*Oxford Bulletin of Economics and Statistics*

ORIGINAL ARTICLE OPEN ACCESS

# The Long-Term Effects of In Utero Exposure to Rubella

Irene Mosca[1] | Anne Nolan[2,3]

[1]Department of Economics, Maynooth University, Maynooth, Ireland | [2]Economic and Social Research Institute, Dublin, Ireland | [3]Department of Economics, Trinity College Dublin, Dublin, Ireland

**Correspondence:** Irene Mosca (irene.mosca@mu.ie)

**Received:** 7 July 2022 | **Revised:** 18 December 2024 | **Accepted:** 16 January 2025

**Keywords:** in utero | Ireland | later-life health | rubella

## ABSTRACT

A rubella infection in early pregnancy poses a significant risk of damage to the foetus. In this paper, we examine the later-life impact of a rubella outbreak that occurred in Ireland in 1956. Matching the outcomes of individuals born in 1954–1957 in the 2016 Irish Census of Population to the county-level rubella incidence rate that was prevailing when respondents were in utero in early pregnancy, we find that one extra rubella case per 10,000 population is associated with between 0.4% and 1.2% point increases in the probability of having lower levels of educational attainment, being in poor health and having a disability in later life.

**JEL Classification:** I10, I18, J13

## 1 | Introduction

A large body of research in economics and other disciplines considers the role of early-life circumstances in shaping later-life outcomes. Poorer health and socio-economic status in early life has been shown to be associated with a higher risk of later-life ill-health [1–6], lower educational and occupational attainment [7–9], lower cognition [10, 11] and even poorer social outcomes such as marriage rates [12]. A key dimension of the debate on the role of early-life circumstances concerns the impact of in utero conditions. Originally attributed to Barker, the foetal origins hypothesis establishes that certain chronic health conditions in later adulthood such as stroke and ischaemic heart disease can be linked to in utero development [13–15]. It is argued that the in utero environment (and in particular nutrition during pregnancy) predisposes the foetus to have particular metabolic characteristics, which can lead to future disease [16].

However, much of the early research on the foetal origins hypothesis has been criticised for reliance on studies using observational data [16]. Establishing causality is not easy in this setting as it is likely that those with poor in utero environments also have (unobserved) characteristics (such as different parental resources) that may lead them to have poorer later-life outcomes. In this case, estimates of the impact of foetal health on later-life outcomes might be biased. One solution is to use an exogenous source of variation in foetal health, for example, a random health shock that occurs during pregnancy. Previous research that exploits natural experiments that mimic a random shock in pregnancy include those examining the impact of the 1918 and 1957 influenza pandemics [1, 8, 16–20], the 1946/1947 Dutch famine [9], the 1950–1953 Korean War [21], the 1958–1961 Chinese Famine [10], the 1974 Bangladesh famine [22], the 1992 conflict in Kenya [23], maternal fasting during Ramadan [24], the 2004 hurricane Catarina in Brazil [25] and the 2014/2015 Flint Water Crisis [26, 27]. However, even the most careful research designs can be subject to bias if the wider historical and social context at the time of the health shock is not taken into account [18].

In this paper, we contribute to the evidence on the foetal origins hypothesis by examining the later-life impact of a rubella outbreak that occurred in Ireland in 1956. Rubella is a contagious viral disease that displays mild symptoms including rash,

fever and swollen glands although it is estimated that more than 50% of cases can be asymptomatic [28]. It occurs most often in children and young adults [29]. The rubella virus is transmitted by airborne droplets when infected people sneeze or cough. While symptoms are mild, a rubella infection just before conception and in early pregnancy can result in low birth weight, prematurity, miscarriage, foetal death or congenital defects known as congenital rubella syndrome (CRS) [30, 31].[1] The risk to the foetus decreases with gestational age, and defects are rare when infection occurs after the 18th week of gestation [28, 33].[2] Among the consequences of rubella in early pregnancy are foetal death and CRS.[3] A 32 year follow-up of 125 adults with CRS in the US reported ophthalmic damage as the most common disorder (78%), followed by sensorineural deafness (66%), psychomotor retardation (62%) and cardiac defects (58%). Additionally, CRS is associated with autoimmune diseases, and several studies have reported an increased risk for diabetes and thyroid diseases [28, 35].

We are not aware of peer-reviewed studies documenting that rubella infection in early pregnancy affects differentially outcomes for boys and girls. While some small-scale studies show higher rates of CRS in one sex over another (e.g., [36, 37]), organisations such as the US Centers for Disease Control and Prevention (CDC) caution against using data from such studies for population disease surveillance.[4] There is no treatment for rubella but the disease is preventable with vaccination (which became available from 1969 [34]). In Ireland, a vaccine against rubella was introduced (for girls between their 12th and 14th birthdays) in 1971, and a Measles, Mumps and Rubella (MMR) vaccine was added to the national immunisation schedule in 1988 [30, 38, 39].

Due to the impact of vaccination, the World Health Organisation (WHO) has ruled that rubella has been effectively eliminated in Ireland[5], although small numbers of imported cases are sometimes reported (data from the European Centre for Disease Control show that two cases were reported over the period March 2019–February 2020, but no cases were reported over the period September 2023–August 2024).[6] As of 2019, 81 of the 194 WHO member states had achieved rubella elimination, and an additional six had been verified as having controlled rubella. However, these countries accounted for only 24% of the world's population. Over the 11 year period between 2007 and 2018, just under 140,000 cases of rubella were reported worldwide [40]. Rubella infection in pregnancy is therefore still a concern in many parts of the world [37].

Using micro-data from the 2016 Irish Census of Population and historical data on incidence of infectious diseases published by the Irish Department of Health, we examine the impact of in utero exposure to rubella in early pregnancy around the time of the 1956 outbreak on a variety of health and educational outcomes measured around 60 years later. We match outcomes of individuals who are in the 2016 Irish Census and who were in utero before or during the 1956 rubella outbreak to the county-level[7] rubella incidence rate that was prevailing when respondents were in early pregnancy.

Our estimation strategy to investigate the effects of in utero exposure to rubella (the treatment) on later-life outcomes relies on two different estimators: the two-way fixed effect (TWFE) estimator and the two-stage TWFE estimator described in Gardner et al. [41]. As explained in more detail in Section 4, the main advantage of the two-stage TWFE estimator over the TWFE estimator is that it is robust to heterogeneous treatment effects across time and groups. We find that one extra rubella case per 10,000 population is associated with between 0.4 and 1.2 percentage point increases in the probability of having lower levels of educational attainment, being in poor health and having a disability in later life. These effect sizes translate into meaningful increases in the numbers of individuals reporting lower levels of educational attainment, being in poor health and having a disability in later life in the study population. To illustrate, one additional rubella case per 10,000 population in the first months of pregnancy translates into an additional 470 individuals in poor health and 990 individuals having a disability in the population of 59–62 year olds in 2016.

This paper makes a number of contributions to the literature. This is one of the studies outside the medical literature to focus on the long-term effects of rubella exposure in pregnancy. In contrast to other studies of the foetal origins hypothesis in the economics literature or in related disciplines, the fact that gestational age is a key determinant of foetal damage from rubella means that we can test a more refined hypothesis, that is, that rubella exposure in early pregnancy leads to poorer health and socio-economic outcomes in later-life. We match historical Department of Health data on notifications of rubella and other infectious diseases by quarter and county with 2016 Census data that includes county of birth, year of birth, semester of birth[8], educational attainment, self-reported health and disability. Internationally, the Irish Census is rare in including a question on self-reported health. The sample is also large, comprising 10% of the population in that year. In contrast, studies in the medical literature are typically based on a relatively small number of observations, that is, mothers with a diagnosis of rubella in pregnancy or babies born with CRS, and often lack a control group. Our approach is more comprehensive as we focus on an exogenous source of potential exposure to rubella in pregnancy (this approach is also more likely to capture asymptomatic cases, mildly affected cases and un-reported cases).[9]

This paper is structured as follows. Section 2 provides further context on the 1956 rubella outbreak in Ireland. Section 3 describes the data and the sample selection criteria. Section 4 illustrates the empirical methodology and Section 5 presents the results. Section 6 discusses the results and Section 7 concludes and reflects on policy implications.

## 2 | The 1956 Rubella Outbreak in Ireland

Rubella became a notifiable disease in Ireland in 1948. Clinical diagnosis of rubella is difficult because similar rashes occur in other viral infections and in allergic reactions, and a laboratory diagnosis is therefore essential [28]. The rubella virus was first isolated in 1962, which allowed for the development of methods for antibody detection thereafter [44]. Therefore, prior to 1962, identification of rubella infection was done on the basis of reported symptoms and it is likely that the true incidence of the disease was underreported [38]. In Ireland, notifications are

