Social Science & Medicine 347 (2024) 116767

Contents lists available at ScienceDirect

Social Science & Medicine

journal homepage: www.elsevier.com/locate/socscimed

Disease exposure in infancy affects women's reproductive outcomes and offspring health in southern Sweden 1905–2000

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ARTICLE INFO

Keywords:
Early life exposures
Reproduction
Historical demography
Life course epidemiology
Intergenerational health transfers

ABSTRACT

Ample evidence demonstrates that early-life adversity negatively affects morbidity and survival in late life. We show that disease exposure in infancy also has a continuous impact on reproduction and health across the female life course and even affects early-life health of the next generation. Using Swedish administrative data, obstetric records, and local infant mortality rates as a measure of disease exposure, we follow women's reproductive careers and offspring health 1905–2000, examining a comprehensive set of outcomes. Women exposed to disease in infancy give birth to a lower proportion of boys, consistent with notions that male fetuses are more vulnerable to adverse conditions and are more often miscarried. Sons of exposed mothers are also more likely to be born preterm and have higher birthweight suggesting *in utero* out-selection. Exposed women have a greater risk of miscarriage and of male stillbirth, but their overall likelihood of giving birth is not affected.

1. Introduction

An interdisciplinary literature documents that early-life exposure to adversity relates to worse late-life health (Barker, 1995; Bengtsson and Lindström, 2003; Bozzoli et al., 2009; Costa, 2000; Myrskylä et al., 2014; Schmitz and Duque, 2022; van den Berg et al., 2009; Quaranta, 2014) and worse adult socioeconomic status, possibly because of early-life adversity's impairing effect on health and cognitive ability (Doblhammer et al., 2013; Lawson and Spears, 2016). 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 (Kuh and Shlomo, 2004). Despite theoretical pathways indicating that early-life adversity can have implications for human reproduction and despite that early-life adversities have been shown to affect later life health for women more than men (Lee and Ryff, 2019), there is limited research on how early-life exposures to adversity, and in particular disease exposure, affects fertility and reproductive health. This study fills this 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 for a period in 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 women's reproduction is thus key to understand if and how future generations are affected by peaking disease exposure. We take a comprehensive approach to understand the consequences for reproductive health and examine both female fertility and offspring health outcomes.

There is a very limited literature on early life influences on women's reproduction and particularly for the relation with infectious disease exposure. A few studies examine the relation between early-life conditions more broadly and number of births (parity) and reproductive success (surviving children) among women (Fletcher, 2018; Hayward et al., 2013; Rickard et al., 2010; Zhang et al., 2020), providing evidence on the consequences of maternal physical condition shaped in her earlier life and her reproductive trajectory. 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

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https://doi.org/10.1016/j.socscimed.2024.116767
Received 10 October 2023; Received in revised form 13 February 2024; Accepted 5 March 2024
Available online 12 March 2024

an underestimation of the full effect of women's early life exposure to adversity on their reproductive health. Similarly, these studies do not focus specifically on disease exposure, nor do they provide evidence to whether maternal early-life adversity affects the early-life health of her children 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 and show evidence for both. Further, our results contribute to the work on the relevance of a life-course approach to reproductive health (Mishra et al., 2010) and to the related emerging literature on intergenerational transmissions in health and cross-generation effects of early-life insults (Andreella et al., 2015; Hossin et al., 2021; Richter et al., 2013; van den Berg and Pinger, 2016). We examine the effect of disease exposure in infancy using unique data sources on a broad set of reproductive and offspring health outcomes, including women's likelihood of giving birth, total fertility, miscarriage, stillbirth, offspring sex ratio at birth, birth weight and likelihood of being born pre-term.

We use data from the well-established Scanian Economic-Demographic Database (SEDD) (Bengtsson et al., 2021) linked to the Swedish national register data, which provides longitudinal information and nearly complete records of vital events for both married and non-married women who dwell in an area in southern Sweden. In addition, we use information from purposively digitized obstetric records. Our study sample includes women born in 1890–1950, followed 1905–2000. We compare women exposed to high versus low-medium level of disease in infancy, measuring disease exposure using an exogenous indicator, peaks in infant mortality rates (IMR) for the county and year of birth of each woman. The SEDD covers the population of five rural parishes and the town of Landskrona, which is a fair representation of a Swedish industrial city over the study period. While the study area is not statistically representative of Europe or beyond, the long-term economic and demographic development is similar to those of other contexts (see Bengtsson and Dribe, 2021; Dribe and Svensson, 2024). The establishment of a more comprehensive and centrally organized health care system occurred in the early to mid-20th century (Van Dijk et al., 2024) although many modern medical technologies were absent. Fertility and reproductive outcomes over the period were not only influenced by biological factors and by 1960 Sweden had entered a phase of lower fertility rates and smaller family sizes. Incidents of infant mortality in Sweden in early decades of the 20th century when the sampled women were exposed resembles that in many of today's poorest countries. For example, the IMR in 1925 corresponds to present levels in e.g. Angola, Mali and Mozambique.

