Research links red meat intake, gut microbiome, and cardiovascular disease in older adults

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Does eating more meat—especially red meat and processed meat—raise the risk of cardiovascular disease, and if so, why? Despite intense study,

the impact of animal source foods on atherosclerotic cardiovascular disease (ASCVD) is vigorously debated, and the mechanisms underlying potential effects of animal proteins remain unclear. Understanding the impacts of meat consumption is particularly important in older adults, because they are the most vulnerable to heart disease yet may benefit from intake of protein to offset age-related loss of muscle mass and strength.

Over the years, scientists have investigated the relationship between heart disease and saturated fat, dietary cholesterol, sodium, nitrites, and even high-temperature cooking, but evidence supporting many of these mechanisms has not been robust. Recent evidence suggests that the underlying culprits may include specialized metabolites created by our gut bacteria when we eat meat.

A new study led by researchers at the Friedman School of Nutrition Science and Policy at Tufts University and Cleveland Clinic Lerner Research Institute quantifies the risk of ASCVD associated with meat intake and identifies underlying biologic pathways that may help explain this risk. The study of almost 4,000 U.S. men and women over age 65 shows that higher meat consumption is linked to higher risk of ASCVD—22 percent higher risk for about every 1.1 serving per day—and that about 10 percent of this elevated risk is explained by increased levels of three metabolites produced by gut bacteria from nutrients abundant in meat. Higher risk and interlinkages with gut bacterial metabolites were found for red meat but not poultry, eggs, or fish.

The study, published in the journal *Arteriosclerosis, Thrombosis, and Vascular Biology* (*ATVB*) on August 1, is the first to investigate the interrelationships between animal source foods and risk of ASCVD events, and the mediation of this risk by gut microbiota-generated compounds as well as by traditional ASCVD risk pathways such as blood

[cholesterol](#), [blood pressure](#), and blood sugar.

The research drew on years of data from the National Institutes of Health's (NIH's) Cardiovascular Health Study (CHS), a long-term observational study of risk factors for cardiovascular disease in Americans age 65 and older. Several blood biomarkers were measured at baseline and again during follow-up, including levels of the gut-microbiome generated trimethylamine N-oxide (TMAO) and two of its key intermediates, gamma-butyrobetaine and crotonobetaine, derived from L-carnitine, abundant in red meat.

Highlights

- In this community-based cohort of older U.S. men and women, higher intakes of unprocessed red meat, total meat (unprocessed red meat plus processed meat), and total animal source foods were prospectively associated with a higher incidence of ASCVD during a median follow-up of 12.5 years.
- The positive associations with ASCVD were partly mediated (8-11 percent of excess risk) by plasma levels of TMAO, gamma-butyrobetaine, and crotonobetaine.
- The higher risk of ASCVD associated with meat intake was also partly mediated by levels of blood glucose and insulin and, for processed meats, by systematic inflammation but not by blood pressure or blood cholesterol levels.
- Intakes of fish, poultry, and eggs were not significantly associated with ASCVD.

"These findings help answer long-standing questions on mechanisms linking meats to risk of cardiovascular diseases," said the paper's co-first author Meng Wang, a post-doctoral fellow at the Friedman School. "The interactions between red meat, our gut microbiome, and the bioactive metabolites they generate seem to be an important pathway for risk,

which creates a new target for possible interventions to reduce heart disease."

The 3,931 study subjects were followed for a median of 12.5 years, and their average age at baseline was 73. The study adjusted for established risk factors such as age, sex, race/ethnicity, education, smoking, physical activity, other dietary habits, and many additional risk factors.

"Interestingly, we identified three major pathways that help explain the links between red and processed meat and cardiovascular disease—microbiome-related metabolites like TMAO, blood glucose levels, and general inflammation—and each of these appeared more important than pathways related to blood cholesterol or blood pressure," said co-senior author, Dariush Mozaffarian, dean for policy at the Friedman School. "This suggests that, when choosing animal-source foods, it's less important to focus on differences in total fat, saturated fat, or cholesterol, and more important to better understand the health effects of other components in these foods, like L-carnitine and heme iron."

By leveraging extensive clinical and dietary data among a large elderly community, the research "links the gut microbial TMAO pathway to animal source foods and heightened atherosclerotic cardiovascular disease risks," said co-senior author Stanley L. Hazen, section head of preventive cardiology and rehabilitation at Cleveland Clinic. "The study also argues for dietary efforts as a means of reducing that risk, since dietary interventions can significantly lower TMAO."

More study is needed to determine if the findings are generalizable across ages and nationalities. The authors also noted that while microbiome biomarkers were directly measured in the blood, the dietary habits of study participants were self-reported, and study findings are observational and cannot prove cause-and-effect.

Ahmed Hasan, a medical officer and program director in the Atherothrombosis & Coronary Artery Disease Branch at the National Heart, Lung, and Blood Institute, part of the NIH, agrees. "While more studies are needed, the current reports provide a potential new target for preventing or treating heart disease in a subgroup of people who consume excessive amounts of red meat," said Hasan, who was not a part of the study.

For now, consumers are encouraged to follow current recommendations for a heart-healthy lifestyle, including adapting a [healthy diet](#) that is rich in vegetables, fruits, whole grains, and other heart-healthy foods, NHLBI's Hasan said. Other heart-healthy lifestyle changes also include aiming for a healthy weight, managing stress, managing blood pressure, getting more exercise, getting adequate sleep, and quitting smoking, he added.

Higher levels of TMAO, related metabolites linked to higher risk of death

The *ATVB* study is part of ongoing collaboration among scientists at the Friedman School and Cleveland Clinic to uncover the role that the gut microbiome plays in human health, especially cardiovascular health. In a paper in [JAMA Network Open](#) in May, many of the same researchers reported that TMAO and related metabolites in [older adults](#) are positively associated with a higher risk of death whether deaths were related to cardiovascular disease or another disease. Participants with the highest levels of plasma TMAO and its biomarkers had a 20 to 30 percent higher risk of death compared with those having the lowest levels.

This study included more than 5,000 participants from the CHS. Findings were notable because there have been few studies of TMAO

and risk of death in the general population; previous research typically looked at clinical patients with underlying conditions such as diabetes, kidney disease, and heart disease. While identified risk factors are concerning, the good news is that TMAO levels are potentially modifiable. "Now that we know more about the severity of risks associated with TMAO, we can explore effective approaches to change these levels in the body," said the paper's co-first author, Amanda Fretts of the University of Washington Department of Epidemiology.

Both the *ATVB* and *JAMA Network Open* studies support the importance of the microbiome and specific metabolites to human health, with the *ATVB* paper specifically linking the gut microbiome with meat intake, and impacts on heart health.

On the *ATVB* paper, Zeneng Wang of Cleveland Clinic was co-first author. On the *JAMA Network Open* paper, Hazen was co-first author; Rozenn Lemaitre of the University of Washington and Mozaffarian were co-senior authors.

  More information: Dietary Meat, Trimethylamine N-Oxide-Related Metabolites, and Incident Cardiovascular Disease Among Older Adults: The Cardiovascular Health Study, *Arteriosclerosis Thrombosis and Vascular Biology* (2022). DOI: 10.1161/ATVBAHA.121.316533

Amanda M. Fretts et al, Association of Trimethylamine N-Oxide and Metabolites With Mortality in Older Adults, *JAMA Network Open* (2022). DOI: 10.1001/jamanetworkopen.2022.13242

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