

# Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis

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## Abstract

Intestinal microbiota metabolism of choline and phosphatidylcholine produces trimethylamine (TMA), which is further metabolized to a proatherogenic species, trimethylamine-*N*-oxide (TMAO). We demonstrate here that metabolism by intestinal microbiota of dietary L-carnitine, a trimethylamine abundant in red meat, also produces TMAO and accelerates atherosclerosis in mice. Omnivorous human subjects produced more TMAO than did vegans or vegetarians following ingestion of L-carnitine through a microbiota-dependent mechanism. The presence of specific bacterial taxa in human feces was associated with both plasma TMAO concentration and dietary status. Plasma L-carnitine levels in subjects undergoing cardiac evaluation ( $n = 2,595$ ) predicted increased risks for both prevalent cardiovascular disease (CVD) and incident major adverse cardiac events (myocardial infarction, stroke or death), but only among subjects with concurrently high TMAO levels. Chronic dietary L-carnitine supplementation in mice altered cecal microbial composition, markedly enhanced synthesis of TMA and TMAO, and increased atherosclerosis, but this did not occur if intestinal microbiota was concurrently suppressed. In mice with an intact intestinal microbiota, dietary supplementation with TMAO or either carnitine or choline reduced *in vivo* reverse cholesterol transport. Intestinal microbiota may thus contribute to the well-established link between high levels of red meat consumption and CVD risk.

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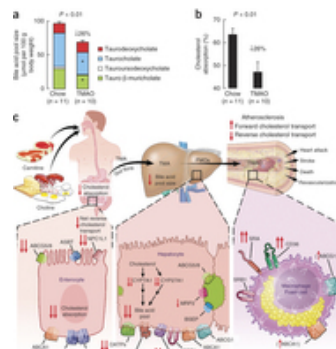
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Figure 6: Effect of TMAO on cholesterol and sterol metabolism.



(a,b) Measurement of total bile acid pool size and composition (a) and cholesterol absorption (b) in adult female (>8 weeks of age) *Apoe*<sup>-/-</sup> mice on normal chow diet versus diet supplemented with TMAO for 4 weeks.

Data are expressed as mean ± SEM.

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### Contributions

R.A.K. participated in laboratory, mouse and human studies, assisted in statistical analyses, helped design the experiments and drafted the manuscript. Z.W. performed the initial metabolomics study and assisted with mouse and mass spectrometry analyses. B.S.L. synthesized d3- and d9-carnitine for studies, assisted with mass spectrometry analyses and helped draft the manuscript. E.B.B. and X.F. assisted in performance of mass spectrometry analyses of the large human clinical cohort study. Y.W. and L.L. performed the statistical analyses and critically reviewed the manuscript. J.D.S. helped with aortic root atherosclerosis analyses and critical review of the manuscript. J.A.D. assisted in experimental design. J.A.B. and B.T.S. assisted in laboratory and mouse experiments. E.O. and A.J.L. performed and helped interpret mouse cecal microbiota analyses. J.C., F.D.B., H.L., G.D.W., J.D.L. and R.M.K. assisted in human subject microbiota analyses and helped interpret human microbiota data. M.W. and J.M.B. assisted with measurement of bile acid pool size and helped with critical review of the manuscript. W.H.W.T. helped with human studies and critical review of the manuscript. S.L.H. conceived of the idea, helped design the experiments, provided the funding for the study and helped draft and critically revise the manuscript.

### Competing financial interests

Z.W. and B.S.L. are named as co-inventors on pending patents held by the Cleveland Clinic relating to cardiovascular diagnostics and have the right to receive royalty payments for inventions or discoveries related to cardiovascular diagnostics from Liposciences. W.H.W.T. received research grant support from Abbott Laboratories and served as a consultant for Medtronic and St. Jude Medical. S.L.H. and J.D.S. are named as co-inventors on pending and issued patents held by the Cleveland Clinic relating to cardiovascular diagnostics and therapeutics patents. S.L.H. has been paid as a consultant or speaker by the following companies: Cleveland Heart Lab., Esperion, Liposciences, Merck & Co. and Pfizer. He has received research funds from Abbott, Cleveland Heart Lab., Esperion and Liposciences and has the right to receive royalty payments for inventions or discoveries related to cardiovascular diagnostics from Abbott Laboratories, Cleveland Heart Lab., Frantz Biomarkers, Liposciences and Siemens.

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### Supplementary information

#### PDF files

1. Supplementary Text and Figures (2 MB)  
Supplementary Tables 1–5, Supplementary Figures 1–23 and Supplementary Methods