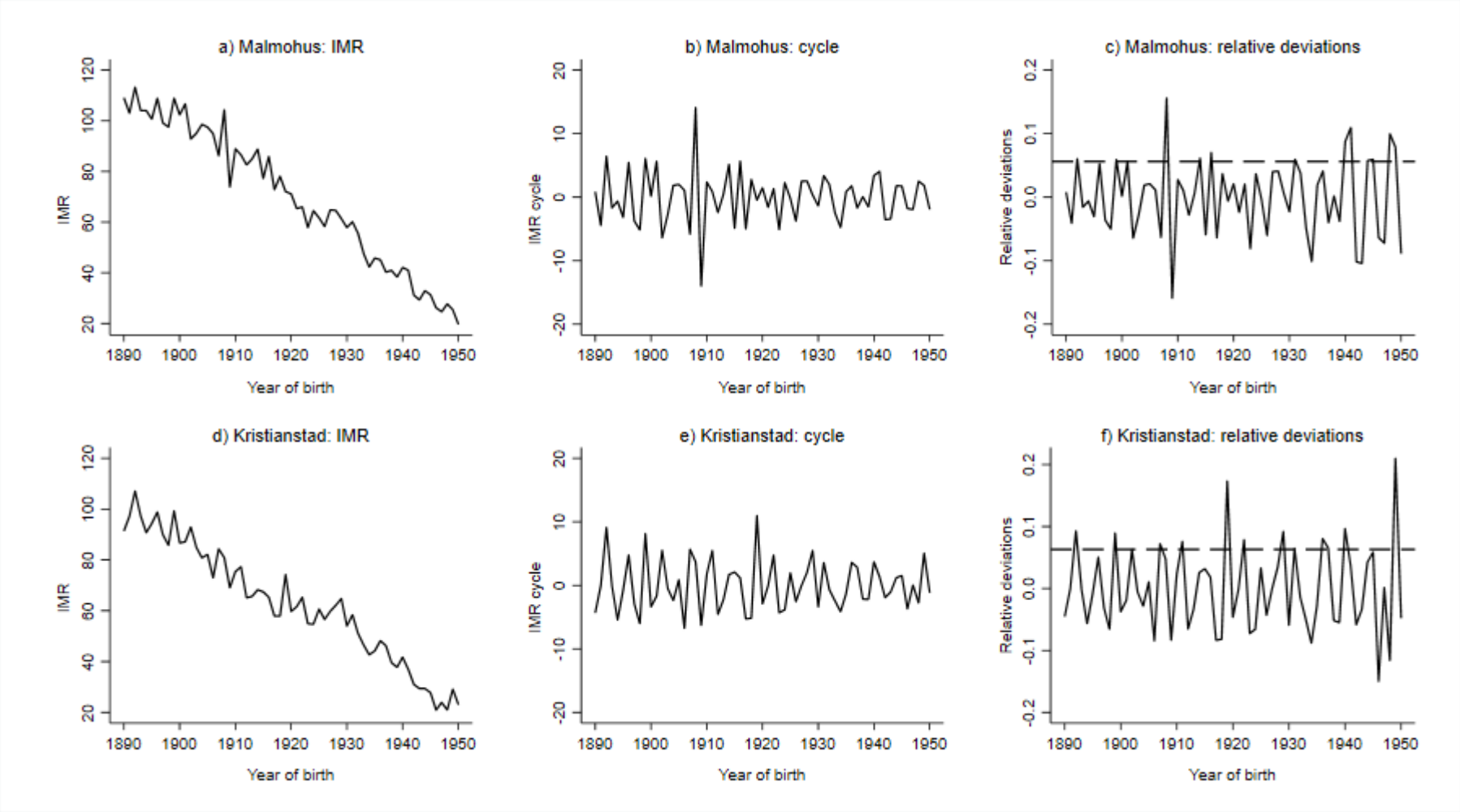


Figure S2: Infant mortality rates, deviations from the trend and relative deviations from the trend, 1890-1950, Malmöhus and Kristianstad counties



Notes: S2a and S2d show the IMR series. S2b and S2e show the deviation from the trend in IMR, after detrending using an HP filter with a filtering factor of 6.25. S2c and S2f show relative deviations from the trend, calculated as cycle divided by the trend. In S2c and S2f the dashed lines show the threshold used to select years with high disease load. This threshold corresponded to the 80th percentile in the distribution of relative deviations from the trend in the specific county.

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