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EDITORIAL

Consequences of a Great Crisis on Chronic Diseases: How Childhood Exposures May Shape Future Health

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History, as the saying goes, repeats itself. And, during these historical coronavirus disease 2019 (COVID-19) pandemic times, a rheumatologist may wonder—what does the COVID-19 pandemic mean for rheumatology patients (1)? No one knows for sure, of course. But, if history really does repeat itself, infants and toddlers worldwide may be at risk. In this issue of *Arthritis & Rheumatology*, VanEvery et al examine the association between early life exposure to a prolonged crisis and future risk of rheumatoid arthritis (RA) (2). Specifically, the authors analyze data collected from adult participants enrolled in the Kailuan Study in China who were exposed to the Great Chinese Famine (1959–1961) during early life.

Major historical crises, notwithstanding their obvious tragedies, provide the medical community opportunities to study the relationships between environmental stressors and disease. In fact, previous studies of natural disasters, including other famines around the world, have established a link between exposures to crises and chronic diseases such as diabetes, obesity, metabolic syndrome, and even osteoarthritis (3–5). These studies are often able to examine a large population over time, as is the case for the Kailuan Study cohort of over 101,510 participants. Interestingly, the authors were able to show that early life exposure to the Great Chinese Famine from 1959 to 1961, including in utero exposures, independently increased the risk of RA development later in life, especially in those who were exposed between ages 0 and 3 years (multivariate adjusted odds ratio 4.53). The increased risk of RA was the same among seropositive patients and seronegative patients, and there were no interactions observed between famine exposure and smoking or obesity on the risk of developing RA.

The impact of nutrition on health and chronic disease has been examined for many years across all major fields of research. Indeed, various metabolic pathways have linked nutritional precursors like NAD to sirtuins and aging that may have major implications for age-related phenotypes like osteoarthritis (6,7). Some have even linked early life exposure to famines with epigenetic changes that manifest as chronic disease later in life (8), while others have investigated the link between nutrition and chronic disease from the microbiome perspective (9). Therefore, any alterations in diet, including a lack of proper nutrition, are worth investigating, and future research endeavors that study the interactions between metabolism and immune homeostasis appear promising.

Now, while the observed association between early life nutrition and chronic diseases like RA are indeed intriguing, if not frightening for young parents, these studies require careful interpretation. For instance, it has been noted that studies involving the Kailuan Study database may require additional attention to appropriate controls when analyzing the link between famine exposure and chronic disease (10). In the study by VanEvery and colleagues, the authors control for age-related discrepancies by adjusting for age under 40 years and still discovered significant findings. Also, despite the large cohort of registered participants, the actual number of participants from a severe famine region was small, thereby limiting the statistical power of the study.

Furthermore, despite the historical context of a 3-year famine, famine exposure and nutritional exposure must not be confused. In the study by VanEvery and colleagues, and others like it, early life data such as birth weight and diet, which affirms the early life nutritional status of affected individuals, are not readily available. Therefore, any nutritional inferences are circumstantial at best. In fact, bearing in mind that the study population mostly consisted of participants from less-severe famine regions, one must remember that the Great Chinese Famine was not only a problem of food supply, but also one of "entitlement" and food distribution among various socioeconomic groups (11). Therefore, socioeconomic confounders also need to be considered.

Other significant confounders of famine-era studies include further environmental exposures that may have caused great impact on health outcomes of disease. For example, the time period of The Great Famine was also a time when the People's Republic of China heavily endorsed and enforced The Great Leap policies, which emphasized not only grain farming, but also industrial steel production in the general population (12). Heavy metal exposure during this time was the greatest from 1959 to 1960.

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Environmental exposures, such as heavy metals, are a known risk factor for developing RA (13), which further limits any nutritional inferences with regard to famine-era exposure and RA risk. Indeed, it has been shown that nutritional deprivation is not the only way that the immune system is altered during a famine or crisis, but exposure to stress in general may be a contributing factor. For example, stress in expectant mothers increases the risk of asthma in affected children, possibly related to altered glucocorticoid responses (14).

Based on these findings, several questions need to be answered. First, it is important to know whether famine modifies the association between RA and other health outcomes. It has been shown that Chinese famine exposure exacerbated the association between hypertension and cardiovascular disease (15). It is equally important to identify factors modifying the relationship between famine exposure and RA. Second, if the underlying mechanisms of RA are different for those exposed to famine than for those who were not exposed to famine, should the treatment and management also be different?

This historical examination of exposure to crisis in early life and future health risk is particularly relevant today. No matter what the single most important risk factor was at the time of crisis exposure, whether it be nutrition or otherwise, numerous studies of this kind have shown that early life exposure to historically stressful events increases the risk of chronic diseases like RA. Therefore, it is even more imperative for future prospective studies to identify modifiable risk factors and intervene before it is too late for future generations. Otherwise, history will indeed repeat itself.

AUTHOR CONTRIBUTIONS

Drs. Lee and Shi drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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