2. Theoretical framework

Fig. 1 shows a schematic overview of the expected effects on reproductive outcomes of exposure to high infectious disease load 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 (Preston et al., 1998). 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 (Caruso et al., 2005; Crimmins and Finch, 2006; Finch and Crimmins, 2004) and inadequate development of vital organs and the immune system may lead to disease and reduced longevity (Caruso et al., 2005; Crimmins and Finch, 2006). Associations between adverse early life exposures and ovarian function have been noted both in clinical and experimental studies (Chan et al., 2015). Non-lethal childhood infections can afflict damage to women's physiology, including impairment of the reproductive function (Elias et al., 2005). A woman's likelihood of (quick) conception but also her ability to carry a pregnancy to term may therefore be affected. Fig. 1 represents the theorical model of the study, showing how exposure in infancy to high levels of disease may affect women's life courses with, in sequence, their own likelihood of death, and their fecundity, likelihood of spontaneous abortion, stillbirth, and the health of their children at birth.

Mothers in worse health may also have offspring who are in worse health at the start of life (Aizer and Currie, 2014). For example, health disadvantaged women are less likely to gain the recommended weight during pregnancy, in turn affecting offspring birth weight. The link between disease exposure in infancy and reproductive and offspring health may also work through epigenetic change (Bateson et al., 2004; Cavalli and Heard, 2019; Jablonka and Raz, 2009), or epigenetic inheritance (Cavalli and Heard, 2019; Jablonka and Raz, 2009; Lummaa and Clutton-Brock, 2002). Recent evidence suggests that the number and quality of immune cells, transferred from mothers to fetuses in all mammalian pregnancies and which may be affected by disease load, matters for fetal immune development and infections in early life (Stelzer et al., 2021). On the other hand, effects can also stem from offspring health selection. Among disease-exposed and less healthy women, more robust fetuses may be selected *in utero* (Bruckner et al., 2010; Catalano et al., 2006). Women with a frail health may experience more spontaneous abortions compared to women in better health. This selection could result in a lower likelihood of a (live) birth, but also increase the likelihood of relatively more robust offspring being 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 (Hayward et al., 2016). 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 (Alter et al., 2001; Costa, 2000; Doblhammer et al., 2013; Myrskylä, 2010). Although scarring effects of early-life adversity on health commonly dominate selection effects (Hatton, 2011), selection sometimes dominates in earlier ages and scarring at later ages so that there is a crossover with age (Quaranta, 2014). There is evidence of health selection into marriage after exposure to early-life health shocks, which may exacerbate the overall effect of health shocks on reproductive outcomes (Fletcher, 2018; Pink et al., 2020).

The literature examining the influence of maternal health on offspring health tends to focus on the role of present state of health rather than the

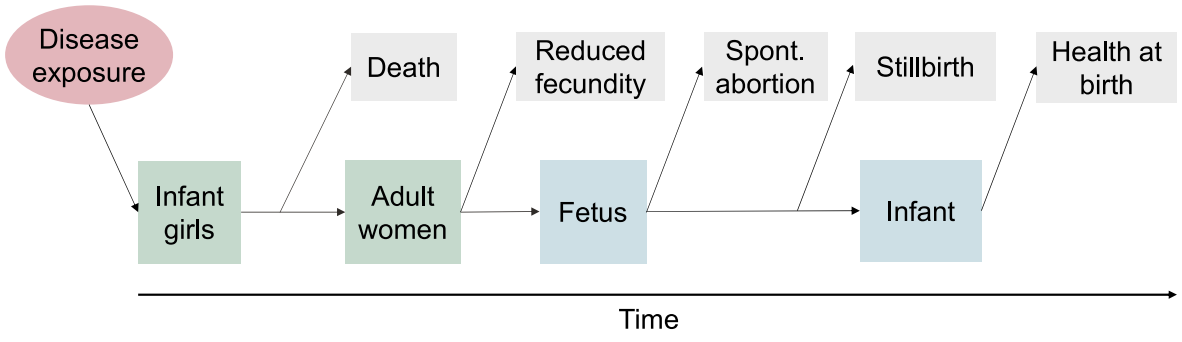

Fig. 1. Theoretical model: Exposure in infancy to high levels of disease and women's reproduction and offspring health.

cumulative maternal health history or stock of health (see e.g. Andersson and Bergström, 1998; Bruckner et al., 2010; Bulik et al., 2008; Torche and Kleinhaus, 2012). Women reproducing in poor health 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*) (Nobles and Hamoudi, 2019) 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 (Catalano et al., 2006; Trivers and Willard, 1973). Empirical work points to sex ratio deviations following disadvantageous maternal health conditions at the time of conception or during pregnancy (Andersson and Bergström, 1998; Bulik et al., 2008; Torche and Kleinhaus, 2012). Whether sex ratio also deviates in relation to maternal early life exposures is still unknown. 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.