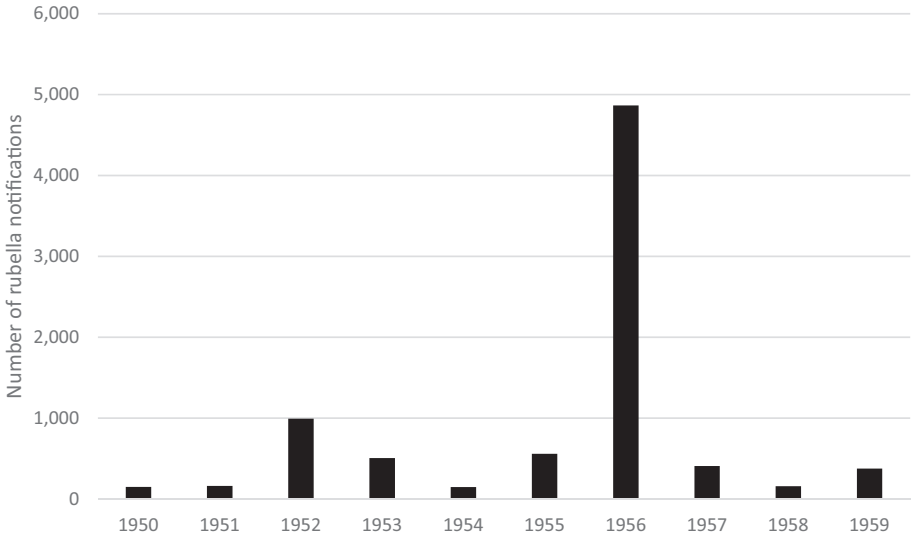


**FIGURE 1** | Annual notifications of rubella, Ireland, 1950–1959. *Source:* Department of Health, [45, 46].

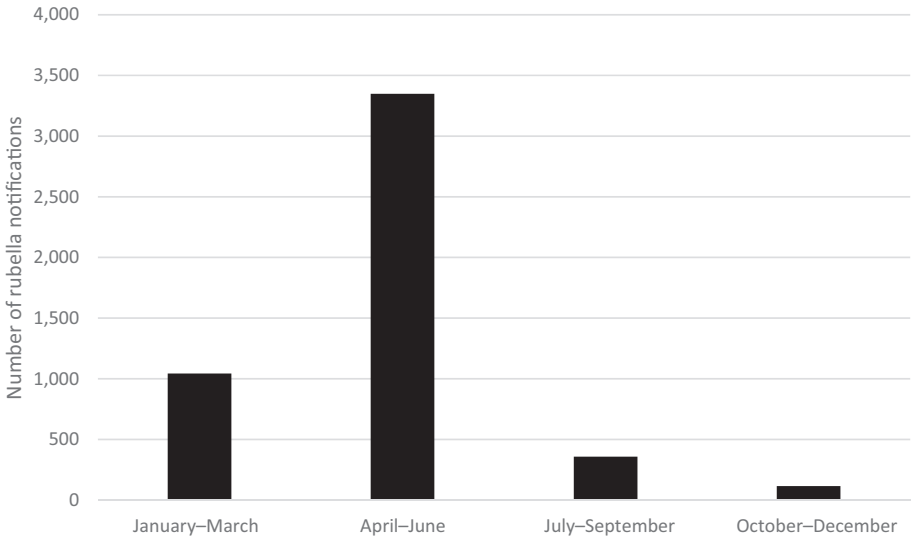


**FIGURE 2** | Quarterly notifications of rubella, Ireland, 1956. *Source:* Department of Health, [46].

compiled by practicing physicians and notified to the local medical officer of health/director of public health.

Figure 1 illustrates the number of rubella cases reported per annum in Ireland throughout the 1950s. The 1956 outbreak can be clearly identified, with a near five-fold increase in annual cases compared to the next-highest year (1952). While the number of cases may appear low, the fact that diagnostic tests were not available, and that approximately 50% of cases can be asymptomatic, means that the incidence figures reported in Figure 1 are likely to be underestimated. The 1956 rubella outbreak began in the early months of the year.[10] Figure 2 shows how the number of cases started to increase in the first quarter, reached a peak in the second quarter of the year, before falling off sharply from July onwards.

The outbreak affected primarily urban areas of the country, although there were outbreaks in more rural counties too. Figure 3 shows the rubella incidence rate, defined as notifications per 10,000 population, by county in January to June 1956. More than 15 cases per 10,000 population were recorded in Dublin and between 2.5 and 15 cases of rubella per 10,000 population were recorded in counties Meath, Westmeath, Kildare, Cork, Limerick and Tipperary. The remaining counties experienced fewer than 2.5 notifications per 10,000 population and most often fewer than 1 notification per 10,000 population.

Other infectious diseases were common in Ireland in the 1950s. Table 1 shows that throughout the 1950s, diseases such as measles, whooping cough (pertussis), scarlet fever and diarrhoea were recorded in large numbers. For example, the annual incidence of whooping cough ranged between 5 and 17.5 cases per 10,000 population. Table 1 also illustrates that while there were other infectious disease outbreaks in the 1950s (most notably measles in 1959), the 1956 outbreak of rubella was not accompanied by other infectious disease outbreaks.

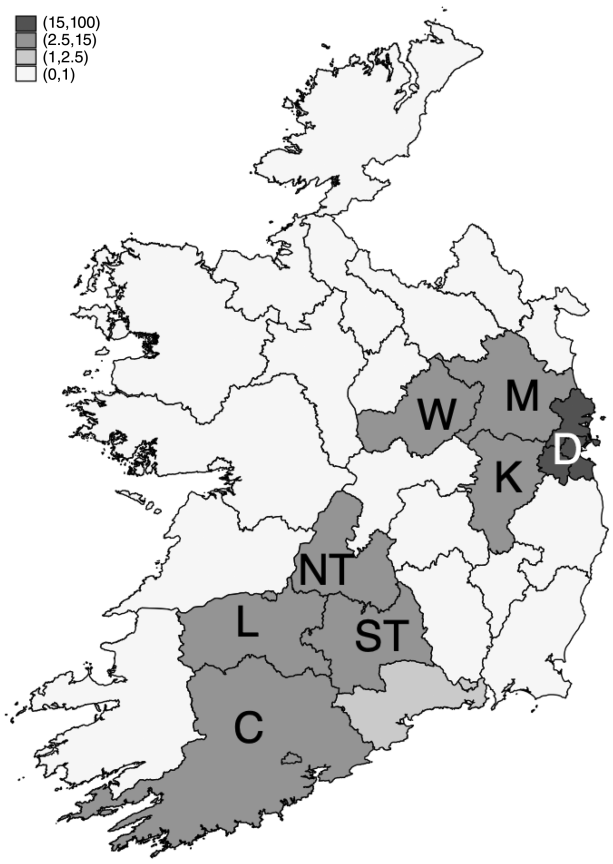


**FIGURE 3** | Rubella incidence by county, Ireland, January to June 1956. Rubella incidence is defined as notifications per 10,000 population in period January to June 1956. C, Cork; D, Dublin; K, Kildare; L, Limerick; M, Meath; NT, North Tipperary; ST, South Tipperary; W, Westmeath. Tipperary county is divided into two administrative areas, Tipperary North and Tipperary South in the map, but in the 1950s notifications were reported for the two administrative areas together (Tipperary). *Source:* Authors' calculations from Central Statistics Office [67].

## 3 | Data and Sample Selection

We use micro-data from individuals born between March 1954 and February 1957 in the 2016 Irish Census of Population and historical data on incidence of infectious diseases published by the Irish Department of Health. Specifically, we match outcomes of individuals who are in the 2016 Irish Census and who were in utero before or during the 1956 rubella outbreak to the county-level rubella incidence rate that was prevailing when respondents were in utero, in early pregnancy. As explained in more detail in Section 4, individuals born between March 1954 and August 1956 were in utero before the rubella outbreak occurred (or were in utero in later stages of pregnancy). Individuals born between September 1956 and February 1957 were in utero in early pregnancy when the rubella outbreak occurred.

Rubella notifications were first published quarterly and by county by the Department of Health in 1952. While data on rubella incidence is therefore available for cohorts born in 1953 and 1952, we exclude them from our analysis for the following reason. In September 1966, the then Minister for Education, Donogh O'Malley, unexpectedly announced that all secondary schooling in Ireland would become free in the following academic year [47]. The following academic year would start in September 1967. Prior to the reform, student fees were levied by all providers of secondary schooling in Ireland. All individuals born in 1954 onwards were equally affected by the reform, in the sense that by the time they reached secondary-school age, secondary education was free. However, individuals born in 1953 or 1952 might have been affected or not affected by the reform. This depended on their exact age in September 1967 and on whether they were still in education in September 1967 or had left education before then. As educational attainment is one of the outcomes investigated in the analysis of this paper, we argue that it is important to keep the sample as homogeneous as possible and therefore exclude individuals born before 1954.

**TABLE 1** | Notifications of infectious diseases (per 10,000 population), Ireland, 1950–1960.

| | 1950 | 1951 | 1952 | 1953 | 1954 | 1955 | 1956 | 1957 | 1958 | 1959 | 1960 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Acute anterior poliomyelitis | 0.7 | 0.2 | 0.3 | 0.8 | 0.3 | 0.4 | 1.8 | 0.5 | 0.9 | 0.1 | 0.6 |
| Diarrhoea and enteritis (children < 2 years of age) | 3.7 | 5.2 | 4.3 | 4.7 | 3.3 | 5.2 | 3.6 | 4.4 | 4.9 | 5.5 | 4.7 |
| Diphtheria | 0.5 | 0.3 | 0.1 | 0.1 | 0.1 | 0.3 | 0.8 | 0.3 | 0.2 | 0.2 | 0.2 |
| Dysentery | 0.1 | 0.1 | 0.3 | 0.4 | 0.7 | 0.5 | 0.3 | 0.6 | 0.8 | 1.1 | 1.0 |
| Erysipelas | 1.2 | 1.0 | 1.0 | 0.9 | 0.7 | 0.6 | 0.7 | 0.6 | 0.5 | 0.4 | 0.4 |
| Infectious hepatitis | 0.7 | 0.5 | 1.1 | 1.5 | 1.1 | 1.0 | 1.7 | 1.5 | 1.7 | 2.0 | 4.4 |
| Infectious mononucleosis | 0.4 | 0.3 | 0.2 | 0.2 | 0.3 | 0.3 | 0.2 | 0.2 | 0.3 | 0.5 | 0.5 |
| Influenza pneumonia | 0.0 | 2.5 | 0.2 | 0.6 | 0.4 | 0.7 | 0.5 | 2.3 | 0.7 | 1.0 | 0.5 |
| Measles | 23.6 | 21.4 | 35.2 | 28.0 | 38.3 | 25.2 | 27.6 | 25.4 | 18.3 | 53.2 | 6.3 |
| Rubella | 0.5 | 0.6 | 3.4 | 1.7 | 0.5 | 1.9 | 16.8 | 1.4 | 0.6 | 1.3 | 1.7 |
| Scabies | 1.9 | 1.7 | 1.1 | 1.1 | 0.8 | 0.7 | 1.1 | 0.9 | 1.3 | 1.1 | 1.2 |
| Scarlet fever | 12.4 | 8.3 | 10.2 | 9.2 | 5.3 | 3.9 | 3.5 | 3.5 | 4.0 | 4.2 | 3.4 |
| Whooping cough | 12.2 | 13.4 | 14.8 | 16.2 | 6.9 | 11.7 | 17.5 | 6.2 | 5.0 | 15.5 | 8.4 |

*Source:* Department of Health [45, 46].

