# Study shows gut bacteria byproduct predicts heart attack and stroke

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A microbial byproduct of intestinal bacteria contributes to heart disease and serves as an accurate screening tool for predicting future risks of heart attack, stroke and death in persons not otherwise identified by traditional risk factors and blood tests, according to Cleveland Clinic research published today in *The New England Journal of Medicine*.

The research team was led by Stanley Hazen, M.D., Ph.D., Vice Chair of Translational Research, Chair of the Department of Cellular and Molecular Medicine for the Lerner Research Institute and section head of Preventive Cardiology & Rehabilitation in the Miller Family Heart and Vascular Institute at Cleveland Clinic, and W.H. Wilson Tang, M.D., Department of Cardiovascular Medicine in the Miller Family Heart and Vascular Institute and Lerner Research Institute.

The current study is an extension of Dr. Hazen's previous work, in which he found that a chemical byproduct called trimethylamine N-oxide (TMAO) is produced when intestinal bacteria digest the nutrient phosphatidylcholine, commonly known as lecithin. The prior research showed that TMAO levels in the blood were associated with heart disease. Dr. Hazen and colleagues have now confirmed that gut flora are essential in forming TMAO in humans and demonstrated a relationship between TMAO levels and future cardiac events like heart attack, stroke, and death—even in those with no prior evidence of cardiac disease risk.

To demonstrate the role of gut flora in forming TMAO, human subjects were asked to eat two hard-boiled eggs (a common dietary source of lecithin) and a capsule of labeled lecithin (as a tracer). After ingestion, TMAO levels in the blood increased. However, when these same subjects were given a brief course of broad-spectrum antibiotics to suppress their gut flora, their TMAO levels were suppressed, and no additional TMAO was formed, even after ingesting lecithin. These results demonstrated that the intestinal bacteria are essential for the formation of TMAO.

In the second phase of the study, the researchers measured TMAO levels in a large, independent, clinical cohort – consisting of more than 4,000 adults undergoing cardiac evaluation at Cleveland Clinic – over a three-year follow-up period. They found that higher TMAO blood levels were associated with higher future risks of death and nonfatal heart attack or stroke over the ensuing three-year period, independent of other risk factors and blood test results. These results complement those of another recent study of Dr. Hazen's linking gut flora metabolism of a structurally similar nutrient found in animal products, carnitine, to TMAO production and heart attack risk.

"Heart disease remains the No. 1 killer, and while we know how to reduce cholesterol, treat blood pressure, and reduce cardiac risks through diet and other interventions, a substantial residual risk still remains," Dr. Hazen said. "We need to find new pathways to attack heart disease, and these findings strongly suggest that further research into the involvement of gut microbiome in the development of cardiovascular disease could lead to new avenues of prevention and treatment of heart disease."

Dr. Hazen further suggested, "These studies show that measuring blood levels of TMAO could serve as a powerful tool for predicting future cardiovascular risk, even for those without known risk factors. More studies are needed to confirm that TMAO testing, like cholesterol, triglyceride or glucose levels, might help guide physicians in providing individualized nutritional recommendations for preventing cardiovascular disease. Our goal is not to suggest dietary restrictions of entire food groups. Eggs, meat and other animal products are an integral part of most individuals' diets. Our work shows, however, that when digesting these foods, gut flora can generate

a chemical mediator, TMAO, that may contribute to cardiovascular disease."

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