3. Materials and methods

3.1. Source material

Our longitudinal data 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 fertility and offspring health outcomes (Fig. 1). The historical sample consists of data from SEDD, 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 Supplementary Section 1). The SEDD was constructed using population and income and taxation registers and updated with information on births, marriages, and deaths from church books. The material is of high quality and complete regarding vital events (Bengtsson and Lindström, 2000). For the period after 1967, individuals from the SEDD area are followed in the national registers from Statistics Sweden (Statistics Sweden, n.d.). For a description of SEDD see (Dribe and Quaranta, 2020). The database has been used to track long-term developments in health, including health advantages across generations (Van den Berg et al., 2023). For a general overview of previous research using SEDD see (Bengtsson and Dribe, 2021).

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 (15–49) in the SEDD areas in the years 1905–2000. We begin observing women from age 15, since the average age of menarche was around 16 or 17 years at the beginning of the 20th century, and in our data only 0.07% of births occurred before age 15. All women are included in the study sample during the period in which they live in the study area. In the full study sample used for the first part of the analysis, we have information on 28,254 women and 18,590 births. Supplementary Tables S1–S3 provide descriptive statistics.

For a subsample of women, obstetric records were digitized and linked to SEDD (Quaranta, 2022). Obstetric records consist of midwifery records of children born at home in the five rural parishes between 1918 and 1945, and hospital birth records of children from Landskrona and the five rural parishes born 1926–1967. 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 (Hossin et al., 2021), and for the first time allows to link mother's disease exposure in early life to offspring health. More information about our digitized material is found in Supplementary Section II.

The obstetric records contain a wide range of information on the health of the mother and the child and medical details about the pregnancy and delivery, including infant birth weight and birth length, information about women's earlier miscarriages, and the woman's date of last menstruation. We calculated gestational age as the number of days between the reported first day of the last menstrual period and the date of birth, 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 this part of the analysis. The subsample based on obstetric records that is used to study offspring health outcomes consists of 7177 children (4576 mothers).

3.2. 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 numbers of births and infant deaths were collected from official sources for the years 1890–1950 (Centralbyrån, 1890) and we calculated county-level IMR by dividing the number of infant deaths by the number of births. Each county's IMR series was de-trended by applying a Hodrick-Prescott filter (Hodrick and Prescott, 1997) with a filtering factor of 6.25. Given the very large decline in IMR 1890–1950 (from around 100 to around 20 per 1000), we calculated relative deviations from the trend in IMR for each county. Following (Quaranta, 2013, 2014), we defined as high IMR years the years in which the relative deviation in IMR after detrending was in the top 20th percentile of deviations for that county. Fig. 2 shows the IMR, deviations from the trend and relative deviations from the trend for the two counties. By considering relative rather than total deviation from the trend, we avoid possible biases related to the fact that, given the large IMR decline across cohorts, larger absolute deviations from the trend are observed in years with higher IMR.

Research that considers exogenous indicators of early life conditions such as IMR uses these indicators in different ways. Some authors believe that the associations between the trends in early life conditions and later life health are informative, often in relation to work that focus on macro-level data and/or variations across geographical areas (Bozzoli et al., 2009; Crimmins and Finch, 2006; Finch and Crimmins, 2004), while others claim that it is important to assess the effect of short-term variations in early life exposures on later life health (Bengtsson and Lindström, 2003, 2000; Hayward et al., 2016; Myrskylä, 2010; van den Berg et al., 2009; Quaranta, 2013, 2014). The argument made in the latter case is that the trend components of early life conditions are highly correlated with other environmental characteristics that reflect, for example, secular development of healthcare and the economy, and it is not possible to easily disentangle such effects from the variable of interest. As shown in Supplementary Section III, we in fact observe that IMR strongly correlates with both economic and healthcare characteristics, but the time-series measuring years with high IMR does not. Such associations and the strong secular decline in IMR observed indicate that the long-term effect of disease exposure should not be studied by considering the full values of IMR. Moreover, these calculations show that peaks in IMR are not related to economic and healthcare developments.

In our study, we consider as indicator of high disease exposure short-term variations in IMR. Years when IMR was higher than its trend are likely to have been years with disease outbreaks, including epidemics (Bengtsson and Lindström, 2003, 2000; Bozzoli et al., 2009; Hayward et al., 2016; Quaranta, 2013, 2014). Cause specific mortality data was not available at the county level, but using data from SEDD parishes, we show that the share of infant deaths caused by infectious and respiratory disease was higher in years with peaking IMR (Supplementary Section III). Women born in years with peaks in IMR are more likely to have been exposed to the diseases that killed a larger than normal number of infants, but have survived to adult ages. In these birth cohorts, above-average exposure to disease may have caused long-term health effects,

