High-fat maternal diet can cause brain damage in the unborn child

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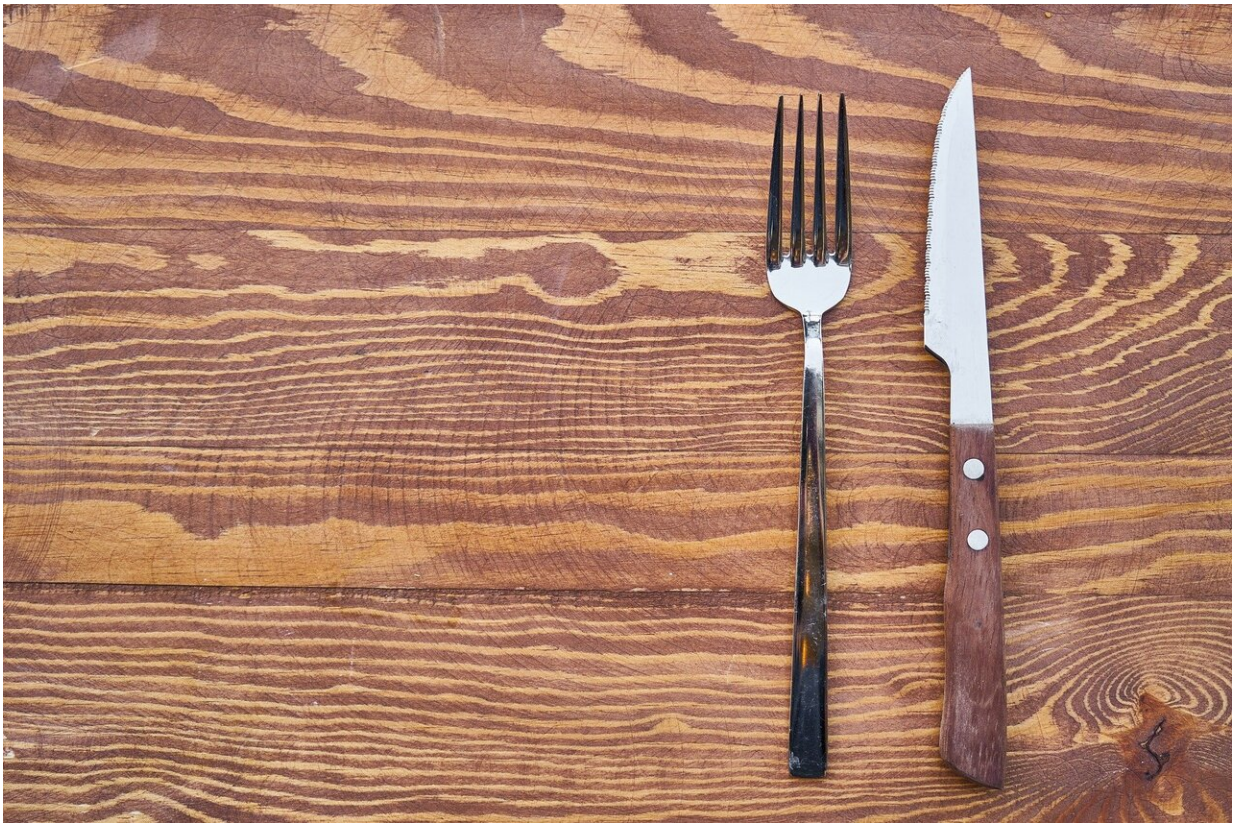

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A research team at MedUni Vienna's Center for Brain Research has found that high-fat maternal diets can cause life-long changes in the brains of the unborn offspring. When a pregnant woman consumes a diet

high in polyunsaturated omega-6 fatty acids, her body produces an excess of endogenous cannabinoids (endocannabinoids), which overload the fetal system and impair the development of healthy brain networks. Such a mechanism seems relevant to pathologies such as ADHD, schizophrenia and anxiety disorders. It is unlikely that such damage can simply be reversed by a subsequent change of diet.

The study, which has been published in the journal *Molecular Psychiatry*, examined in cell- and mouse models, how intake of high-fat diets throughout pregnancy (rich in polyunsaturated omega-6 fatty acids) impacts fetal brain development. When the mother consumes a high-fat diet during pregnancy, both mother and child produce an excess of endocannabinoids, which can even be transferred from the mother to the fetus. Endocannabinoids can then overload the corresponding cannabinoid receptors in the fetal brain and limit their ability to signal. As a result, nerve cells will no longer be able to correctly integrate into the brain to fulfil their prospective functions. The study also shows that these impairments persist throughout life of the affected offspring and can serve as critical triggers to developing psychiatric disorders later in life.

Endocannabinoids are substances produced by the body. They are part of the endocannabinoid system, which serves as a fundamental communication system in the brain as well as other organs. In the adult brain, endocannabinoids limit communication ('chemical neurotransmission') between neurons by binding to cannabinoid receptors. In the developing brain, endocannabinoids determine when and where neurons are positioned and if they form connections with each other. This means that any substance that influences either endocannabinoid levels or directly affects cannabinoid receptor function will inevitably impinge upon brain development.

"By acting like a 'stop signal,' a prolonged overload of endocannabinoids

impairs the developmental program of many neurons in the fetal brain," explains principal investigator Tibor Harkany, head of the Department of Molecular Neurobiology at MedUni Vienna's Center for Brain Research. "Persistently muting cannabinoid receptors, we believe, alters the epigenetic programs of affected nerve cells. Epigenetic mechanisms determine the pattern of gene expression in any cell. If damaged, the cells are no longer able to carry out their functions adequately. This will limit their ability to adapt their proper shape or select communication partners because of a shortage of proteins required as cellular building blocks or signaling molecules."

On a large scale, inhibiting the creation of connections between brain cells will impair the formation of important neuronal networks, the functional building blocks of the brain. This can result in psychiatric disorders such as ADHD, schizophrenia and anxiety disorders.

Damage is likely irreversible

"As far as we can tell, the pathological changes of nerve cells we have found are irreversible," explains Harkany. "It is of limited use to changing to a healthy, low-fat diet after birth when the damage has already been done." Although the study is based on animal models, Harkany stresses that other studies already indicate harmful effects in humans, while this report identifies the very molecular mechanisms that can also apply to humans.

Is treatment still possible?

"In order to find effective treatments, we will need active agents that directly intervene in the epigenetic regulation of gene expression," explains lead author Valentina Cinquina. "We have not yet trialled any such drugs but it is an exciting prospect to work on such interventions,

which can perhaps be used safely and effectively in the future." For example, so-called histone deacytylase Inhibitors (HDACs) are extensively tested for their treatment potential in Alzheimer's disease and various cancers.

More information: Valentina Cinquina et al. Life-long epigenetic programming of cortical architecture by maternal 'Western' diet during pregnancy, *Molecular Psychiatry* (2019). DOI: 10.1038/s41380-019-0580-4

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