First evidence that prenatal exposure to famine may lead to persistent epigenetic changes

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A study initiated by researchers at Columbia University Mailman School of Public Health and the Leiden University Medical Center in the Netherlands suggests that prenatal exposure to famine can lead to epigenetic changes that may affect a person's health into midlife. The findings show a trickle-down effect from pregnant women to the DNA of their unborn children and the timeframe over which such early damage can operate. While previous studies have suggested that adult disease risk may be associated with adverse environmental conditions early in development, these data are the first to show that early-life environmental conditions can cause epigenetic changes in humans that persist throughout life. The full study findings are published online in the *Proceedings of the National Academy of Science*.

The research indicates that children conceived during the Dutch Hunger Winter in 1944-45, caused by a food embargo on the Netherlands in World War II, experienced persistent detrimental health effects six decades later. The authors found that the children exposed to the famine during the first 10 weeks after conception had less DNA methylation of the imprinted IGF2 gene than their unexposed same-sex siblings.

By contrast, children exposed to the famine at the end of pregnancy showed no difference in methylation compared to their unexposed siblings. These findings support the conclusion that very early development is a crucial period in establishing and maintaining

epigenetic marks. Epigenetic changes, while not altering the DNA sequence, can alter which genes are expressed. Genes that might otherwise be activated could be silenced by epigenetic changes or vice versa, and this could impact an individual's risk for adverse health outcomes later in life.

"We believe that our study provides the first evidence that certain environmental conditions early in human development can result in persistent changes in epigenetic information," says L.H. Lumey, MD, MPH, PhD, associate clinical professor of Epidemiology at the Mailman School of Public Health and senior author. "If there are indeed relationships between adverse conditions during development and adult health, then these epigenetic changes might provide a mechanism to explain the link." Ezra Susser, MD, DrPH, co-author, and Anna Cheskis Gelman and Murray Charles Gelman Professor and chair of Epidemiology at the Mailman School, noted, "These findings are particularly intriguing in light of our reports on increased rates of schizophrenia after early gestational exposure to famine." Drs. Lumey and Susser are also leaders of the Imprints Center for Genetic and Environmental Lifecourse Studies at the Mailman School, which includes the Dutch Famine Study as one of its affiliated studies.

The findings also show that birth weight is not a good marker for individuals with changes in methylation. Epigenetic differences were found among individuals who were exposed to famine early in gestation who have normal birth weights. For comparison purposes, the researchers also studied individuals who were exposed late in gestation and who therefore had lower birth weights. They did not see methylation changes in this group however. The study used sibling controls to avoid many potential study biases.

"Our study illustrates that to monitor the crucial stages of early development, we can not rely on birth weight alone as an indicator of

maternal nutrition. We must use our knowledge of the crucial events that took place during that period," observes Dr. Lumey. As the next step, the Leiden group led by Drs. Heijmans and Slagboom will examine with Dr. Lumey the effect of famine on other human genes. They are also interested in the effect of other specific exposures during early development, including folic acid supplementation around conception as these may have an effect on methylation in the developing fetus.

"Understanding how epigenetic control responds to well defined early exposures may shed light on the link between development and health over a life time and ultimately suggest new ways to prevent human disease," said Dr. Lumey.

Source: Columbia University's Mailman School of Public Health