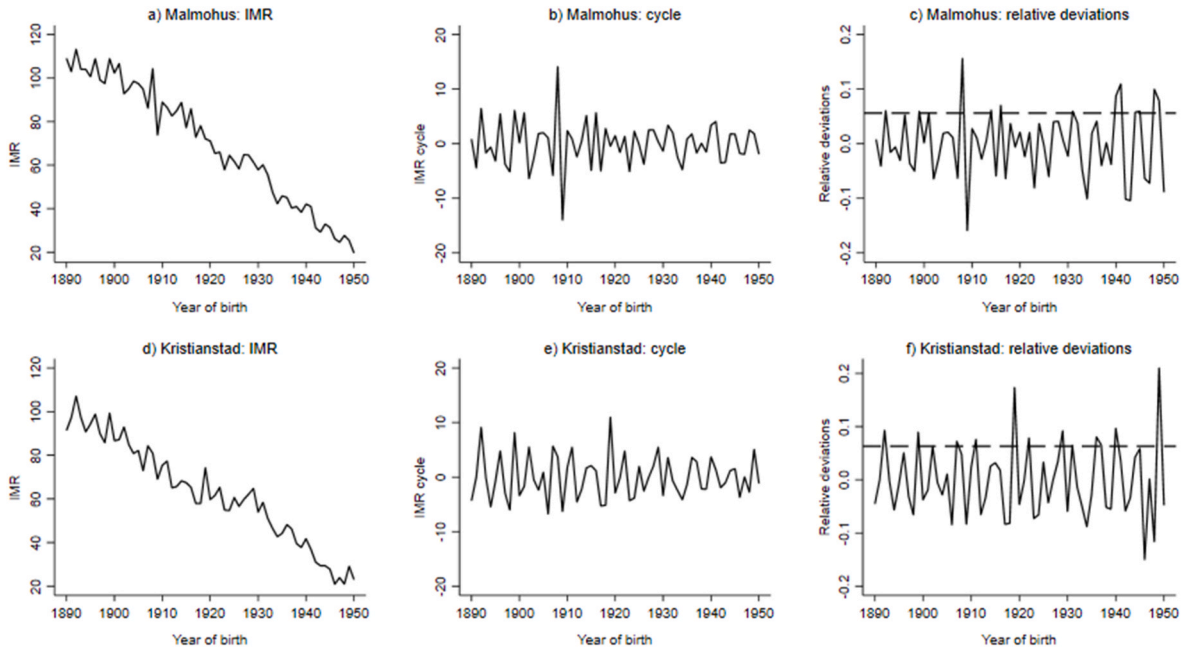

Fig. 2. Infant mortality rates, deviations from the trend and relative deviations from the trend, 1890–1950, Malmöhus and Kristianstad counties
Panel 6a and 6d show the IMR series for Malmöhus and Kristianstad counties. Panels 6b and 6e show the deviation from the trend in IMR. Panels 6c and 6f show relative deviations from the trend. In panels 6c and 6f the dashed lines show the threshold used to select years with high disease load (80th percentile in the distribution of relative deviations from the trend in the specific county). Years defined as high disease years were 1892, 1899, 1908, 1914, 1916, 1931, 1940, 1941, 1944, 1945, 1948 and 1949, for Malmöhus county and 1892, 1899, 1902, 1907, 1911, 1919, 1922, 1929, 1931, 1936, 1937, 1940, 1949 for Kristianstad County.

dependent on the type of disease and whether or not women fell sick. Whereas individual sickness and exposure to specific types of disease cannot be directly measured by our chosen indicator, it measures whether or not women were infants in years with a larger than usual disease load among infants. This measurement has the advantage of being exogenous and thus of not suffering from confounding from 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. Addressing the long-term health effects of a mild event is more informative to understand the factors that shape reproductive health than exceptional events such as famine or the Spanish Flu, given that survivors of such events are likely to be strongly selected on their health. Peaking IMR can also be caused by other events affecting survival of young and vulnerable children, but in the period of our study Sweden was politically stable and neutral throughout the world wars, and peaking food prices, possibly as a result of heat waves and cold spells, were no longer related to increased mortality rates as they had been a century earlier (Bengtsson and Bröstrom, 2011). As discussed further below, we conduct a sensitivity analysis to assess the dependence of our findings on our chosen measurement of disease exposure.

All our analyses compare women born in counties and years with high IMR to those born in years and counties with low-medium IMR. These groups are defined as exposed and non-exposed women. Statistical models control for birth year to account for the declining trend in IMR and other general changes related to fertility and overall health and medical conditions. Through such analyses we can study the long-term effects on reproduction of being exposed to a high disease in the year of birth relative to have been born in similar periods and having been exposed to a low-medium disease load. Our analyses consider averages across the population. Given that not all women born in a year with a local disease outbreak are likely to have fallen sick, our results likely underestimate the true long-term effect of disease exposure in early life. Moreover, our results measure the net effect that is shaped both by selection on health and scarring of health.

3.3. Outcome variables

We follow women residing in SEDD areas across their lives and study a comprehensive set of reproductive outcomes. Prior to analyzing reproductive health in section IV of the Supplementary Material we show that when considering mortality as an outcome there is evidence of a slight dominance of selection during childhood and adolescence and of scarring during reproductive stages, in relation to disease exposure in early life.