While data on rubella incidence is also available for cohorts born after February 1957, we exclude them due to concerns over potential endogeneity. For example, changes to parental behaviours in terms of fertility choices and/or residential location following the rubella outbreak may mean that the cohorts born after February 1957 are different in some way from the slightly older cohorts who were exposed to the rubella outbreak and from the older cohorts who were not exposed to the outbreak. The analytic sample therefore comprises those born March 1954–February 1957 inclusive.

## 4 | Empirical Methodology

### 4.1 | Two-Way Fixed Effects Approach

Our estimation strategy first exploits variation in in utero exposure to rubella across counties and over time using the following TWFE regression model which is estimated via OLS:

$$Y_{ijt^*} = \text{RubellaUtero}_{jt^*} + \tau_{t^*} + \gamma_j + \epsilon_{jt^*} \quad (1)$$

where $Y_{ijt^*}$ is a (binary) outcome for individual i in the 2016 Census born in county j in semester $t^*$. $\text{ubellaUtero}_{jt^*}$ is the county-level rubella incidence rate that was prevailing when individuals born in county j in semester $t^*$ were in utero (in the first months of pregnancy). $\text{RubellaUtero}_{jt^*}$ is our treatment of interest and is a continuous variable. $\tau_{t^*}$ are semester of birth fixed effects where $t^* = \{1, 2, \ldots 6\}$ so that $t^* = 1$ for the eldest cohort, born in the semester March 1954 to August 1954 and $t^* = 6$ for the youngest cohort, born in the semester September 1956 to February 1957. The youngest cohort is the cohort that was in utero in early pregnancy when the rubella outbreak occurred. $\gamma_j$ are county of birth fixed effects. Standard errors are clustered at the county level.

One concern with this strategy is that rubella incidence may also capture the wider disease environment in the county as well as the county's capacity for tracking infectious diseases. To address this concern, we also estimate Equation (1) adding time-varying controls for the wider infectious disease environment that respondents would have been exposed to when they were in utero. Examples of these controls are county-level incidence rates of measles and scarlet fever. It is important to note that the inclusion of these time-varying disease environment controls assumes that they affected treated and untreated individuals similarly, and that the treatment, that is, in utero rubella exposure, did not affect later values of these control variables. As these assumptions might be problematic (see [48]) we estimate Equation (1) first without and then with time-varying disease environment controls. We also investigate heterogeneity by gender adding a *gender times rubella exposure* interaction term in the TWFE regression.

### 4.2 | Two-Stage Two-Way Fixed Effects Approach

Although our identification strategy relies primarily on the occurrence of the 1956 rubella outbreak, rubella cases were notified—although in considerably lower numbers—also in previous years, as already shown in Figure 1. Therefore, there is some heterogeneity in treatment effects across groups (counties of birth) and time (semesters of birth) in our setting. Recent developments in the econometrics literature have highlighted that the TWFE estimator can generate biased estimates when treatment effects are heterogeneous across groups and time.[11] We address this limitation of the TWFE estimator by relying on an alternative estimator, namely the two-stage TWFE estimator described in Gardner et al. [41]. This two-stage estimator is robust to treatment-effect heterogeneity in the presence of staggered treatment timing and accommodates continuous treatments.

The regression-based two-stage estimation procedure is as follows. The first-stage regresses the relevant outcome (described below) on county of birth fixed effects and semester of birth fixed effects using the subsample of untreated observations. The second-stage subtracts the estimated county of birth and semester of birth fixed effects from observed outcomes and regresses the residualised outcomes on the treatment. In regression form, the first-stage estimates the model $Y_{ijt^*} = \tau_{t^*} + \gamma_j + \epsilon_{jt^*}$ on the sample of untreated observations and the second-stage regresses adjusted outcomes $Y_{ijt^*} - \widehat{\tau_{t*}} - \widehat{\gamma_j}$ on the treatment. This two-stage approach recovers the average difference in outcomes between treated and untreated individuals, after removing county of birth and semester of birth effects. We estimate the two-stage TWFE model first without and then with the time-varying disease environment controls. When included, these are added on the right-hand-side of the first stage equation. Finally, we investigate heterogeneity by gender adding a *gender times rubella exposure* interaction term in the two-stage TWFE regressions.

Critical to the two-stage TWFE approach is the classification of untreated individuals who are used in the estimation of the first-stage regression. We employ two alternative definitions. First, we define an individual as untreated if rubella exposure per 10,000 population in their county of birth when they were in utero is exactly zero. Second, we define an individual as untreated if rubella incidence per 10,000 population in their county of birth when in utero is low, which we define as less than 2.5 cases of rubella per 10,000 population.

### 4.3 | Variables

#### 4.3.1 | Adult Health and Educational Attainment

We focus on three outcomes. The first outcome is self-reported health, which has been consistently shown to be an accurate and reliable predictor of mortality [52]. Census respondents are asked to rate their health on a five-point scale. The responses individuals can choose from are: very good; good; fair; bad and very bad. We dichotomise responses so that the outcome 'poor health' is equal to one for respondents who report to be in bad or very bad health; zero otherwise.

The second outcome is having a disability. Census respondents are asked to report whether they have any long-lasting condition or disability. If respondents report a disability, they are assigned a value of one. Otherwise, they are assigned a value of zero.

The third outcome is highest level of education attained. Respondents are asked to choose the highest level of education attained

from the following list: no formal education, primary, lower secondary, upper secondary, technical or vocational, advanced certificate, higher certificate, ordinary degree, honours degree, postgraduate degree or doctorate. Responses are dichotomised so that individuals who have at most primary education are assigned a value of one; and individuals who have attained at least lower secondary education are assigned a value of zero.

#### 4.3.2 | In Utero Exposure to Rubella

In the 1950s, rubella (and other infectious disease) notifications were reported quarterly by the Irish Department of Health. The four quarters were: January–March; April–June; July–September; October–December. In the 2016 Census micro-data at our disposal, six bimonthly periods of birth are available. These are January–February; March–April; May–June; July–August; September–October and November–December.[12] As the medical literature highlights the fact that the risk of congenital malformations and other adverse birth outcomes (e.g., stillbirth) as a result of rubella infection are concentrated in the first 18 weeks of gestation, we need to restrict the relevant period of exposure to rubella infection to early pregnancy.

However, identifying exactly when individuals who are in the 2016 Census of Population were in utero in early pregnancy is challenging, primarily because we do not know (a) exact date of birth and (b) gestation length. In addition, historic data on rubella notifications from the Irish Department of Health were reported quarterly (not monthly). We also have to take into account that rubella notifications were generally higher in the first half of the year (see Figure 2). In order to align these various sources of data (bimonthly period of birth, quarter of notification and seasonality of notification), we aggregate quarterly rubella notifications into two semesters: January–June and July–December. We also aggregate the six bimonthly periods of births into two semesters of birth: March–August and September–February. We then calculate RubellaUtero as follows. For those born in semester March to August of year T, RubellaUtero is the average incidence rate in the county of birth for the semester July–December of year $T-1$. For those born in the semester September of year T to February of year $T+1$, RubellaUtero is the average rubella incidence rate in the county of birth for the semester January to June of year T. Therefore, rubella incidence rate is 'lagged'. This is because our aim is to provide a measure of exposure to rubella in utero, and specifically in early pregnancy. As illustrated in Figure 2, the rubella outbreak occurred in January to June 1956. This implies that respondents born in September 1956 to February 1957 were in utero—and in the first months of pregnancy—when the outbreak occurred.

#### 4.3.3 | In Utero Exposure to Other Infectious Diseases

The historical reports of the Department of Health used in the analysis to compile the rubella incidence rate also include data on notifications by county and quarter of the following 12 infectious diseases: acute anterior poliomyelitis; diarrhoea (and enteritis); diphtheria; dysentery; erysipelas; infectious hepatitis; infectious mononucleosis; influenza pneumonia; measles; scabies; scarlet fever; and whooping cough. For all diseases, we map to each 2016 Census respondent the county-level incidence rate that was prevailing when the respondent was in utero, and specifically in the first months of pregnancy. As illustrated in Table 1, the incidence of measles, whooping cough, diarrhoea and scarlet fever was comparable to, or in excess of, that of rubella over the period. The incidence of the other diseases was considerably lower.

We add five controls in the specifications that include time-varying controls for the wider disease environment. These are county-level incidence of: (1) measles; (2) whooping cough; (3) diarrhoea; (4) scarlet fever and (5) other diseases. The incidence of other diseases captures the aggregate incidence of poliomyelitis, diphtheria, dysentery, erysipelas, infectious hepatitis, infectious mononucleosis, influenza pneumonia and scabies. As for RubellaUtero, respondents born in March–August of year T are assigned the average incidence rate for the semester July–December of year $T-1$. Respondents born between September of year T and February of year $T+1$ are assigned the average incidence rate for the semester January–June of year T.

### 4.4 | Identification Assumptions

The validity of the estimation models employed in the analysis of this paper rely on three important assumptions. The first is that there were no anticipation effects. In our setting, this assumption could fail if, for example, counties with relatively higher rates of disease prior to the outbreak were more likely to identify rubella infections and/or to recommend appropriate preventive actions for women of child-bearing age. As illustrated in Table 2, Dublin had a very high rate of disease in comparison with other counties. To illustrate, 71.0% of notifications of dysentery in 1954 were recorded in Dublin. The remaining 29.0% were recorded in the rest of the country. Similarly, 59.4% of notifications of measles in 1955 were recorded in Dublin. The remaining 40.6% were reported in the rest of the country. Focusing on rubella, 63.8% of notifications of rubella were recorded in Dublin in 1955. The remaining 36.2% were reported in the rest of the country. However, only around a quarter of the population was living in Dublin at the time. There is also evidence that a far higher proportion of women gave birth in hospital (rather than at home) in Dublin compared to the rest of the country [53, 54], which is likely to have led to a different pregnancy and birth experience for pregnant women in Dublin compared to those giving birth in the rest of the country.

