

# Long-term mortality effects of century crises: A warning from the past for the decades after COVID-19?

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Almost 3 years have passed since the first coronavirus disease 2019 (COVID-19) case was reported in Switzerland in spring 2020. A recent study has shown that COVID-19 has reached historic proportions as a crisis for Switzerland that has not been seen since 1918 [1]. In the last 3 years, numerous studies have been published on the short-term impacts of COVID-19, including the risk associated with COVID-19 infection during pregnancy and its impact on neonates [2–6]. All these studies have highlighted important direct or indirect effects of COVID-19 that occur during or shortly after infection. However, the long-term effects of the COVID-19 pandemic in the decades to come cannot be studied yet. This applies especially to the effects of in-utero exposure of current birth cohorts later in adulthood. Questions regarding the long-term health effects of maternal COVID-19 infection on offspring remain unanswered.

We must analyse history to understand how past crises affected in-utero exposure and long-term health consequences. Only a look back into history can reveal that such crises can have long-term effects. For example, the “Spanish flu” is the first well-documented crisis in Switzerland for which an in-utero exposed birth cohort can be studied across its lifespan. The “foetal origin hypothesis”, proposed by Barker [7, 8], argued that foetal malnutrition caused by hunger, infections, and stress can have lasting effects on future health. Based on this hypothesis in addition to studies using data from the 1918 pandemic, there is already evidence that poor foetal health may increase the risk developing various health issues, such as cardiovascular disease, hypertension, diabetes, and kidney problems, which lead to an increased risk of mortality [9–12].

In the last 200 years, Switzerland has been impacted by several severe crises despite the fact that the two world wars had less of an impact on Switzerland than other countries. In 1817, countless people died in Switzerland in the last large hunger crisis [13]. According to the historical literature, hundreds of pregnant women were undernourished, which led to prenatal malnutrition. In 1918/1919 and towards the end of World War 1, the Spanish flu struck Switzerland at a time when scarce supplies were having an increasing impact on the nutritional and health status of the population [14]. Experts believe that at least one-half of the population was infected by the influenza virus during the 1918 pandemic, especially younger adults, in-

cluding many young pregnant women [15]. Increased rates of preterm birth, still birth, and low-birth-weight neonates were observed as immediate impacts of the Spanish flu on pregnant women [16–18]. Modern medical literature states that suboptimal intrauterine conditions resulting from maternal malnutrition, hypoxia, psychological stress, or even mild exposure to an infectious disease can have lasting effects on foetal development and are often associated with reduced birth weight [19]. Therefore, if we consider the severe health crisis years in Switzerland over the last 200 years, how was the in-utero exposure of birth cohorts at that time associated with health and all-cause mortality later in life?

To emphasise the powerful effects of in-utero exposure on long-term mortality in Switzerland, I adapted the Lexis surface plots recently published by Jones et al. for England and Wales from 1910 to 2010 [20]. The Lexis surface plot was applied for the first time on Swiss data from 1876 to 2021 (figure 1) and showed the annual change in age-specific mortality. To calculate these changes, Swiss mortality and population data from 1876 to 2021 were obtained from the Human Mortality Database [21]. The figure shows the data categorised by sex. The x-axis represents the year of mortality, and the y-axis represents the age of the persons in the respective year. Orange and red represent an increase in mortality compared with the previous year, while blue and green represent decreased mortality.

First, we studied the vertical lines. A closer look at the year 1918 reveals a red vertical bar for men and women up to the age of 50 years. This reflects the high mortality of young adults due to the Spanish flu. In 2020, the first year of the COVID-19 pandemic, an orange bar is visible from age 70 years and older, indicating a higher mortality for older people in 2020 compared with 2019. The differences are not as large as in the case of the Spanish flu, where the bar is dark red; however, an increased mortality is still visible, more so in males than females.

To identify the effects on birth cohorts, the diagonal lines were considered. Each diagonal line corresponds to a birth cohort and the corresponding mortality effect later in life. The first prominent red diagonal line is visible from 1877 to 1908; it starts in 1877 at 59 years of age and increases to 90 years in 1908. This line represents the birth cohort of 1818, which was exposed in utero to the last severe hunger

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crisis in Switzerland in 1817. Across all years and ages, this birth cohort has higher mortality compared with earlier and later cohorts. Unfortunately, we cannot follow this birth cohort across all ages because Swiss data before 1877 is lacking.