Fertility is measured by studying the likelihood of giving birth. Furthermore, sex ratio at birth and stillbirths are considered. We also study the total number of births and total number of children surviving to age 5. For the last two outcomes we restrict the analysis to births between age 18 and 42 (97% of all births) and only consider 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 we refer to these women as women observed for their full reproductive period. For the same sample, we study the likelihood of being childless, defined as not giving birth to any child in ages 18–42.

In a final step, for a subsample of mothers and children, we focus on offspring health at birth using information from obstetric records to examine offspring birthweight, ponderal index, likelihood of being small for gestational age (SGA), likelihood of being born preterm, and number of miscarriages (only in obstetric records from hospitals). Ponderal index is used as an indicator of fetal growth status, and it is calculated as weight (kg)/length^3 (m). Infants are defined as 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 (Maršál et al., 1996). Infants are defined as being born preterm if they were born in weeks 30–37 of gestation.

3.4. Empirical specification

In all models, the main explanatory variable is the level of IMR in the

woman's year and county of birth. All models control for the woman's year of birth as a continuous variable. Unless otherwise stated, models also control for the woman's age (categorical: 15–24, 25–34 and 35–49). We used different types of statistical analysis, depending on the type of outcome variable: Cox models for time-to-event, linear regressions for continuous, Poisson regressions for count, and logistic regressions for binary outcomes. For outcomes that consider more than one birth per woman, we have included clustered standard errors (Cox models) or a random effects component (logistic regressions) on the mother, to account for her shared characteristics between her births.

Cox proportional hazard models are 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 as is commonly done in the literature. By using 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 and is therefore not included as control in the models. Second and higher order births are studied using the interval between births as the time variable. Using tests based on Schoenfeld residuals, no violation in the proportional hazards assumption was observed in the models for the variable measuring the disease exposure in the woman's year of birth.

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 likelihood of being childless is modelled using logistic regression. These models do not control for age, since the outcomes are measured over the woman's full reproductive period.

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 also estimated to study the likelihood that the child born is a male. We analyze the likelihood that a birth is a stillborn child using logistic regressions. Only singleton births are considered in this analysis, and we can only study births taking place until 1967 since we have no information on stillbirth after this year.

To analyze offspring birthweight and ponderal index we estimate linear regressions. Models are estimated for the full sample, and separately by sex and by gestational week, considering two groups, preterm (gestational weeks 30–37) and term/post-term (gestational weeks 38–43). We also analyze the likelihood of being SGA and the likelihood of being preterm, both using logistic regressions.

To study the impact of disease exposure in early life on miscarriages, we estimate logistic regressions considering as outcome a binary variable measuring whether a woman experienced two or more miscarriages. We concentrate on two or more miscarriages rather than on single events as sporadic pregnancy losses is typically thought to represent failure of abnormal embryos to become viable, while loss of multiple pregnancies associates with parental factors including immune dysfunction and endocrine disturbances (Larsen et al., 2013). The models control for the woman's year of birth and total number of births. Important to note that our data on miscarriages originates from obstetric records whereby we only observe (multiple) miscarriages that are followed by a live birth. The results should be interpreted with caution, since the number of women for whom we observe two or more miscarriages is low (62 women, 1.42% of the women in the hospital obstetric records sample). At the same time, a majority of miscarriages take place in early pregnancy, before women are aware of their pregnancy, and miscarriages that are not followed by a live birth are not included in our data, therefore the total (unobserved) differences in the number of miscarriages between exposed and non-exposed women is likely to be larger than reported.

4. Results

4.1. Fertility outcomes

No statistically significant effects of disease exposure in infancy on the likelihood of experiencing a first birth (Fig. 3a; Supplemental Table S5) are observed for the full sample of women, but a marginally statistically significant lower hazard of birth is observed (hazard ratio 0.93; p-value 0.08) when restricting the sample 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. These results confirm the Cox model findings, with no significant associations between women's exposure to high IMR in infancy and the likelihood or timing of birth for first or higher order births (Supplemental Table S6). Exposure to disease does not have a significant effect on total number of births, the total number of children surviving to age 5 and the likelihood of being childless (Supplemental Tables S7 and S8).

We next calculate offspring sex ratios at birth and find indication of *in utero* selection of male fetuses among women exposed to disease in their year of birth. Offspring sex ratio is 107.8 males per 100 females for exposed mothers, and 100.7 per 100 females for non-exposed mothers (p-value 0.05 in Chi-squared test for differences in means). A 7% lower odds in the likelihood that a child born is a male is observed among children of exposed mothers (p-value 0.04; Fig. 3b; Supplemental Table S9).

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; Fig. 3c; Supplemental Table S10). 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. These findings are in line with those relating to sex ratios at birth, indicating selection among males.

4.2. Offspring health at birth

We next examine offspring health at birth focusing on indicators obtained from obstetric records: offspring birthweight, ponderal index, likelihood of being born small for gestational age, likelihood of being born preterm and of the women experiencing two or more miscarriages. No previous studies have analyzed the impact of mother's disease exposure in early life on these outcomes. The study sample for these analyses is smaller and relates to the period 1905–1967 (see methods section and Supplementary Section II).

