Study reveals how 'forever chemicals' may impact heart health in older women

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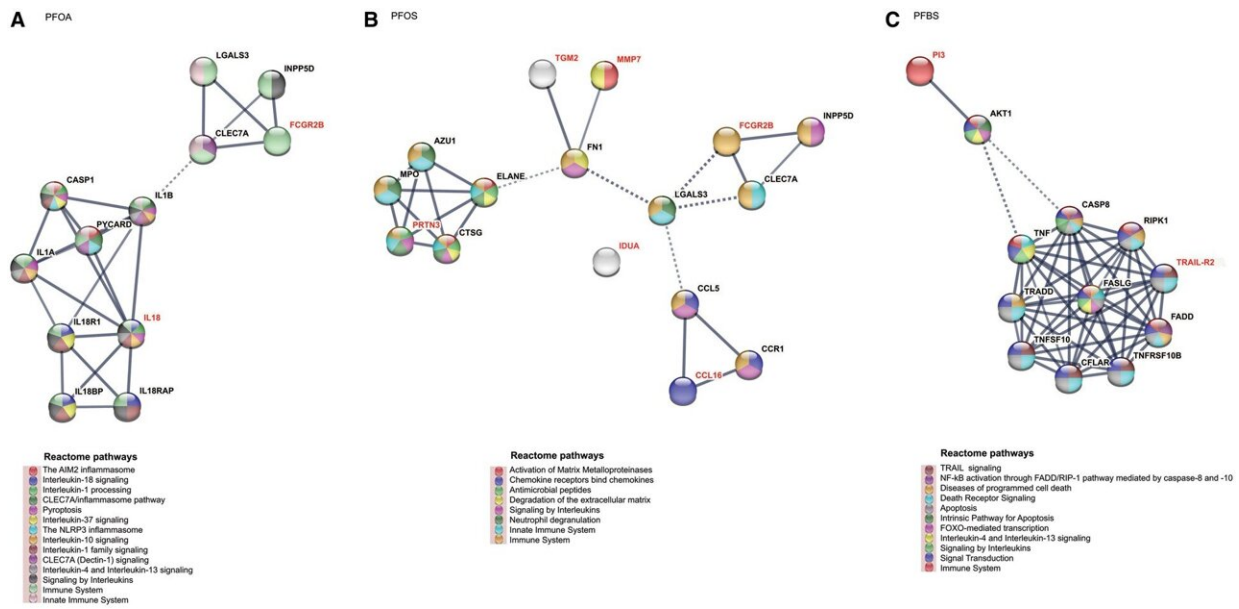

Reactome pathway analysis of protein-to-protein interaction associated with CMD. A) PFOA, B) PFOS, C) PFBS. Disease group proteins that had a significant association with PFAS and that meet a minimum high confidence interaction score of >0.700 are included. The edges between the protein nodes are proportional to the node indicates the reactome pathway with which the protein is associated. Credit: *Toxicological Sciences* (2024). DOI: 10.1093/toxsci/kfae065

New research from the University of Illinois Urbana-Champaign has linked multiple types of per- and polyfluoroalkyl substances (PFAS, also

known as "forever chemicals") with increased risk of cardiovascular diseases in postmenopausal women. Specifically, the study reveals how PFAS chemicals interact with pro-inflammatory pathways in older women, providing potential explanations for the increased risk.

The work is published in the journal *Toxicological Sciences*.

"Previous research suggests PFAS exposures may play a role in the development of cardiovascular disease during the menopause transition, but the biological mechanisms were not well understood," said lead study author Alicia Arredondo Eve, a postdoctoral researcher in the Department of Food Science and Human Nutrition (FSHN) in the College of Agricultural, Consumer and Environmental Sciences (ACES) at Illinois.

"We focused on specific PFAS chemicals as well as the cardiovascular diseases that are more common in older women."

It's difficult to escape PFAS. The man-made chemicals coat nonstick pans, waterproof clothing, food wrappers, receipts, and many more items we come in contact with daily, not to mention being present in much of our water supply. Some forms—and there are thousands of chemical variants—could persist in the environment for hundreds or thousands of years, hence their "forever chemicals" moniker.

Not surprisingly, studies suggest nearly all Americans carry PFAS in their blood and other bodily tissues. But premenopausal women are a little better off. Thanks to childbirth, breastfeeding, and their monthly menstrual cycle, premenopausal women expel more PFAS than men and postmenopausal women. After menstruation stops, PFAS accumulates and can cause problems.

Scientists are still piecing together exactly what PFAS chemicals do in

the body, but they appear to disrupt hormone signaling, interfering with normal reproductive and cardiovascular function. Most PFAS studies have focused on men or women during their reproductive years, but Arredondo Eve and co-author Zeynep Madak-Erdogan say postmenopausal women experience unique cardiovascular issues.

Motivated to fill the knowledge gap, the researchers analyzed data and samples from 70 postmenopausal women in Turkey. About a third of the women had been diagnosed with coronary artery disease, the world's leading form of heart disease. Another third had coronary microvascular disease, which is common in postmenopausal women. The remaining third had no sign of heart disease.

All of the samples were tested for the presence and levels of two long-chain "legacy" PFAS (no longer manufactured in the U.S.)—PFOS and PFOA—and a newer short-chain PFAS chemical known as PFBS. Next, the researchers used complex machine-learning techniques to analyze the relationships between the PFAS and various blood metabolites and proteins.

"When you have multiple factors and you want to focus on one or two, machine learning techniques are very efficient in reducing that number," said Madak-Erdogan, an associate professor in FSHN. "We found PFOS was closely associated with coronary artery disease, while PFOA was more predictive of coronary microvascular disease."

Further, the two chemicals interacted with proteins and pathways associated with inflammation. Chronic inflammation, triggered by stress, poor diet, infections, or other causes, is a risk factor for both coronary artery and coronary microvascular disease. While interactions with inflammatory pathways weren't a surprise given the diseases in question, an unexpected pattern emerged.

"The PFAS we studied affected the abundance of circulating pro-inflammatory factors differently. We did not expect that," Arredondo Eve said. "PFOA and PFOS aren't that different in terms of their chemical structure. Our results show you can't lump all PFAS together."

Higher levels of PFOA, which predicted coronary microvascular disease, were associated with higher levels of amino acids isoleucine and leucine and higher levels of pro-inflammatory cytokines. On the flipside, higher PFOS, related to coronary artery disease, was associated with lower isoleucine and leucine levels.

In addition to these opposing effects on metabolites, each PFAS was associated with a distinct set of pro-inflammatory proteins. The researchers say further preclinical research is needed to understand the mechanistic basis of these differences.

Ultimately, the study corroborates earlier research linking exposure to PFAS with cardiovascular disease in postmenopausal women, providing hints at how the chemicals interact with pro-inflammatory processes in the body. Unfortunately, the authors say there's not much women can do to get rid of PFAS after they get into the body. Instead, they caution women to avoid prolonged exposure by choosing PFAS-free clothing, cookware, and other materials.

"We need more education as to how we can reduce our exposure to PFAS," Madak-Erdogan said. "There also needs to be more action to regulate and mitigate these chemicals getting into the environment."

The team plans to continue studying the effects of PFAS on women's health.

More information: Alicia Arredondo Eve et al, PFAS and their association with the increased risk of cardiovascular disease in

postmenopausal women, *Toxicological Sciences* (2024). DOI: 10.1093/toxsci/kfae065