The second identifying assumption is that the variation in rubella notifications across counties around the 1956 outbreak is exogenous. Controlling for county fixed effects and semester of birth fixed effects should account for unobserved factors such as the distribution of socioeconomic status and public health resources that differ across counties and time. In order for some omitted factor to be driving the results, it would have to vary in exactly the same nonlinear pattern as rubella exposure, differentially affect those in utero in the early months of 1956, and not before (or thereafter). Possible factors include institutional or policy changes that were implemented at the same time as rubella exposure. While the 1940s and 1950s were a period of considerable policy development in Irish healthcare [43, 55, 56], our review of the literature suggests no obvious health policy changes around

**TABLE 2** | Notifications of infectious diseases (Dublin as percentage of total), 1952–1960.

| | 1952 | 1953 | 1954 | 1955 | 1956 | 1957 | 1958 | 1959 | 1960 |
|---|---|---|---|---|---|---|---|---|---|
| Acute anterior poliomyelitis | 16.7% | 20.8% | 28.0% | 37.0% | 21.8% | 16.3% | 36.7% | 35.9% | 54.9% |
| Diarrhoea and enteritis (children < 2 years of age) | 64.6% | 76.2% | 55.9% | 73.0% | 78.6% | 79.2% | 84.9% | 82.3% | 78.1% |
| Diphtheria | 27.5% | 0.0% | 79.4% | 87.0% | 93.9% | 93.8% | 88.7% | 92.9% | 92.6% |
| Dysentery | 70.7% | 44.5% | 71.0% | 42.7% | 48.9% | 55.3% | 83.9% | 65.9% | 71.9% |
| Erysipelas | 55.9% | 51.5% | 47.4% | 50.9% | 46.6% | 48.2% | 49.3% | 57.9% | 36.8% |
| Infectious hepatitis | 54.9% | 59.4% | 52.5% | 44.4% | 63.3% | 59.0% | 52.2% | 49.0% | 52.4% |
| Infectious mononucleosis | 87.7% | 86.8% | 79.2% | 85.2% | 62.5% | 75.9% | 79.6% | 84.7% | 60.8% |
| Influenza pneumonia | 57.1% | 21.6% | 20.3% | 34.9% | 2.7% | 35.0% | 32.5% | 23.6% | 25.0% |
| Measles | 46.1% | 50.8% | 43.9% | 59.4% | 53.9% | 46.3% | 25.4% | 40.7% | 52.8% |
| Rubella | 88.7% | 82.3% | 77.9% | 63.8% | 87.6% | 52.8% | 72.9% | 45.5% | 66.4% |
| Scabies | 75.8% | 87.4% | 80.9% | 95.3% | 89.5% | 93.0% | 96.0% | 93.0% | 91.6% |
| Scarlet fever | 23.5% | 29.4% | 45.3% | 46.7% | 49.4% | 49.2% | 49.4% | 55.0% | 50.2% |
| Whooping cough | 59.8% | 62.2% | 24.3% | 58.8% | 57.1% | 31.1% | 47.1% | 57.3% | 31.2% |

*Source:* Authors' Calculations from Department of Health [45, 46].

the 1956 outbreak. While the 1953 Health Act did include provisions around the extension of healthcare eligibility to mothers and children, these were largely continuations of trends towards greater public provision and financing of healthcare in Ireland that had been initiated in the late 1940s [55]. The exception was in Dublin, and in particular north Dublin, where maternity and child healthcare services were particularly well-resourced compared to other areas of the country even prior to the 1953 Act [57].

While the violation of the 'no anticipation' and exogeneity or 'no other policy changes' assumptions cannot be tested, it is evident that Dublin was therefore very different to the rest of the country in its disease environment, the circumstances of pregnancy and birth, and maternity and infant care resources, and for this reason, we exclude it from our analytic sample.

The final key identifying assumption is the parallel trends assumption. In our setting this assumption implies that, if the 1956 rubella outbreak had not occurred, the difference in outcomes between those in utero in counties that experienced and did not experience the outbreak would have stayed the same during the outbreak as it was before the outbreak. Focusing on the remaining 25 counties, Figure 4 examines the trajectories of the outcome variables for individuals born in counties that did experience and did not experience the outbreak and who were in utero either before or during the 1956 outbreak. The counties that experienced the outbreak are Meath, Westmeath, Kildare, Cork, Limerick and Tipperary as illustrated in Figure 3 above. The cohort that experienced the outbreak in utero is the cohort born in the semester September 1956 to February 1957. Figure 4 provides suggestive evidence that the two groups of counties were trending similarly before the occurrence of the 1956 rubella outbreak. The distance between the two groups of counties stays roughly constant in the leadup to the occurrence of the rubella outbreak, lending some credibility to the parallel trends assumption.[13]

## 5 | Results

### 5.1 | Descriptive Statistics

Descriptive statistics are presented in Table 3. The relevant sample for analysis includes respondents born between March 1954 and February 1957. These respondents are divided into two groups. The first group includes respondents born in the five semesters 'March 1954 to August 1956'. When the rubella outbreak occurred, these respondents were either in (late) infancy or in utero, in the last months of pregnancy. Importantly for our analysis, this group of respondents was not exposed to the rubella outbreak in early pregnancy. The second group includes individuals born in 'September 1956 to February 1957'. When the rubella outbreak occurred, these respondents were in utero, and specifically in the first months of pregnancy. In Table 3, descriptive statistics are presented for the two groups together in Column (2), and for the two groups separately in Columns (3) and (4).

Two points about Table 3 are worth making. The first is that health outcomes appear to be poorer for individuals who were in the first months of pregnancy during the rubella outbreak, that is, individuals born in September 1956 to February 1957, although these individuals are younger. The second is that, as expected, there is a sizeable difference in the rubella incidence rate between the two groups (0.241 per 10,000 population for those born in March 1954 to August 1956 and 2.204 per 10,000 population for those born in September 1956 to February 1957).

### 5.2 | TWFE and Two-Stage TWFE Regression Results

The TWFE and two-stage TWFE regression estimates are summarised in Table 4. Coefficients are reported for RubellaUtero. Clustered standard errors are reported in brackets. The clustering is at the level of the county of birth. Given the relatively

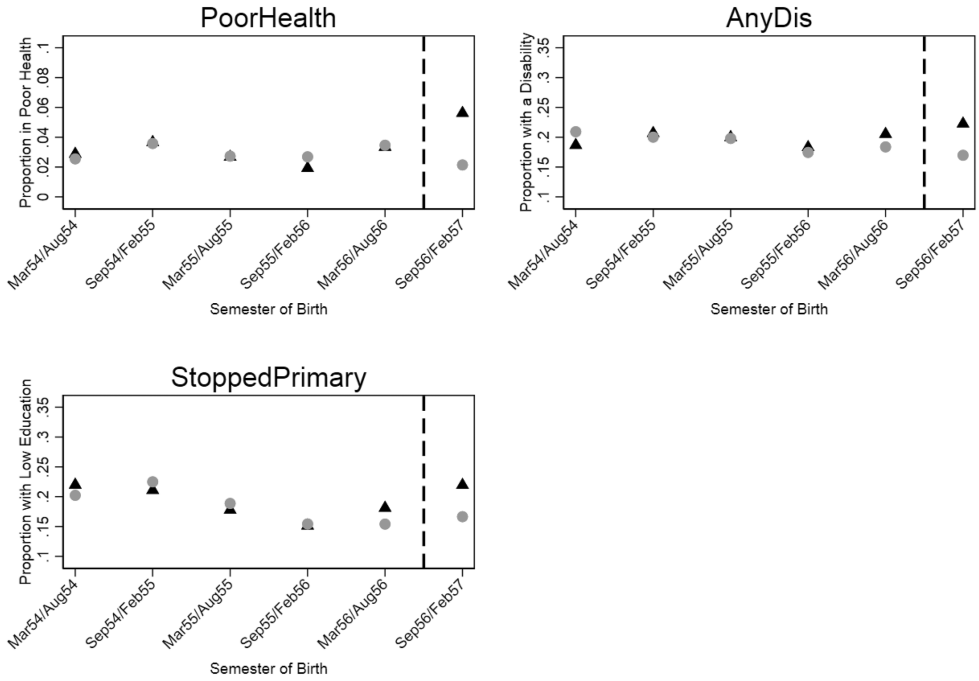


**FIGURE 4** | Outcome by semester of birth for counties that experienced the 1956 rubella outbreak (triangle) and counties that did not experience the 1956 rubella outbreak (circle). The sample used in the analysis includes individuals in the 2016 Irish Census born outside Dublin in March 1954 to February 1957.

**TABLE 3** | Mean (standard deviation) of main regression variables.

| | (1) | (2) | (3) | (4) |
|---|---|---|---|---|
| | | Cohorts | | |
| | Variable measurement | Born in March 1954 to February 1957 | Born in March 1954 to August 1956 | Born in September 1956 to February 1957 |
| PoorHealth | Dummy variable: 1 for bad/very bad health; 0 for very good /good/fair health | 3.0% | 2.9% | 3.4% |
| AnyDis | Dummy variable: 1 for any long-lasting condition or disability; 0 otherwise | 19.1% | 19.1% | 19.3% |
| LowEduc | Dummy variable: 1 for at most primary education; 0 otherwise | 18.0% | 18.1% | 17.8% |
| RubellaUtero | Rubella incidence rate (per 10,000 population) in county of birth when respondent was in utero, in the first months of pregnancy | 0.563 | 0.241 | 2.204 |
| | | (1.573) | (0.823) | (2.903) |
| Number of observations | | 9497 | 7938 | 1559 |

*Note:* The sample used in the analysis includes individuals in the 2016 Irish Census born outside Dublin in March 1954 to February 1957.

low number of clusters (25 in total), we also present {in curly brackets} *p*-values obtained using the wild cluster bootstrap procedure (again with the county of birth as the clustering variable) as described in [58–60].