Offspring birthweight does not differ significantly between mothers exposed to high IMR in infancy in the full sample, but results differ by gestational week and sex (Supplemental Table S11). Among offspring born pre-term (gestational weeks 30–37), birthweight of offspring of exposed mothers is on average higher (96.89 g, p-value 0.08), while no statistically significant differences are found for offspring born in gestational weeks 38–43. Among pre-term born offspring we find large differences between boys born to exposed versus non-exposed mothers (143.52 g, p-value 0.05), while no statistically significant differences are found for girls (Fig. 4a; Supplemental Table S11).

Similar patterns are observed when considering offspring ponderal index (Fig. 4b–Supplemental Table S12). 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 are noted for girls. Furthermore, there are no significant differences in the odds of being born SGA in relation to maternal disease exposure in infancy, neither when studying boys or girls together, nor separately (Fig. 4c–Supplemental Table S13). 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

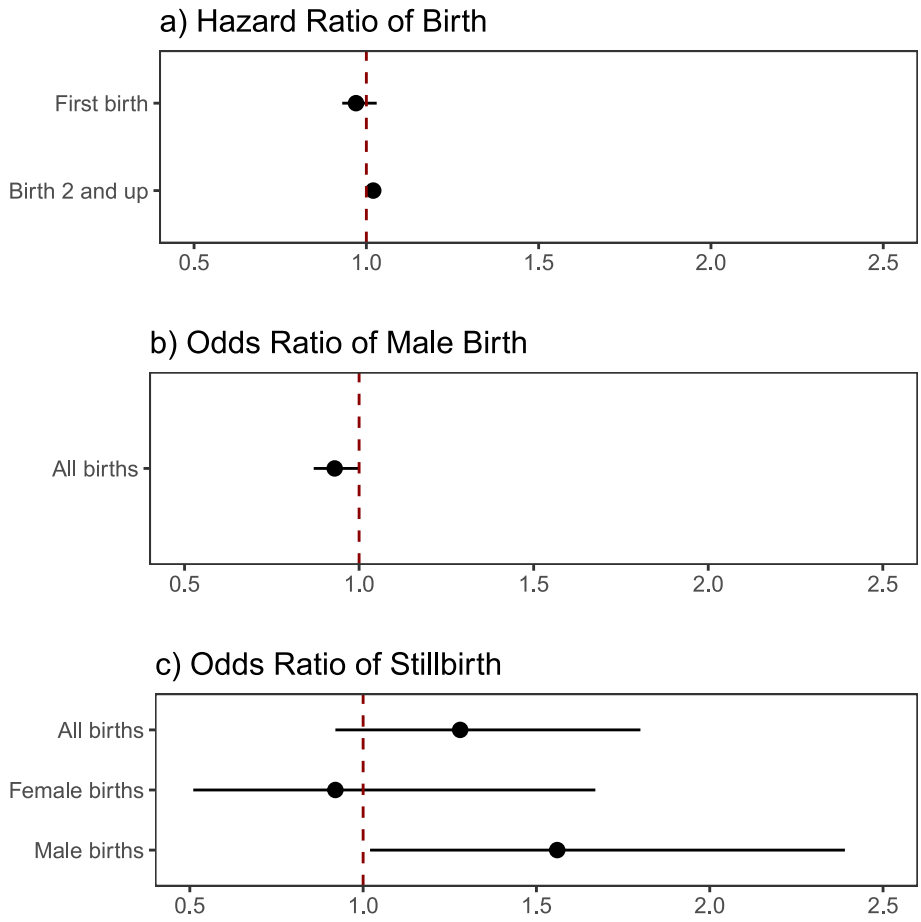

Fig. 3. Women's disease exposure in early life and life course and fertility outcomes, southern Sweden, 1905–2000
The results presented in this figure originate from different models, for women exposed to high IMR at birth. Panel a) is the hazard ratio of birth, for first (women = 25,787; births = 9277) and second and higher order births (women = 12,256; births = 8359). Panel b) is the odds ratio that a new-born offspring is male (women = 11,550; births = 20,361). Panel c) is the odds ratio that a new-born offspring is stillborn by sex (births = 17,668, stillbirths = 225), for 1905–1967.

estimated (OR 0.51, p-value 0.15).

Taken together, the analyses of offspring health suggest 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. Among boys, the odds of being born preterm (weeks 30–37 of gestation), are higher if having a mother that was adversely exposed (O.R. 1.48, p-value 0.01; Fig. 4d; Supplemental Table S14). Moreover, we find a higher likelihood of having experienced at least two miscarriages among exposed mothers (O.R. 1.98, p-value 0.02; Fig. 4e; Supplemental Table S15). Overall, the findings relating to offspring health are in line with the evidence of male fetal selection observed above when analyzing the impact of woman's early life disease exposure on offspring sex ratio at birth and stillbirths.

