Editorial

Pressing the trimethylamine *N*-oxide narrative

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We read with interest the correspondence titled "Gut Microbe-Generated Trimethylamine *N*-Oxide from Dietary Choline is Prothrombotic in Subjects", published by Zhu *et al.* in the journal *Circulation* (1). This work builds on an emerging body of evidence which has suggested a role for the gut-derived metabolite, trimethylamine *N*-oxide (TMAO), in the development of cardiovascular disease (CVD). This current study is an important clinical test of hypotheses generated from innovative preclinical and observational evidence, and seeks to build upon the nature of TMAO's relationship with CVD risk in humans. To assess this relationship, Zhu *et al.* enrolled 18 subjects (10 omnivores and 8 vegetarians) and provided choline bitartrate as a supplement (450 mg choline/day) for 2 months. Following choline supplementation, fasting plasma TMAO concentrations increased and were associated with increased ADP-induced platelet aggregation, an effect that was partially blunted by aspirin.

While the results of this trial are enticing and add to the evolving TMAO story, history reminds us to be cautious about the preemptive translation of this evidence into public health and clinical recommendations. The field of nutrition has seen multiple instances where promising associations, coupled to preclinical evidence and trials with surrogate outcomes, have not yielded clear evidence of benefits in large randomized controlled trials, and in some cases, have led to unintended harm (2-5). This current trial was relatively small, with no control group or random treatment allocation, and utilized a single, *ex vivo* surrogate outcome without established thresholds to assess thrombotic risk (6,7). Despite provocative results that appear in line with some previous animal evidence, caution is warranted in their interpretation. Indeed, not all cohort studies have found associations between choline, TMAO and CVD risk (8,9), and many have not accounted for confounding factors, such as impaired kidney function, insulin resistance and an altered gut microbiome (10). Additionally, not all animal models have found an adverse effect of TMAO on cardiovascular health. In ApoE knockout mice engineered to express human cholesteryl ester transfer protein (CETP), a protective effect of TMAO on the atherosclerotic process was observed suggesting that the lipid environment interacts with TMAO to impact CVD pathogenesis (11).

Interpretation of these findings and their relevance to dietary guidance for the public and patients remains challenging, despite widespread media oversimplification of the results of this study (12). The dose of choline supplemented in this study was relatively large (approximating recommended intake levels) and administered in addition to background dietary choline intakes. Furthermore, the form of choline utilized in this study was choline bitartrate, a water-soluble form of choline which serves as a potent substrate for microbial production of TMA at high doses; however, foods are comprised of primarily phosphatidylcholine, a relatively poor substrate for TMA biosynthesis (13-15). Whether the lower TMAO levels achieved by consumption of foods sources of phosphatidylcholine, such as eggs, affects thrombotic risk remains to be investigated in a trial. While not focused on in media coverage, extrapolation of these results to TMA/TMAO containing foods, such as fish, is particularly challenging, given the long-standing recommendation to consume fatty fish rich in long chain –3 fatty acids to reduce the risk of CVDs. In a recent study, a commonly consumed fish (cod) produced substantially higher TMAO levels than eggs and beef (15). The inverse association between fish

consumption and CHD risk suggests that either TMAO is not a causal factor in disease development or that other factors in the food matrix (i.e., –3 fatty acids) may modify the potential effect of TMAO (16,17).

As animal model, epidemiological and clinical data continue to emerge regarding the role of TMAO in cardiovascular health, it appears that many factors, such as age, comorbidities, the gut microbiome, and nutrient intakes, modify the relationship between TMAO and disease risk. Whether these risks are causal and for whom they are relevant requires further evidence from randomized controlled trials. Any recommendations to modify choline, carnitine and/or TMA/TMAO intakes must be targeted at specific populations and consider the potential unintended consequences of reducing relevant food sources and other associated nutrients. For example, misrepresentation of the relationship between choline and health may have negative impacts on subsets of the population, such as pregnant women, for whom choline needs are high (18,19). Future trials employing gold standard designs with adequate power, in defined populations, using an array of pre-specified surrogate outcomes assessing thrombotic risk, and advanced statistical modeling to account for relevant confounding factors and relevant interactions will be critical to advancing our understanding TMAO's role in cardiovascular health.

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Footnote

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