Columns (1) and (2) in Table 4 show TWFE regression estimates. Columns (3) to (6) show two-stage TWFE regression estimates. Time-varying controls for the wider disease environment are excluded in the specifications of Columns (1), (3) and (5) and included in the specifications of Columns (2), (4) and (6). The first-stage regression uses observations who were in utero when county-level rubella incidence was exactly zero in the specifications of Columns (3) and (4) and observations who were in utero when rubella incidence was low (< 2.5) in the specifications of Columns (5) and (6).

The results of Table 4 (presented graphically in Figure 5) show that there is a positive and statistically significant relationship

**TABLE 4** | Effect of in utero county-level rubella incidence rate (RubellaUtero) on later-life outcomes.

| Estimation method | (1) TWFE | (2) TWFE | (3) Two-stage TWFE | (4) Two-stage TWFE | (5) Two-stage TWFE | (6) Two-stage TWFE |
|---|---|---|---|---|---|---|
| Outcome | | | | | | |
| PoorHealth | 0.0037*** | 0.0039** | 0.0050*** | 0.0050*** | 0.0043*** | 0.0043*** |
| | [0.0013] | [0.0014] | [0.0017] | [0.0019] | [0.0015] | [0.0015] |
| | {0.003} | {0.004} | {0.017} | {0.030} | {0.025} | {0.019} |
| AnyDis | 0.0087** | 0.0084** | 0.0104** | 0.0123** | 0.0091*** | 0.0091** |
| | [0.0035] | [0.0037] | [0.0044] | [0.0052] | [0.0034] | [0.0037] |
| | {0.059} | {0.068} | {0.103} | {0.081} | {0.063} | {0.095} |
| LowEduc | 0.0071*** | 0.0077*** | 0.0090*** | 0.0105*** | 0.0074*** | 0.0079*** |
| | [0.0020] | [0.0021] | [0.0024] | [0.0028] | [0.0021] | [0.0027] |
| | {0.002} | {0.014} | {0.002} | {0.002} | {0.004} | {0.058} |
| Time-varying control variables included | No | Yes | No | Yes | No | Yes |
| Rubella incidence in untreated counties used in first stage | — | — | 0 | 0 | < 2.5 | < 2.5 |
| *N* | 9497 | 9497 | 9497 | 9497 | 9497 | 9497 |

*Note:* The sample used in the analysis includes individuals in the 2016 Irish Census born outside Dublin in March 1954 to February 1957. Standard errors, corrected for clustering at the county level, are in brackets. *p*-values from wild cluster bootstrap procedure are in curly brackets and are based on 999 replications.
*Statistically significant at 10% level; ** at 5% level; *** at 1% level.

between exposure to rubella in early pregnancy and the probability of being in poor health, having a disability in later life (aged 59 to 62) and having attained a low level of educational attainment. To illustrate, for the outcome of self-reported health, the coefficient of RubellaUtero ranges between 0.0037 and 0.005. This means that one extra rubella notification per 10,000 population in the first months of pregnancy is associated with a 0.37 to 0.5 percentage point increase in the probability of being in poor health in later-life. Table 3 illustrates that 3.0% of the 9497 respondents in the sample are in poor health. Focusing on the estimate of Table 4, Column (3), one extra rubella case per 10,000 population therefore translates into 47 extra individuals in the sample reporting poor health.[14] Taking into account that the sample comprises 10% of the total 2016 Census population, this translates into 470 extra individuals in the population of individuals aged 59–62 (born March 1954—February 1957 outside of Dublin) in 2016. Following the same line of reasoning, the coefficient estimate of 0.0104 of Table 4, Column (3) shows that one extra rubella notification per 10,000 population would translate into 990 extra individuals having a disability in this population of 59–62 year olds.

We finally investigate heterogeneity by gender adding a *gender times rubella exposure* interaction term in the TWFE and two-way TWFE regressions. Results for the three outcomes under investigation are presented in Table 5. The results of Table 5 indicate that although effects are always larger for males than for females, the gender differences are never statistically significant at any conventional statistical level.

### 5.3 | Robustness Checks

To consider the robustness and the validity of the estimates of Table 4, three sets of additional regressions are estimated. The relevant coefficients from these additional regressions are shown in Table 6. Columns (1) and (2) in Table 6 show TWFE regression estimates. Columns (3) and (4) show two-stage TWFE regression estimates. Columns (1) and (3) report estimates for the specification that does not include time-varying controls for the wider disease environment. Columns (2) and (4) report estimates for the specification that includes such controls. *p*-values obtained using the wild cluster bootstrap procedure for the treatment variable of interest are also presented {in curly brackets}.

In the first set of regressions, the treatment variable of interest is exposure to rubella in the semester of birth. Therefore, rubella exposure is no longer lagged. For the first-stage of the two-stage TWFE approach, we define an individual as untreated if rubella exposure per 10,000 population in their county of birth in their semester of birth is exactly zero. The results of Table 6, Panel (A) show that there is no statistically significant relationship between rubella incidence in the semester of birth and later life health, disability and educational attainment, with the only exception of the TWFE estimates for the outcome PoorHealth. The findings of Table 6, Panel (A) are generally in line with our expectations as the literature shows that rubella is an inconsequential disease if contracted by the mother in later pregnancy or by a new-born [28, 33].

In the second set of regressions, the 'rubella shock' under investigation is backdated. This time-based placebo shock assumes that

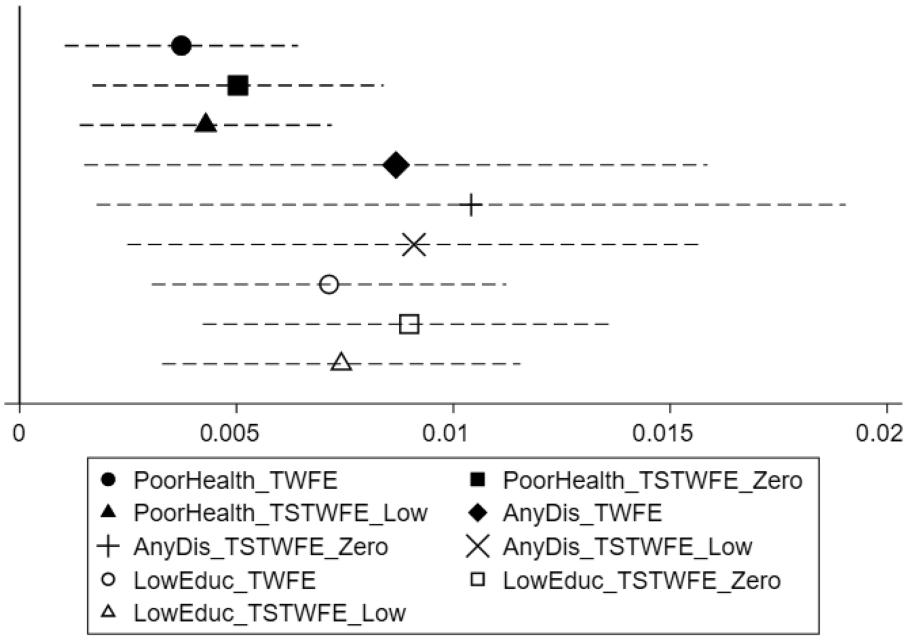


**FIGURE 5** | Effect of in utero county-level rubella incidence rate (and 95% confidence intervals) on later-life outcomes. The sample used in the analysis includes individuals in the 2016 Irish Census born outside Dublin in March 1954 to February 1957. _TWFE indicates two-way fixed effect estimation. _TSTWFE indicates two-stage two-way fixed effect estimation. _Zero indicates that only observations who were in utero when incidence of rubella in their county of birth was exactly zero are used in the first-stage regression. _Low indicates that observations who were in utero when incidence of rubella in their county of birth was less than 2.5 per 10,000 population are used in the first-stage regression. Time-varying controls for the wider disease environment are excluded.

the rubella outbreak occurred in January to June 1954. Therefore, it is assumed that the cohort who was in the first months of pregnancy when the 'backdated' rubella outbreak occurred is the cohort born in September 1954 to February 1955. We assign to this cohort the same rubella incidence rate that was assigned to the cohort born in September 1956 to February 1957 in the analysis presented in Table 4. We assign the 'true' county-level rubella incidence rate that was prevailing when respondents were in early pregnancy to the surrounding older and younger cohorts. For the first-stage of the two-stage TWFE approach, we define an individual as untreated if rubella exposure per 10,000 population in their county of birth when in utero is exactly zero. The results of Table 6, Panel (B) show that in this second set of regressions there is no statistically significant relationship between rubella incidence when in utero and later life health, disability and educational attainment.

In the third set of regressions, the treatment variable of interest is exposure to scarlet fever in utero. Scarlet fever was a common infectious disease in Ireland in the 1950s. Evidence shows that the risk to the foetus if the expectant mother has scarlet fever during pregnancy is low [61].[15] Therefore, we do not expect to find any relationship between exposure to scarlet fever in early pregnancy and later life health or disability and educational attainment. A scarlet fever outbreak occurred in Ireland in the first and second quarter of 1953, thus potentially affecting in utero, in early pregnancy those who were born in September 1953 to February 1954. The regressions of Table 6, Panel (C) include individuals born in September 1953 to February 1956. For the first-stage of the two-stage TWFE approach, we define an individual as untreated if scarlet fever exposure per 10,000 population in their county of birth when in utero is less than 2.5. The 2.5 threshold is chosen as the incidence of scarlet fever was high — and in excess of that of rubella — over the period as illustrated in Table 2. In line with our expectations, no evidence of a statistically significant relationship between in utero exposure to scarlet fever and later-life health or disability and educational attainment is found.

## 6 | Discussion

In this paper, we investigated the long-term effects of in utero exposure to rubella. Rubella is a contagious viral disease that displays mild symptoms and is generally inconsequential in childhood or adulthood. However, a rubella infection in early pregnancy poses a significant risk of damage to the foetus. Using historic data on rubella infections linked to the 2016 Irish Census of Population, we found that one extra rubella case per 10,000 population is associated with between 0.4 and 1.2 percentage point increases in the probability of having lower levels of educational attainment, being in poor health and having a disability in later life.