We also conduct a sensitivity analysis to address possible biases in the results related to the years identified as having a high disease load, to possible dependencies of our disease exposure variable on macro-level economic conditions, and to omitted variable bias relating to the woman's socioeconomic status at birth and marital status. For all outcomes, the results of the additional models estimated remain consistent with those of the main models (see Supplementary Section V).

5. 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. 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 (Catalano et al., 2006; Trivers and Willard, 1973). Our results are in line with research showing that women of low socioeconomic status exposed to whooping cough in infancy had a lower proportion of boys (Quaranta, 2013). 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 aligns with e.g. (Hayward et al., 2016) who do not find robust evidence on that early-life adversity affects reproductive success measured in terms of number of children. Notably, the results of our study suggest that parity likely is too crude of a measure of reproduction when examining the role of early life adversity, and that a richer set of outcomes is needed to comprehensively assess the full effect of early-life disease on women's health in mid-life and the health of their offspring at birth.

The large 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 disease exposure also have had an

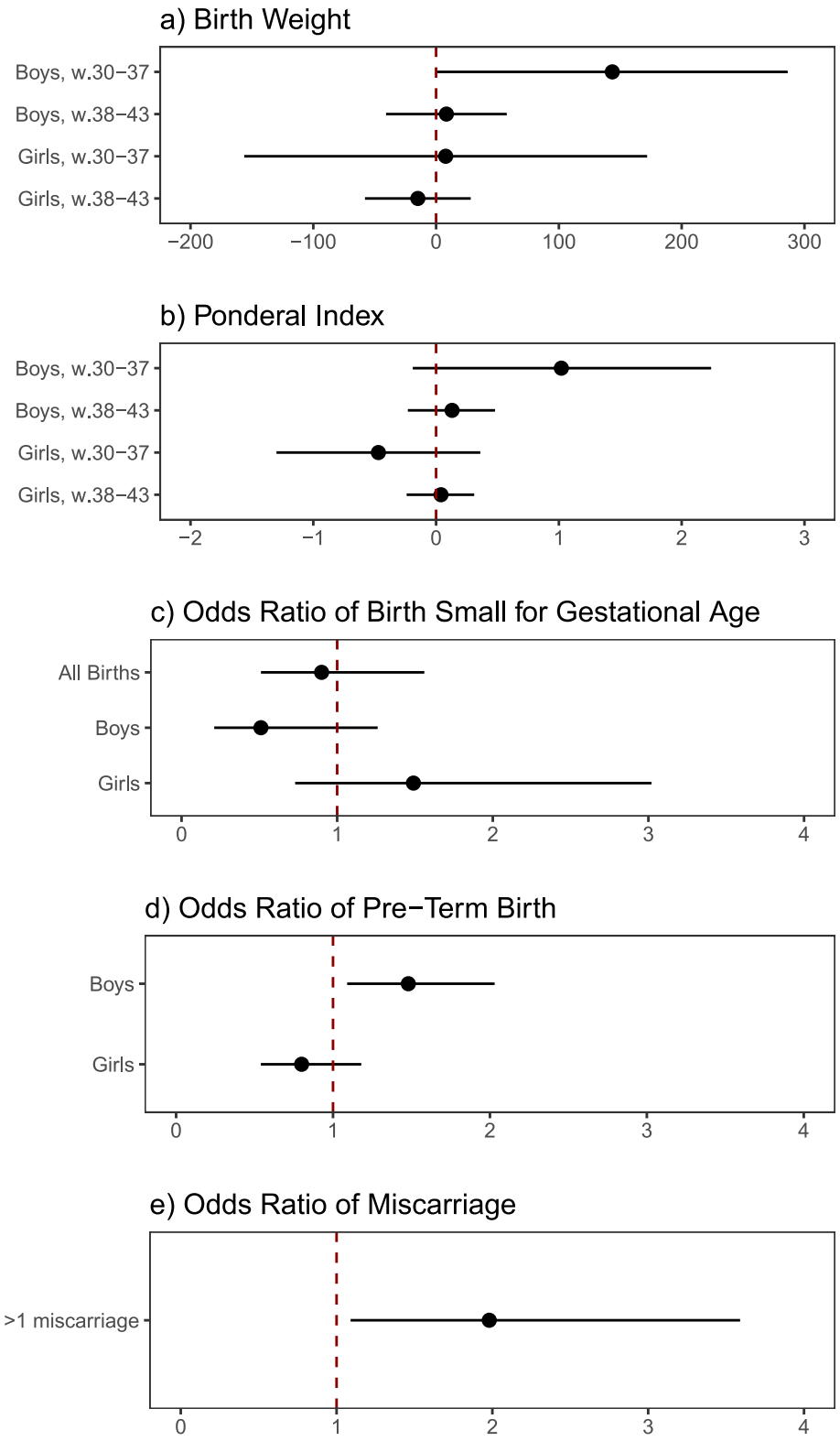

Fig. 4. Women's disease exposure in early life and offspring health at birth, southern Sweden, 1918-1967
The results presented in the figure are based on the subsample for whom obstetric records were available and originate from different models, for women exposed to high IMR at birth. Panel a) is the birth weight (n = 7177) of boys and girls born preterm (gestational age 30–37 weeks) and term/post-term births (gestational age 38–43 weeks). Panel b) is the ponderal index of new-born offspring by sex. Panel c) is the odds ratio that a birth is pre-term, Panel d) is the odds ratio that a new-born offspring is born pre-term (gestational age 30–37 weeks) by sex. Panel e) is the odds ratio that women who gave birth had two or more miscarriages (women = 4364; 62 women with two or more miscarriages; information on miscarriages is available when followed by a live birth in the obstetric records).