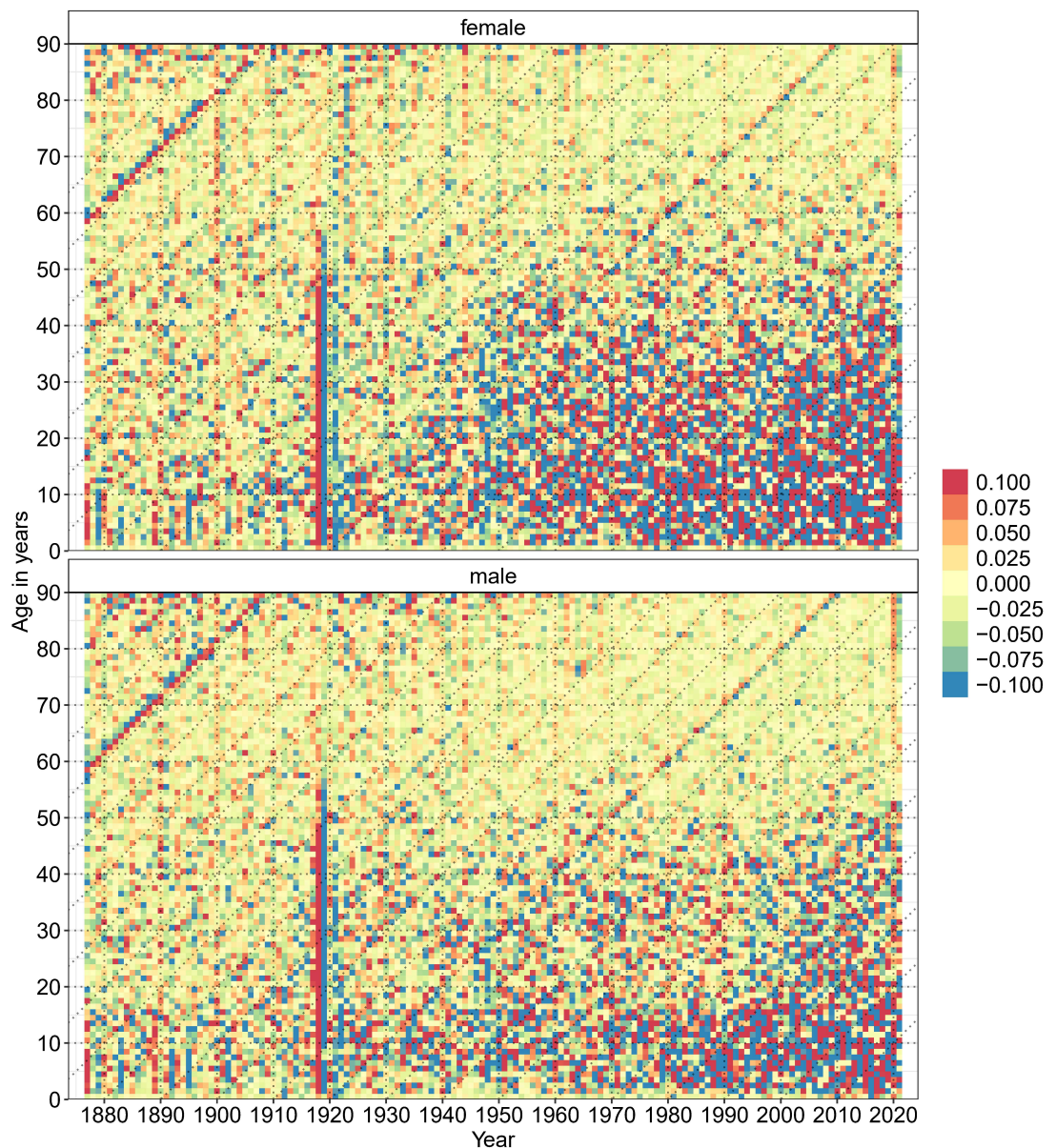
The next visible diagonal line represents the birth cohort of 1919 (in-utero exposure during the end of World War 1 and the Spanish flu). This diagonal line is especially prominent from the 1970s, when the birth cohort was aged 51 years and older. For males, the line is even clearly visible from 1919 onwards. This underlines the higher mortality risk of the 1919 birth cohort, especially from the age of 50 years. It remains unclear which causes of death were more prevalent in the 1919 birth cohort as compared to those of prior and following years. However, modern medical litera-

ture states that adverse neonatal health is associated with increased risk for type 2 diabetes, hypertension, and coronary heart diseases in later life [9], with the latter being associated with the greatest increased risk of mortality [22].

The red and blue points in figure 1 from the 1950s onwards, for ages up to 40 years, should not be interpreted. At those ages, mortality was very low due to the small sample size; therefore, the variance is large, as a minimal number of deaths leads to larger differences in the annual change in mortality.

Even if it is only visual and descriptive, this first small adaptation of a recently published method to analyse Swiss data clearly shows the impact of in-utero exposure to severe health crises in the past, not only in the immediate cri-

**Figure 1:** Lexis surface plot (adapted to Swiss data from Jones et al. [20]) for annual change in age-specific mortality. Orange and red represent an increase in mortality compared with the previous year, while blue and green represent decreased mortality. Vertical lines represent period effects, while diagonal lines represent cohort effects.



sis year, but also on the long-term mortality of the affected birth cohorts, even decades later.

Whether we will see similar patterns in the following decades for the 2020/2021 birth cohort is uncertain at this time. The only certainty is that many pregnant women were exposed to COVID-19 during the pandemic, and we do not yet know how this will affect the 2020/2021 birth cohort in adulthood and later life, even if the course of infection in the mothers was mild. However, the increased mortality of the 1918 and 1919 birth cohorts later in life should make us vigilant and remind us to monitor the birth cohorts of 2020/2021 in the future.

#### Acknowledgements

The author thanks Kaspar Staub, Frank Rühli, Nicole Bender, Joël Floris, Marcel Zwahlen and Olivia Keiser for support and previous collaborations.

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