There are two potential pathways through which rubella infection in pregnancy may lead to poorer outcomes in later life. First, via the direct effect of rubella infection in early pregnancy. As discussed earlier, rubella infection in early pregnancy leads to a high probability of giving birth to a baby with congenital rubella syndrome (CRS). Miscarriages and stillbirths may also occur. The second pathway is via the indirect effects of rubella infection in early pregnancy. Almond and Currie [16] note that maternal infections in pregnancy can affect foetal health by diverting

**TABLE 5** | Effect of in utero county-level rubella incidence rate on later-life outcomes by gender.

| Estimation method | (1) TWFE | (2) TWFE | (3) Two-stage TWFE | (4) Two-stage TWFE | (5) Two-stage TWFE | (6) Two-stage TWFE |
|---|---|---|---|---|---|---|
| PoorHealth | | | | | | |
| RubellaUtero | 0.0048*** | 0.0049*** | 0.0060*** | 0.0060*** | 0.0053*** | 0.0053*** |
| | [0.0014] | [0.0016] | [0.0018] | [0.0020] | [0.00154] | [0.0014] |
| RubellaUtero × Females | −0.0021 | −0.0021 | −0.002 | −0.002 | −0.002 | −0.002 |
| | [0.0020] | [0.0020] | [0.0019] | [0.0019] | [0.0019] | [0.0019] |
| | {0.017} | {0.030} | {0.124} | {0.067} | {0.124} | {0.067} |
| AnyDis | | | | | | |
| RubellaUtero | 0.0100** | 0.0098** | 0.0118*** | 0.0135*** | 0.0104*** | 0.0104*** |
| | [0.0037] | [0.0041] | [0.0044] | [0.0049] | [0.0034] | [0.0035] |
| RubellaUtero × Females | −0.0027 | −0.0028 | −0.0027 | −0.0024 | −0.0026 | −0.0025 |
| | [0.0041] | [0.0041] | [0.0041] | [0.0041] | [0.0040] | [0.0041] |
| | {0.367} | {0.899} | {0.475} | {0.752} | {0.475} | {0.752} |
| LowEduc | | | | | | |
| RubellaUtero | 0.0127** | 0.0131*** | 0.0145*** | 0.0158*** | 0.0130*** | 0.0134*** |
| | [0.0048] | [0.0044] | [0.0046] | [0.0045] | [0.0047] | [0.0047] |
| RubellaUtero × Females | −0.0112 | −0.0111 | −0.011 | −0.0107 | −0.0112 | −0.0111 |
| | [0.0072] | [0.0072] | [0.0070] | [0.0069] | [0.0070] | [0.0070] |
| | {0.809} | {0.528} | {0.501} | {0.592} | {0.501} | {0.592} |
| Time-varying control variables included | No | Yes | No | Yes | No | Yes |
| Rubella incidence in untreated counties used in first stage | — | — | 0 | 0 | < 2.5 | < 2.5 |
| *N* | 9497 | 9497 | 9497 | 9497 | 9497 | 9497 |

*Note:* The sample used in the analysis includes individuals in the 2016 Irish Census born outside Dublin in March 1954 to February 1957. Standard errors, corrected for clustering at the county level, are in brackets. *p*-values from wild cluster bootstrap procedure are in curly brackets and are based on 999 replications.
*Statistically significant at 10% level; ** at 5% level; *** at 1% level.

maternal energy towards fighting infection, by restricting food intake, or through negative consequences arising from the body's own inflammatory response. The latter may also be aggravated by maternal stress during pregnancy in locations and periods with high incidence of disease (although we note the limited publicity at the time of the 1956 rubella outbreak in Ireland). Other behavioural changes may also be possible; for example, parents of rubella-affected children may invest more in their affected child to compensate for their disability.[16] Behaviour during and after pregnancy may also change in response to a health shock such as a rubella infection, for example, it may make the mother more aware of good health during the remainder of her pregnancy. However, we believe that this indirect pathway is less likely in this instance as rubella infection is generally a mild infection for the mother (although very damaging to the foetus if it occurs in early pregnancy) and it is estimated that approximately 50% of cases are asymptomatic.

Therefore, assuming that our results represent largely a direct effect of rubella infection in early pregnancy on later-life outcomes, we need to make sure that our results reflect the effect of exposure to the 1956 rubella outbreak in early pregnancy, and not some other factor that is correlated with exposure and with later-life health and socio-economic outcomes. Section 4 discussed potential threats to identification, including anticipation, other policy changes and violation of parallel trends. While we could not test the violation of 'no anticipation' and exogeneity or 'no other policy changes' assumptions, we concluded that Dublin was very different to the rest of the country in its disease environment, the circumstances of pregnancy and birth, and maternity and infant care resources, and for this reason, we excluded it from our analytic sample. However, three additional sources of potential selection need to be considered for the remaining 25 counties included in our analysis to ensure that the cohort that was exposed to the 1956 outbreak does not differ from surrounding cohorts in terms of their composition that may bias the estimated results. The three additional sources of selection that we investigate are: selection in terms of pregnancy; selection in terms of birth; and selection in terms of premature later-life mortality.

Selection in pregnancy could occur if families responded to the outbreak of rubella by changing behaviour during pregnancy or before, either in order to prevent conception or to prevent infection once pregnant. While this cannot be tested empirically, we

**TABLE 6** | Effect of county-level disease incidence rate on later-life outcomes, robustness checks.

| | (1) | (2) | (3) | (4) |
|---|---|---|---|---|
| **Estimation method** | **TWFE** | **TWFE** | **Two-stage TWFE** | **Two-stage TWFE** |
| (A) Treatment is exposure to rubella at birth, cohorts born March 1954 to February 1957 | | | | |
| PoorHealth | −0.0026** | −0.0027** | −0.001 | −0.0018 |
| | [0.0012] | [0.0011] | [0.0009] | [0.0015] |
| | {0.082} | {0.030} | {0.118} | {0.101} |
| AnyDis | −0.0032 | −0.0016 | 0.0004 | −0.0004 |
| | [0.0019] | [0.0019] | [0.0031] | [0.0034] |
| | {0.103} | {0.349} | {0.813} | {0.847} |
| LowEduc | 0.0003 | 0.0005 | 0.0027 | 0.0011 |
| | [0.0020] | [0.0025] | [0.0035] | [0.0046] |
| | {0.877} | {0.867} | {0.303} | {0.7280} |
| Time-varying control variables included | No | Yes | No | Yes |
| *N* | 9497 | 9497 | 9497 | 9497 |
| (B) Treatment is in utero exposure to rubella, outbreak backdated to January to June 1954, cohorts born March 1954 to August 1956 | | | | |
| PoorHealth | 0.001 | 0.0013 | 0.0003 | 0.0002 |
| | −0.0012 | −0.0013 | −0.0016 | −0.0015 |
| | {0.567} | {0.509} | {0.841} | {0.881} |
| AnyDis | 0.0033 | 0.0035 | 0.0021 | 0.0040 |
| | [0.0044] | [0.0047] | [0.0051] | [0.0045] |
| | {0.575} | {0.593} | {0.475} | {0.363} |
| LowEduc | −0.0019 | −0.001 | −0.002 | −0.0013 |
| | [0.0017] | [0.0014] | [0.0025] | [0.0025] |
| | {0.119} | {0.187} | {0.110} | {0.390} |
| Time-varying control variables included | No | Yes | No | Yes |
| *N* | 7938 | 7938 | 7938 | 7938 |
| (C) Treatment is in utero exposure to scarlet fever, cohorts born September 1953 to August 1956 | | | | |
| PoorHealth | 0.0009 | 0.0009 | 0.0008 | 0.0011 |
| | [0.0010] | [0.0009] | [0.0009] | [0.0009] |
| | {0.731} | {0.647} | {0.742} | {0.634} |
| AnyDis | 0.0025 | 0.0024 | 0.0018 | 0.0018 |
| | [0.0028] | [0.0028] | [0.0022] | [0.0024] |
| | {0.769} | {0.745} | {0.818} | {0.813} |
| LowEduc | −0.0013 | −0.0005 | −0.0009 | 0.0005 |
| | [0.0017] | [0.0017] | [0.0016] | [0.0019] |
| | {0.473} | {0.792} | {0.539} | {0.799} |
| Time-varying control variables included | No | Yes | No | Yes |
| *N* | 9419 | 9419 | 9419 | 9419 |

*Note:* The sample used in the analysis includes individuals in the 2016 Irish Census born outside Dublin. Standard errors, corrected for clustering at the county level, are in brackets. *p*-values from wild cluster bootstrap procedure are in curly brackets and are based on 999 replications.

*Statistically significant at 10% level; ** at 5% level; *** at 1% level.

believe it is unlikely that this type of behaviour change would be a significant factor in this instance for a at least two reasons. First, the sale and importation of artificial contraceptives had been banned in Ireland in 1935, and only fully legalised in 1985 [55]. Second, there was very little public discussion at the time (in terms of news reporting or public health advice) [63, 64] about the outbreak, so it is unlikely that potentially-affected women outside Dublin would have modified their fertility behaviour, or behaviour in pregnancy, in an attempt to prevent infection. Finally, moving to another area of the country to give birth (to avoid rubella infection in pregnancy) is also considered unlikely. While there are no data on temporary moves (e.g., giving birth in a different county before moving back to county of residence), research on internal migration in Ireland in the mid-20th century notes that internal migration rates were low, largely because the major population movement during the period was emigration (which far surpassed internal migration to Dublin, the capital city). In addition, internal migration of married couples was infrequent (and most births in the 1950s occurred in marriage), and the most common age for single women to move was between the ages of 15–19 [65, 66].

