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Fatty Acid Profiles May Be Linked to PAH Risk

Ryan Quigley:
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I'm Ryan Quigley, and today I'll be discussing the relationship between circulating fatty acid profiles and the risk of pulmonary arterial hypertension, based on a large prospective cohort study published in *Medicine* in 2026.

But before we get into the study, let's briefly review pulmonary arterial hypertension, or PAH.

PAH is a progressive cardiopulmonary disorder characterized by elevated pulmonary arterial pressure and increasing pulmonary vascular resistance. Over time, these changes lead to vascular remodeling, right ventricular strain, and eventually right heart failure. Although the condition is relatively rare, it carries substantial morbidity and mortality. Increasing evidence suggests that metabolic abnormalities, including disruptions in lipid and fatty acid metabolism, may contribute to the development and progression of PAH.

Fatty acids are bioactive molecules involved in several key physiologic processes, including energy metabolism, cell membrane integrity, inflammatory signaling, and vascular regulation. While imbalances in fatty acid composition have been linked to cardiovascular diseases such as atherosclerosis and heart failure, their relationship with pulmonary vascular disease has not been extensively studied.

With that background in mind, let's turn to the study.

Investigators used data from the UK Biobank, a large prospective population cohort that includes extensive clinical and metabolomic information from more than 500,000 participants across the United Kingdom. In this analysis, researchers evaluated 272,057 individuals who had available metabolomic data and no prior diagnosis of pulmonary arterial hypertension at baseline.

Circulating fatty acid concentrations were measured from plasma samples using nuclear magnetic resonance–based metabolomics. The study assessed eight fatty acid biomarkers, including DHA; linoleic acid; monounsaturated fatty acids; omega-3 fatty acids; omega-6 fatty acids; polyunsaturated fatty acids; saturated fatty acids; and total fatty acids. Participants were then followed until the diagnosis of PAH, death, or the end of follow-up in October 2022.

At follow-up, investigators found that 1,420 participants developed PAH. Compared with individuals who did not develop PAH, these participants were generally older, more often male, and had higher body mass index and higher rates of comorbidities such as diabetes, hypertension, and cardiovascular disease.

The primary analyses demonstrated consistent inverse associations between circulating fatty acid levels and the risk of developing PAH. Each one-standard-deviation increase in several fatty acids—including DHA, linoleic acid, omega-3, omega-6, and polyunsaturated fatty acids—was associated with roughly an 11 to 19 percent reduction in PAH risk.

Even fatty acids that initially showed weaker associations, such as monounsaturated and saturated fatty acids, demonstrated modest inverse relationships with PAH risk after adjustment for demographic, lifestyle, and clinical variables.

Additional analyses suggested potential dose–response patterns. Higher fatty acid concentrations were associated with progressively lower PAH risk, with protective effects becoming more pronounced at higher levels.

The investigators also examined the timing of disease onset. Accelerated failure-time models indicated that individuals in the highest quartiles of certain fatty acids experienced delayed onset of PAH, in some cases by approximately five to ten years compared with individuals in the lowest quartile.

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Subgroup analyses suggested that the inverse associations were strongest among older adults, women, and individuals with lower body mass index. However, the protective associations were less consistent among participants with diabetes and among non-White populations, indicating that metabolic or demographic differences may influence these relationships.

From a mechanistic standpoint, several pathways may explain these findings. For example, omega-3 polyunsaturated fatty acids are known to reduce vascular inflammation and improve endothelial function, potentially through nitric-oxide–related signaling pathways. Experimental research also suggests that abnormalities in fatty acid metabolism may contribute to pulmonary vascular remodeling and mitochondrial dysfunction, both of which are implicated in PAH pathophysiology.

As with any observational study, there are important limitations. Fatty acid levels were measured at a single time point, which limits the ability to evaluate changes over time. In addition, PAH diagnoses were identified through hospital records and diagnostic codes rather than uniform right heart catheterization data, the clinical gold standard. Residual confounding also cannot be entirely excluded.

Overall, the findings suggest that circulating fatty acid profiles may be associated with the risk and timing of PAH. These metabolic signatures could potentially serve as biomarkers for identifying individuals at increased risk and may help inform future preventive or therapeutic strategies.

This has been an *AudioAbstract*, and I'm Ryan Quigley. To access this and other episodes in our series, visit ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.

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