Famine alters metabolism for successive generations

12 December 2016, by David Orenstein

Major social upheavals during the Great Leap Forward are given some of the blame for a terrible famine that affected China in the late 1950s and early 1960s. Credit: Wikimedia Commons

The increased risk of hyperglycemia associated with prenatal exposure to famine is also passed down to the next generation, according to a new study of hundreds of families affected by widespread starvation in mid-20th Century China.

Hyperglycemia is a high blood glucose level and a common sign of diabetes. The new study in the *American Journal of Clinical Nutrition* reports that hundreds of people who were gestated during a horrific famine that afflicted China between 1959 and 1961 had significantly elevated odds of both hyperglycemia and type 2 diabetes. Even more striking, however, was that their children also had significantly higher odds of hyperglycemia, even though the famine had long since passed when they were born.

Public health researchers at Brown University and Harbin Medical University in China were able to make the findings by studying more than 3,000 local residents and their children. Some of the subjects were gestated during famine and some were gestated just afterward. Some of the studied offspring were born to two, one or no parents who had been famine-exposed.

This study population allowed the scientists, who interviewed and took blood samples from the participants in 2012, to make well-controlled, multigenerational comparisons of the effects of in utero famine exposure that would never be ethical to intentionally create.

"These were unique 'experiments,' so to speak, that were unfortunately done to those populations at a time when the society was under revolutionary, social and political upheavals.," said Dr. Simin Liu, the study's co-corresponding author and a professor of epidemiology and of medicine at Brown. "By studying these families we could determine multiple-generational exposure to nutritional factors and genetic interactions that occur due to famine."

A two-generation association

Among 983 people gestated during the famine years, 31.2 percent had hyperglycemia and 11.2 percent had type 2 diabetes. By comparison, among 1,085 people gestated just after the famine ended, the prevalence of hyperglycemia was 16.9 percent, and the prevalence of type 2 diabetes as 5.6 percent. Controlling for factors such as gender, smoking, physical activity, calorie consumption and body-mass index, the researchers calculated that in utero famine exposure was associated with 1.93-times higher odds of hyperglycemia and a 1.75 times greater chance of type 2 diabetes.

The next generation sustained the significant risk of hyperglycemia when both parents had been famine-exposed. Overall in the second generation,

hyperglycemia prevalence were 5.7 percent for 332 people with no famine-exposed parents, 10.0 percent for 251 people with famine-exposed fathers, 10.6 percent for 263 people with famine-exposed mothers, and 11.3 percent for the 337 people for whom both parents had famine exposure. Adjusting for all the same lifestyle factors, the offspring of two famine-exposed parents had 2.02 times the odds of hyperglycemia of people with no famine-exposed parents. The odds of hyperglycemia from one-parent exposure were also substantially elevated but not quite statistically significant.

The odds of type 2 diabetes were not statistically significant after adjustment for multiple comparisons among the second generation, but co-corresponding author Dr. Sun Changhao, professor of nutrition and dean of the School of Public Health at Harbin, noted that these people were only in their 20s and 30s and could still be at increased risk as they age and that the research team will continue to follow up on these participants.

How is this possible?

Because the study only shows an association between metabolic changes and in utero famine exposure, it can't prove causality or the biological mechanism underlying a cause. But prior research on the effects of famine in humans and in laboratory animals suggest that famine does indeed cause such health risks, the study authors said.

"It is indeed a remarkable finding that is consistent what with what one would have expected from prior findings from animal experiments," said lead author Jie Li, a Brown postdoctoral fellow.

A prior team's study in mice showed a multigenerational effect on metabolism, and other studies of famine exposure in people have produced evidence of changes in the endocrine systems and in prenatal gene expression in reproductive systems.

Liu said he hopes to continue working with colleagues and participants in China to further investigate how gene and environmental interaction may affect health outcomes across generations.

Findings of such work would have implications not only for improving biological understanding of mechanisms but also for clinical and public health interventions.

"Genetic, epigenetic reprogramming, and subsequent gene-diet interaction are all possible explanations," he said. "By establishing this Chinese famine cohort of families, we hope to conduct a much more comprehensive and in-depth assessment of the whole genome and epigenome along with metabolic biomarkers of these participants moving forward."

More information: J. Li et al, Prenatal exposure to famine and the development of hyperglycemia and type 2 diabetes in adulthood across consecutive generations: a population-based cohort study of families in Suihua, China, *American Journal of Clinical Nutrition* (2016). DOI: 10.3945/ajcn.116.138792

Provided by Brown University