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 and 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.

While evidence on exposure to early-life adversity and reproductive health is scarce, our findings are in line with research showing that sex ratios at birth are lower for women reproducing in poorer health at time of conception. Furthermore, we find evidence in line with studies pointing to that the birth weight is upwardly affected when mothers are exposed to stressful events or poor health during pregnancy (Ecklund-Flores et al., 2017; Mélançon et al., 2020). Earlier research in this domain has provided a varied perspective. While a significant body of literature suggests a reduction in birth weight following stressful events during (Wadhwa et al., 1993) or just before pregnancy (Witt et al., 2014), there are also studies that indicate a contrary effect. We demonstrate that effects on fertility outcomes not only relate to women's conditions at the time of pregnancy but also can stem from women's existing health after early-life exposure to adversity. We also show that to fully capture the effects of adverse early life exposures 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. Using indicators such as parity and number of surviving children may underestimate the overall effect of women's health on 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 that we analyze, our results contribute to an improved 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 (see Harville et al., 2021 for a review), but our results align with proposed theoretical mechanisms for long-term effects of disease exposure on survival and health.

The limitations of this study partially relate to the generalizability of our findings to other settings. First, while our study sample and data are unique and allows us to bring novel insights to the question of whether disease exposure has implications for reproductive health, our results should be interpreted in view of the specific context analyzed. The geographical area where our study population resided are not representative of Europe or beyond, although the long-term economic and demographic development is similar to those of other contexts (see Bengtsson and Dribe, 2021 for a review). Furthermore, although a robust healthcare system was instituted in the early to mid-20th century, the historical health context is different from today. While fertility and reproductive outcomes of our population were not only determined by biological factors and our women had access to many modern treatments to sickness and disease, contemporary populations generally have better health and socioeconomic factors and cultural norms are main drivers of reproductive choices, enabled by medical technologies. At the same time, incidents of infant mortality in our context in early decades of the 20th century, when the sampled women were exposed, was similar to that in many of today's poorest countries where disease exposure and outbreaks is still a common phenomenon. Second, 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. Lastly, our indicator of disease exposure, peak infant mortality rate in women's county and year of birth, cannot specifically measure whether women effectively contracted disease in early life and does not take disease susceptibility into account. At the same time, local cohort variation in IMR has the advantage to individual variation in childhood conditions as the individual exposure and later reproductive health outcomes may be jointly affected by unobserved heterogeneity, leading to simultaneity bias. We also show that our results are robust to the inclusion of parental socioeconomic characteristics and that our exposure indicator does not significantly associate with economic trends nor health care developments.

Previous research 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 (Quaranta, 2014). Other work found scarring effects resulting in increased mortality during women's reproductive years following childhood exposure to infectious disease mortality within the family (van Dijk et al., 2019). 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 but also recent resurgences of measles, scarlet fever, pertussis and tuberculosis (Baker et al., 2022), 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 (Bhalotra and Rawlings, 2013), 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 pre-conceptional, prenatal and infant care (World Health Organization, 2013). 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 (United Nations, 2015). Further work on the impact of early life exposures on reproductive health is needed. Future studies should look at heterogeneities in the effects across different groups of society, including the impact on men. Our work also 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.

CRediT authorship contribution statement

Ingrid K. van Dijk: Conceptualization, Formal analysis, Visualization, Writing – original draft, Writing – review & editing, Methodology. **Therese Nilsson:** Conceptualization, Writing – original draft, Writing – review & editing, Methodology. **Luciana Quaranta:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing.

Data availability

The authors do not have permission to share data.

Acknowledgements and Funding Sources

We are very grateful for comments received from Niels van den Berg, Martin Dribe, Alison Gemmill, Matteo Manfredini, Peter Nilsson, Michel Oris and two anonymous reviewers. The authors have been funded through the research program "Landskrona Population Study", funded by the Swedish Foundation for Humanities and Social Sciences (Riksbankens Jubileumsfond, RJ), and through FORTE (dnr 201700866), NordForsk (dnr 104910), Swedish Research Council (2022-01163) and RJ (P21-0139). Funding received from the Crafoord Foundation (dnr 20170687, dnr 20190685), the Ebbe Kock Foundation and the Gyllenstiernska Krapperup Foundation for the digitization of obstetric hospital birth records is also gratefully acknowledged. We are thankful for assistance with the search and digitization of obstetric hospital birth records from Erik Andersson, Birgitta Celinder, Emelie Gustafson and Erik Norberg.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.socscimed.2024.116767.

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