Mouse study finds fathers on unhealthy diets can increase risk of cardiovascular disease in their daughters

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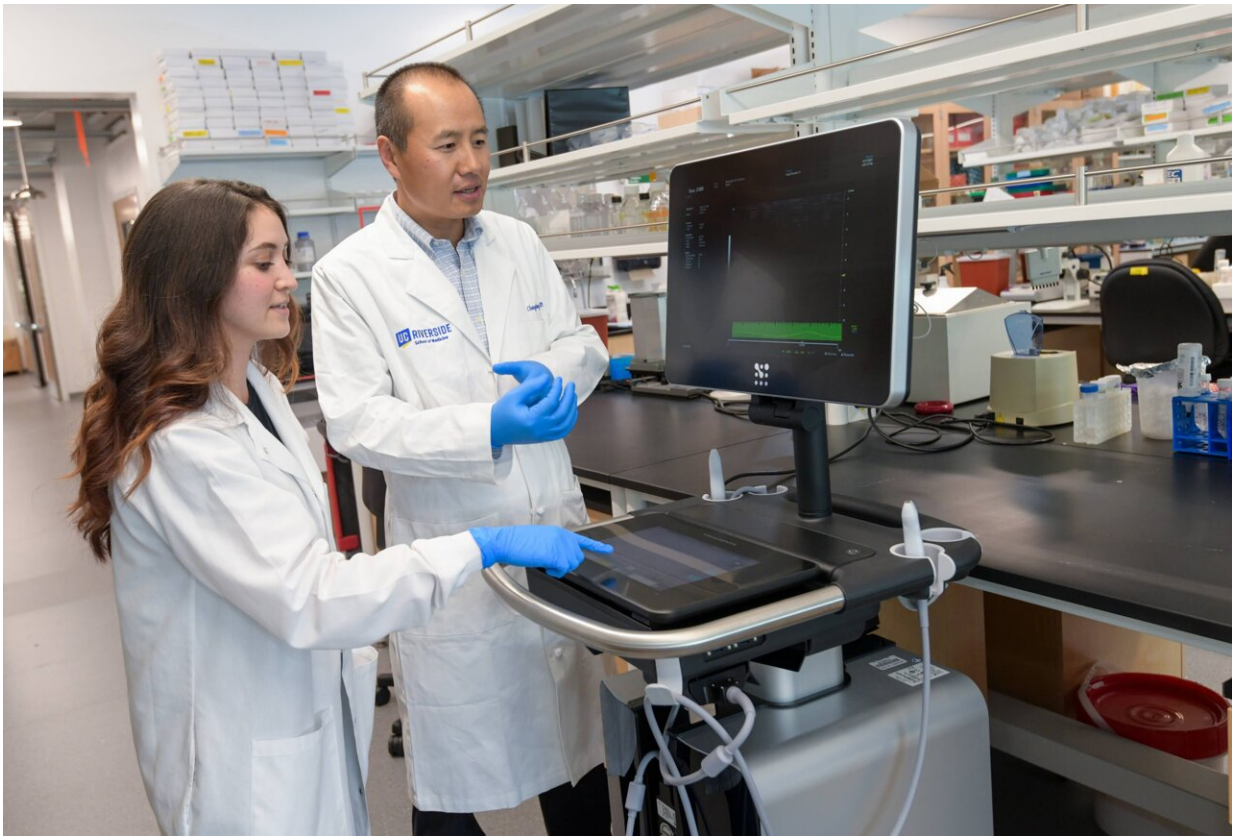

Changcheng Zhou (right) is seen here with Rebecca Hernandez, the first author of the research paper. Credit: Carrie Rosema.

When they become fathers, men who have an unhealthy, high-

cholesterol diet can cause increased risk of cardiovascular disease, or CVD, in their daughters, a University of California, Riverside-led mouse study has found.

The research, published in the journal *JCI Insight*, is the first to demonstrate this result seen only in female offspring.

CVD, the leading cause of death globally, is a group of disorders that affects the heart and blood vessels. Hypertension (high blood pressure) is a leading risk factor for CVD. In the United States, nearly 703,000 people died in 2022 from heart disease, the equivalent of one in every five deaths.

"It had been previously thought that sperm contribute only their genome during fertilization," said Changcheng Zhou, a professor of biomedical sciences in the School of Medicine and the study's lead author.

"However, recent studies by us and others have demonstrated that environmental exposures, including unhealthy diet, environmental toxicants, and stress, can alter the RNA in sperm to mediate intergenerational inheritance."

Ribonucleic acid, or RNA, is present in all living cells. Bearing structural similarities to DNA, this nucleic acid is essential for most biological functions in living organisms and viruses.

"Men who plan to have children should consider eating a healthy, low-cholesterol diet and reducing their own CVD risk factors," Zhou said. "These factors appear to affect their sperm in influencing the health of their female offspring. Our study suggests the sperm passes this information to the next generation."

The study focused on atherosclerosis, a chronic inflammatory disease

that is the leading cause of CVD. In atherosclerosis, plaque, a sticky substance made up of cholesterol, fat, and other substances in the blood, builds up in the walls of arteries. When the plaque hardens, it narrows the arteries, limiting blood flow to the body and reducing the supply of oxygen to tissues of vital organs.

Sperm contains an abundance of small non-coding RNA molecules, which are important for gene regulation and many cellular processes. When they are modified, their functions change significantly across various biological processes.

The researchers found that the small RNA molecules in sperm of mice fed a high-cholesterol diet undergo alterations in response to exposure to the diet. They also found that the altered small RNA molecules can affect early gene expression in mouse embryonic stem cells.

Zhou explained that most studies have focused on the effects of maternal factors on offspring health. The impact of paternal exposures on offspring health has been largely overlooked, he said.

"It is challenging to study the impact of parental exposures on chronic disease development in their offspring because the experiments, in general, are time consuming and require more resources and careful planning," he said.

The researchers are not clear why only female offspring are affected with CVD. In their experiments, Zhou and his team fed male genetically engineered mice a high-cholesterol diet, which caused them to have hyperlipidemia, a disorder that, if left untreated, can lead to heart disease and stroke.

These mice were then mated with female mice that were fed a regular, low-cholesterol diet. Their litter was also fed a low-cholesterol diet. The

female offspring were found to have two- to three-fold increases in atherosclerosis.

"Our study contributes to understanding the etiology of chronic diseases originating from parental exposures," Zhou said. "We hope our findings stimulate investigations of the impact of paternal exposures on offspring cardiovascular health in humans."

Zhou was joined in the study by Rebecca Hernandez, Xiuchun Li, Junchao Shi, and Tejasvi R. Dave of UCR; Tong Zhou of the University of Nevada, Reno; and Qi Chen of the University of Utah, Salt Lake City.

To study sperm RNA, the researchers used the PANDORA-seq method developed at UCR.

More information: Paternal hypercholesterolemia elicits sex-specific exacerbation of atherosclerosis in offspring, *JCI Insight* (2024). DOI: 10.1172/jci.insight.179291

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