Selection in birth is a more serious issue, as the consequences of maternal infection with rubella in the first trimester of pregnancy are severe. Indeed, Almond and Currie [16] note that estimates of the effects of foetal health shocks are generally conservative when the shock also increases mortality. As noted above, it is estimated that 85% of mothers infected with rubella in the first trimester of pregnancy will deliver a child with congenital defects, with congenital deafness being the most common condition. Infection during the first trimester also results in significantly higher incidence of spontaneous abortions and stillbirths [28, 33]. While data on stillbirths (and miscarriages) for the exposed and non-exposed cohorts are not available, we first compare the rates of infant (under 1 year) and neonatal (under 1 month) mortality for the 1956 and 1957 cohorts born outside Dublin to see if they differ systematically from the rates observed for surrounding cohorts. In Figure A1, data on infant and neonatal mortality rates (per 1000 live births outside Dublin) are presented. The risk of mortality in early life in the 1950s was considerably higher than it is today. As is evident from the data in Figure A1, there was a steady improvement in the infant mortality rate throughout the 1950s, with the rate falling from 45 per 1000 live births in 1950 to 31 per 1000 live births in 1959.[17] Although the rate of neonatal mortality was lower and more stable over the decade, it was highest in 1956 at 25.3 deaths per 1000 births.

For neonatal mortality, it is possible to examine cause of death, and in particular the cause of death that is likely to have the strongest association with rubella infection, that is, death from congenital malformations. Figure A2 shows that in 1956 the rate of death from congenital malformations in the counties that experienced the outbreak was higher (at 4.5 per 1000 live births) than in the counties that did not experience the outbreak, where around 3 in 1000 live births resulted in death from congenital malformations. While some of the individuals who were in utero in early pregnancy when the outbreak occurred would have been born in early 1957, it does appear that deaths from congenital malformations were higher in the counties that experienced the outbreak. This means that our estimates must be interpreted as lower bounds of the effect of rubella exposure in utero on later-life health, disability and educational attainment.

Selection in terms of premature mortality in later life is the third potential source of selection that needs to be considered. To test for this, we gather data from each Census of Population from 1961 (the first after the 1956 outbreak) to 2016 and compare the sizes and growth rates of different cohorts through time. Identifying the cohorts exposed to the rubella outbreak in the published Census of Population data is complicated however as the data only identify individuals by their reported age on the Census date (which is in April), rather than their precise date of birth (or even month and year of birth). In addition, the timing and spread of the rubella outbreak in 1956 meant that some of those exposed in utero were born in 1956, and some in early 1957, and only certain counties were affected. Without detailed data on date of birth, or even month and year of birth for each Census, and on county of birth, we cannot further disaggregate the 1956 and 1957 cohorts. Nonetheless, in Figures A3 and A4, we compare the size and growth rates of the 1956 and 1957 cohorts over the period 1961–2016 with the size and growth rates of the surrounding cohorts (1954, 1955, 1958, 1959).[18] The data shows that there is no clear discontinuity in the evolution of the 1956 and 1957 cohorts in comparison with the 1954, 1955 or 1958 cohorts over the period 1961–2016 (the 1959 cohort continues to increase in size after 2006). All cohorts declined in size until about 1991 (consistent with the large net emigration figures that were a feature of the Irish economy over much of the period from 1961 to 1991)[19], before starting to increase slightly during the economic boom in the late 1990s and early 2000s (when net immigration reached its highest ever levels, many of whom were returning Irish migrants). It is only when the 1954–1958 cohorts reached their 50s after around 2006 that their sizes started to decline once again (which may be driven both by mortality and net emigration as result of the financial crisis).

## 7 | Conclusions and Policy Implications

A large body of research in economics and other disciplines considers the role of early-life circumstances in shaping later-life outcomes. The foetal origins hypothesis establishes that certain chronic health conditions in later adulthood can be linked to in utero development [13–15]. However, much of the early research on the foetal origins hypothesis has been criticised for reliance on studies using observational data. Using an exogenous source of variation in foetal health (i.e., a rubella outbreak that occurred in Ireland in 1956), we investigate the long-term effects of in utero exposure to rubella on a variety of later-life outcomes. Rubella is a contagious viral disease that displays mild symptoms and is generally inconsequential in childhood or adulthood. However, a rubella infection in early pregnancy poses a significant risk of damage to the foetus. Matching the outcomes of individuals born in 1954 to 1957 who are in the 2016 Irish Census to the county-level rubella incidence rate that was prevailing when respondents were in utero, we find that one extra rubella case per 10,000 population is associated with between 0.4 and 1.2 percentage point increases in the probability of having lower levels of educational attainment, being in poor health and having a disability in later life. These effect sizes translate into meaningful increases in the numbers of individuals reporting lower levels of

educational attainment, being in poor health and having a disability in later life in the study population. To illustrate, one additional rubella case per 10,000 population in the first months of pregnancy translates into an additional 470 individuals in poor health and 990 individuals having a disability in the population of 59–62 year olds in 2016.

While there is some research in the medical literature that examines the long-term consequences of rubella exposure in pregnancy [28, 35], this is the first study to exploit exogenous variation in the timing and location of a rubella outbreak to examine the impact of rubella exposure in early pregnancy on a variety of outcomes measured around 60 years later. Comparisons with other studies on in utero shocks using quasi-experimental designs is difficult but an analysis of existing literature for the US examining the impact of the 1918 influenza pandemic on a variety of health and educational outcomes show larger effect sizes for influenza exposure, although more recent research has questioned these findings [18]. For example, Almond and Mazumder [1] found that those in utero during the 1918 influenza pandemic in the US were between 4 and 6.5 percentage points more likely to report fair or poor-health when surveyed between 65 and 82 years later. In terms of educational attainment and disability, Almond [17] found that the 1919 birth cohort (i.e., those in utero in 1918) was 4%–5% less likely to complete high school than the cohort trend would predict, and that the 1919 male cohort was 6% more likely to have a work-limiting disability, and 8% more likely to have a work-preventing disability, approximately 50 years later. Differences in how the in utero shock and outcomes are measured, study settings and follow-up periods, as well as differences in the possible underlying mechanisms, are likely to contribute to differences in the magnitude of estimates across different studies.

While there are data limitations in using historic disease notification data (particularly for a disease such as rubella that can be asymptomatic and which did not have a diagnostic test available in the 1950s), and in turn matching these data to Census of Population data, our approach allows us to add to the evidence base on the foetal origins hypothesis by testing a more refined hypothesis, that is, that rubella exposure in early pregnancy is associated with long-term outcomes. While our identification strategy attempts to identify a causal effect by exploiting an exogenous change in disease exposure as a result of a sharp increase in rubella notifications in Ireland in 1956, the usual caveats around inferring causality apply. Nonetheless, we provide useful insights for healthcare providers and policymakers in the countries where rubella infection has yet to be eliminated or controlled, and where rubella infection in pregnancy poses a serious risk to the developing foetus; these countries account for the vast majority (76%) of the global population. More generally, the results highlight the importance of the collection and publication of accurate data on infectious disease notifications for public health surveillance and research.

**Acknowledgements**

Results are based on analysis of strictly controlled Research Microdata Files provided by the Central Statistics Office (CSO). The CSO does not take any responsibility for the views expressed or the outputs generated from this research.

**Endnotes**

[1] The association between rubella in pregnancy and congenital anomalies was first reported by an Australian ophthalmologist in 1941 [32].

[2] It is estimated that 85% of mothers infected with rubella in the first trimester of pregnancy will deliver a child with congenital defects [28]. This figure comes from a large prospective study of maternal infection and foetal outcomes during the 1978/1979 rubella epidemic in the UK. The results showed that the risk of having a rubella-damaged child was 90% if infection occurs between 2 and 10 weeks, 34% between 11 and 12 weeks, 17% between 13 and 16 weeks and 3% between 17 and 18 weeks [28, 33].

[3] CRS is clinically confirmed in an infant if a qualified physician detects at least two of the following complications in the infant: cataract(s), congenital glaucoma, congenital heart disease, loss of hearing, or pigmentary retinopathy, or one of those complications and one of the following: purpura, splenomegaly, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease, or jaundice that begins within 24 h after birth [34].

[4] https://www.cdc.gov/mmwr/volumes/71/wr/mm7106a2.htm.

[5] https://apps.who.int/iris/bitstream/handle/10665/337779/WHO-EURO-2020-1421-41171-55983-eng.pdf?sequence=2&isAllowed=y.

[6] https://www.ecdc.europa.eu/sites/default/files/documents/measles-rubella-monthly-report-april-2020.pdf.

https://measles-rubella-monthly.ecdc.europa.eu/.

[7] The county is the main administrative local area in Ireland. In the 2016 Census micro-data at our disposal, a total of 26 counties are identified. These are: Carlow; Cavan; Clare; Cork; Donegal; Dublin; Galway; Kerry; Kildare; Kilkenny; Laois; Leitrim; Limerick; Longford; Louth; Mayo; Meath; Monaghan; Offaly; Roscommon; Sligo; Tipperary; Waterford; Westmeath; Wexford and Wicklow.

[8] We explain how semester of birth is defined and measured in Section 4.

[9] There have been a number of analyses of the foetal origins hypothesis (and the impact of early-life conditions more generally) in the Irish context. Pringle [42] examines the association between deaths from ischaemic heart disease in those aged 55–64 between 1981 and 1990 in Ireland and infant mortality around the time of their birth (between 1916 and 1935). The analysis is conducted at the county level. A weak, but statistically non-significant, correlation is found. Delaney et al. [43] also use infant mortality rates to proxy early-life living conditions, and examine the association between infant mortality rates and later-life disability (using data from the 2002 and 2006 Census of Population). They find a strong association between early-life infant mortality rates in the respondent's county of birth and later life disability, with the effects strongest for those from lower socio-economic groups.

[10] Before the vaccination era, rubella infection typically occurred in the spring [28].

[11] In an influential paper, Goodman-Bacon [49] shows that the TWFE estimator is a weighted average of many different "2 × 2" difference-in-differences (DiDs), each involving the comparison between a treated and an effective control group in a window before and after the treated group receives treatment. In some of these 2 × 2 DIDs, already-treated groups can act as effective comparison groups leading to the so-called "bad comparisons" problem. As these problematic late versus early comparisons are included in the weighted average, this can lead to biases of the estimated average treatment effect [50, 51].

