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COMMENTARY

Eighty years of an influenza pandemic?

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Epidemiological studies in the *Developmental Origins of Health and Disease* field rely on early life markers. The utility of each marker is inherently dependent on its ability to mirror a specific and, if possible, modifiable early life exposure that affects health and disease in later life. For example, birth weight, while robustly predicting a wide range of outcomes, is a product of a multitude of mechanisms and gives little clue about the specific early life events, which ultimately could serve as targets for intervention.

In their article on the subject, Mazumder *et al.*[1] use a different proxy: birth during and after the 1918–1919 influenza pandemic. This major 'shock' serves as a natural experiment, which brings us much closer to the nature of early life adversity, in this case infection in the mother and the response of her body to combat that infection. The authors found that people who were born in the USA during the first quarter of 1919, in other words who as fetuses were in the mid or last trimester at the height of the pandemic, had higher rates of coronary heart disease. Higher rates of diabetes, by contrast, were associated with birth during the second quarter of 1919, corresponding to pandemic peak during the first or mid trimester. Both of these increases were confined to people born during a specific quarter of a year.

The paper is obviously timely during an ongoing H1N1 influenza pandemic. However, the paper is also of methodological significance. Date of birth is a potentially powerful early life marker and may be underused in *Developmental Origins of Health and Disease* epidemiology. Therefore, it is logical to first consider its potential caveats.

Obviously, the validity of date of birth as an early life marker depends on its validity as an indicator of a specific exposure, in this case maternal influenza. Are there alternative explanations to consider? Many of the 'natural experiments' used to study a specific exposure, for example, the Dutch Famine[2] or parental separation in Finland–Sweden and other child evacuations,[3] occurred during World War II and were accompanied by parallel exposures associated with a multitude of war strains. Are such events a concern during 1918–1919? The period was in many ways exceptional in countries that experienced World War I and its aftermath on own territory, including many European countries. However, parallel events are probably less likely to confound the effects of influenza for the civilian population in the USA. Moreover, most parallel events, or events occurring later to the same cohort, would be expected to extend their effects over a longer period of births.

Mazumder *et al.*[1] used self-reported diagnoses based on the US National Health Interview Survey. Self-report may increase the risk of outcome misclassification. This could introduce bias if the degree of outcome misclassification differed according to period of birth, which, however, seems unlikely. However, ischemic heart disease may be more likely to go undiagnosed in women.[4] For this reason, the authors' finding that the association of influenza exposure with ischemic heart disease was stronger in men than in women should be interpreted with caution. As to diabetes, its rates are very much dependent on the vigilance of the healthcare system to diagnose this often asymptomatic disorder. Subjects who report a diagnosis of diabetes may be more likely to have been brought to a physician's attention because of a complication of diabetes, including ischemic heart disease. Also the authors' calculations suggesting that most of the excess morbidity is attributable to mild cases of maternal influenza require caution. For ischemic heart disease, they report a 25.4% increase in prevalence for people born during the first quarter of 1919. As they report an overall prevalence of 5.4%, the excess prevalence translates to $5.4\% * 25.4\% = 1.4\%$ of all people born during this quarter. This number is lower than the 8% they estimate being born after maternal pneumonia, making it difficult to justify the conclusions related to mild maternal disease.

Does this study give any clue about potential mechanisms linking influenza exposure with disease in later life? Previous studies have suggested many adverse consequences after intrauterine exposure to influenza. While schizophrenia has probably received most attention,[5] the consequences are likely to extend over a much wider spectrum of human capital. Almond showed that people born in the USA in 1919, in particular the earlier half of the year, had throughout their

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adult lives lower indicators of socio-economic status, including educational attainment and income, than expected based on neighboring years' statistics.[6] Mazumder *et al.*[1] now extend these consequences to shorter adult height, also a proxy of human capital. These findings may in part underlie the associations with ischemic heart disease and diabetes, as both disorders are associated with lower socio-economic status and shorter height. However, while lower socio-economic status was associated with births over most of the year 1919,[6] increased risks of ischemic heart disease and diabetes were confined to shorter periods of births. This suggests additional mechanisms specific to these disorders.

The adverse fetal effects of influenza exposure may be associated with placental transfer of maternal immunoglobulins or cytokines or cortisol, or undernutrition of the mother during illness. While these mechanisms have been extensively studied in animals, there is little human data pointing to any particular mechanism in influenza. It is of note that in this study, ischemic heart disease was associated with exposure during later and diabetes during earlier gestation, which reverse to that found in the Dutch Famine studies,[2] suggesting that the mechanisms may be in part different from those operating during severe maternal undernutrition.

Life-long effects on the function of the immune system remain an intriguing possibility. The risk of coronary events increases five-fold during acute respiratory infection,[7] and preliminary evidence suggests that influenza vaccination may protect from coronary events.[8] The severity of immune response to influenza is affected by exposure to earlier influenza strains.[9] However, it is unclear whether influenza virus crosses the placenta and whether priming of a specific adaptive immune response to influenza can be expected after an intrauterine exposure. A possible consequence of this would be a stronger association between intrauterine influenza exposure and incident ischemic heart disease during influenza epidemics, which is a testable hypothesis. Alternatively, alterations in innate immune response, acting through acute response to pathogens or through chronic inflammation, may also contribute to the link between influenza exposure and adult disease. The data of Mazumder *et al.*[1] do not answer these questions, but they highlight their importance by illustrating the life-long burden of maternal influenza during pregnancy. Replicating these results for later influenza epidemics is of particular importance as, of all early life exposures, influenza is one of the most easily preventable.

Statement of interest

None.

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