[12] Due to data protection issues, this was the most disaggregated level of data available for month of birth in the 2016 Census micro-data.

[13] We also tested for parallel trends in health, disability and educational outcomes between the two groups of counties and found that there is no statistical difference in the three outcomes preceding the rubella outbreak.

[14] A total of 285 individuals are in poor health in our sample (285 = 3.0% x 9497). An increase of 0.5 percentage points in the probability of being

in poor health would translate into 332 individuals being in poor health (332 = 3.5% x 9497). 47 is calculated as 332 minus 285.

[15] See also https://www.nhs.uk/conditions/scarlet-fever/.

[16] There is some evidence of 'compensatory' behaviour in previous research; in an analysis of the impact of exposure to polio infection in early life, [62] find that while childhood disability increases the likelihood of early retirement and disability pension receipt at age 50, paralytic polio survivors are more likely to obtain a university degree and to go on to work in white-collar and computer-demanding jobs than their non-paralytic counterparts. These results are consistent with individuals making educational and occupational choices that reflect a shift in the comparative advantage of cognitive versus physical skills.

[17] To put these figures in context, in 2023, the rate of infant mortality in Ireland was 3.0 per 1000 live births [68].

[18] Data are presented for all counties, as cohort population sizes in each Census from 1961 to 2016 are only available for county of residence, rather than county of birth.

[19] See Figure A5 for data on the components of population change (natural increase and net migration) over the period 1951–2016 in Ireland.

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## Appendix A

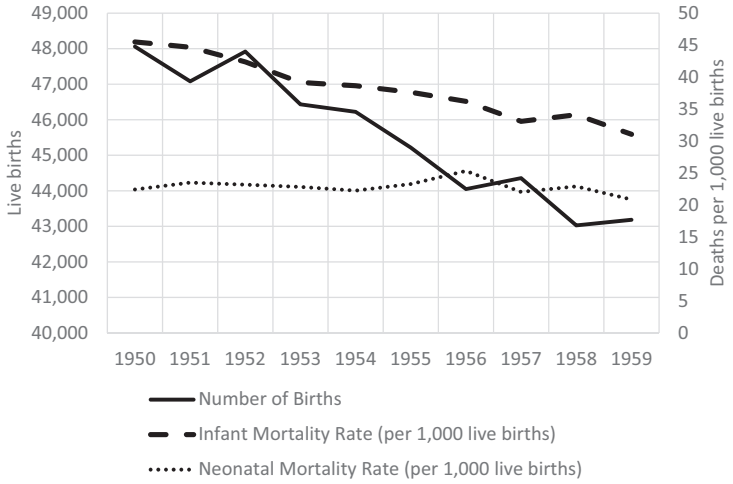


**FIGURE A1** | Number of live births, and infant and neonatal mortality rates, Ireland (excluding Dublin), 1950–1959. *Source:* Central Statistics Office [67].

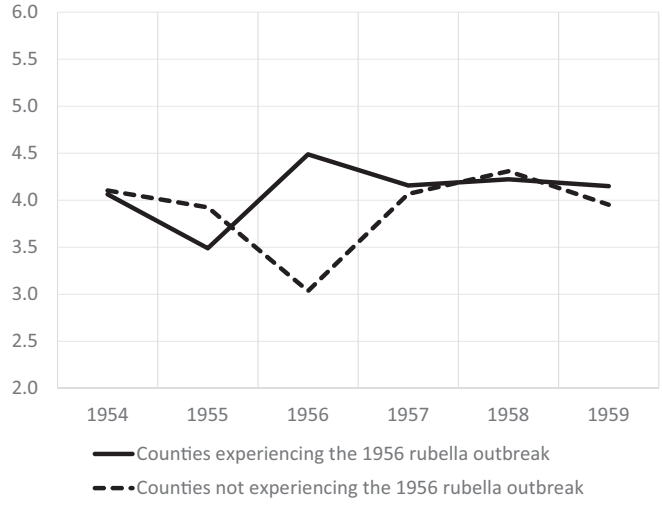


**FIGURE A2** | Neonatal mortality rate (per 1000 live births) from congenital malformations, Ireland (excluding Dublin), 1954–1959. *Source:* Central Statistics Office [67].

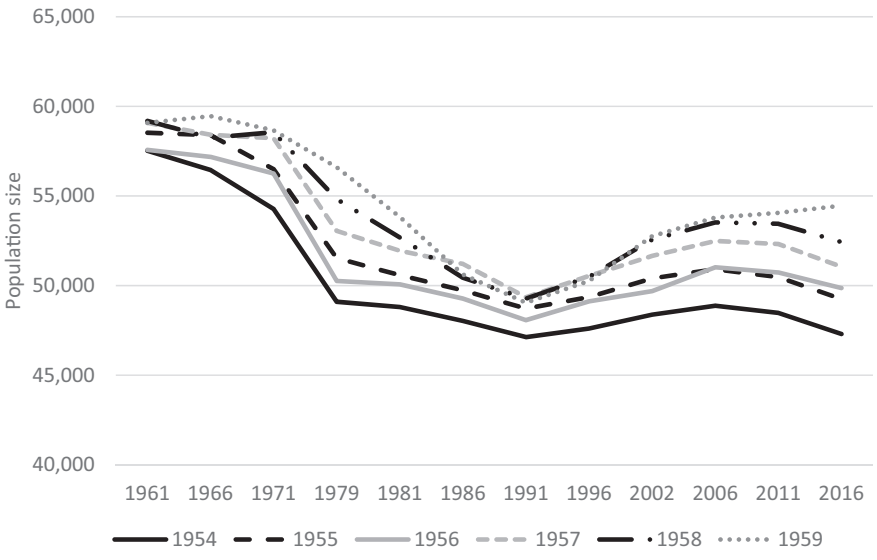


**FIGURE A3** | Population cohort sizes, Ireland, 1961–2016. *Source:* Central Statistics Office [69, 70].

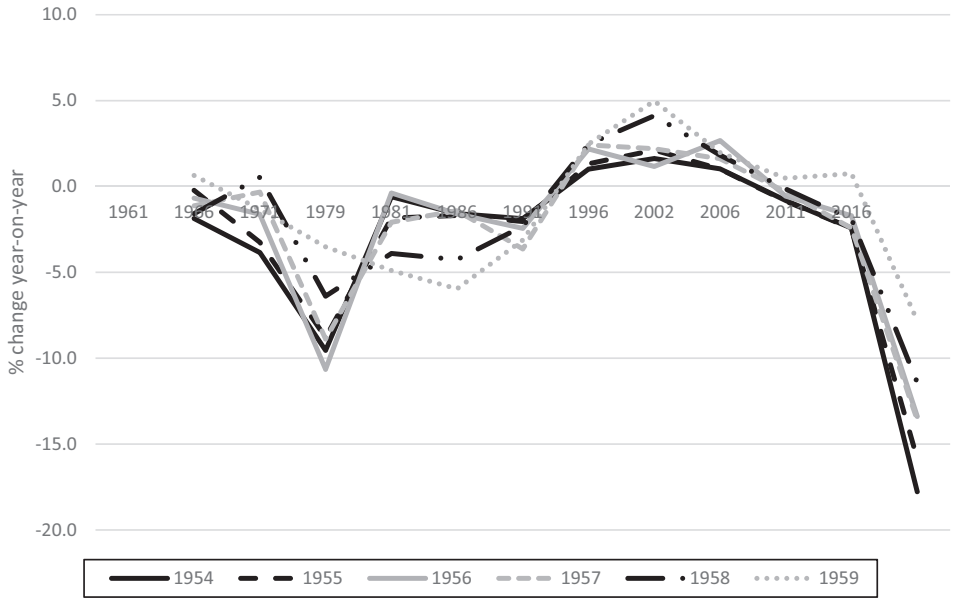


**FIGURE A4** | Population cohort growth rates, Ireland, 1961–2016. *Source:* Central Statistics Office [69, 70].

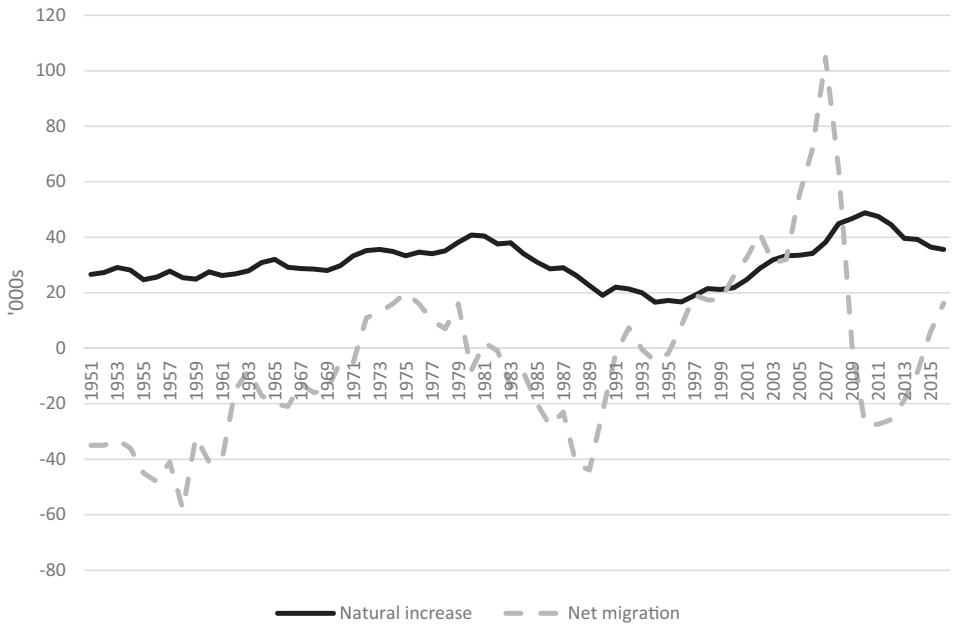


**FIGURE A5** | Components of population change (all ages/birth cohorts), Ireland, 1951–2016. *Source:* Central Statistics Office [67, 69, 70].