Nutrition, Metabolism and Cardiovascular Diseases 35 (2025) 103908

Contents lists available at ScienceDirect

Nutrition, Metabolism and Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Systematic Reviews and Meta-analyses

Circulating trimethylamine N-oxide and cardiovascular, cerebral, and renal diseases including mortality: Umbrella review of published systematic reviews and meta-analyses

Rima Obeid [a,*], Lorenz Mohr [a], Bryan A. White [b], Gunnar H. Heine [c,d], Insa Emrich [e], Juergen Geisel [a], R. Colin Carter [f,g]

[a] Department of Clinical Chemistry and Laboratory Medicine, Saarland University Hospital, Homburg, Saar, Germany
[b] University of Illinois, Department of Animal Sciences; and Fellow American Academy of Microbiology, 1207 W. Gregory Drive, Urbana, Il, 61801, United States
[c] Agaplesion Markus Hospital, Medical Clinic II, Wilhelm-Epstein Straße 4, D-60431, Frankfurt am Main, Germany
[d] Department of Internal Medicine IV–Nephrology and Hypertension, Saarland University Hospital and Saarland University Faculty of Medicine, D-66421, Homburg, Germany
[e] Saarland University Medical Center, Department of Internal Medicine III, Cardiology, Angiology, and Intensive Care Medicine, Homburg, Germany
[f] Departments of Pediatrics and Emergency Medicine and the Institute of Human Nutrition, Columbia University Irving Medical Center, New York, NY, United States
[g] Columbia University Vagelos College of Physicians and Surgeons, New York, NY, United States

ARTICLE INFO

Handling Editor: Dr L D'Erasmo

Keywords:
Trimethylamine-N-Oxide
Cardiovascular
Stroke
Risk factor
Prognostic factor

ABSTRACT

Aims: Several systematic reviews/meta-analyses of observational studies have demonstrated associations between circulating trimethylamine-N-oxide (TMAO) and cardiovascular, cerebral, and renal diseases, including mortality. However, causal roles for TMAO in these diseases are controversial. Interventions are lacking to show whether lowering TMAO in clinical trials could reduce the risks of these diseases. TMAO could still serve as a prognostic marker for the mentioned outcomes, but investigating this potential role requires robust methodologies. We conducted a systematic search and critical evaluation of published systematic reviews/meta-analyses in the field.

Data synthesis: We identified 27 systematic reviews/meta-analyses on the association between TMAO and stroke (n = 7), cardiovascular disease including cause-specific and/or all-cause mortality (n = 14), and other related outcomes (n = 6). The majority of the systematic reviews/meta-analyses found higher blood TMAO concentrations in patients who were positive for the outcomes. Primary studies included populations with multiple risk factors for the given outcomes and did not sufficiently account for potential confounders. Prospective studies examining associations between baseline TMAO and subsequent disease outcomes in healthy populations were entirely absent. Furthermore, we identified serious flaws in methods, conduct and reporting in the majority of the published systematic reviews/meta-analyses, thus leading to critically low confidence in the results.

Conclusions: High quality systematic reviews/meta-analyses examining the associations between TMAO and cardiovascular or cerebral disease are needed to examine potential causal and/or predictive roles of TMAO in these diseases. This study is registered at the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42024534940).

1. Background

Trimethylamine-N-oxide (TMAO) is the product of N-oxidation of trimethylamine (TMA) by the hepatic Flavin-containing monooxygenase-3 (FMO3). TMA is produced by the effect of gut bacteria on dietary choline, betaine, or carnitine. Consumption of red meat (rich in carnitine [1]), fish or sea-food, egg and dairy products [2–7] is associated with higher plasma TMAO concentrations, though not all

Abbreviations: AMSTAR, A MeaSurement Tool to Assess systematic Reviews; CVD, cardiovascular disease; FMO-3, Flavin-containing monooxygenase-3; MACE, major adverse cardiac and cerebrovascular event; PRIOR, preferred reporting items for overviews of reviews; PROSPERO, International Prospective Register of Systematic Reviews; TMAO, trimethylamine-N-oxide.

* Corresponding author.
E-mail address: Rima.obeid@uks.eu (R. Obeid).

https://doi.org/10.1016/j.numecd.2025.103908
Received 27 November 2024; Received in revised form 2 February 2025; Accepted 7 February 2025
Available online 8 February 2025

studies confirmed this association [2,8,9]. In healthy adults, plasma concentrations of TMAO range between 2.5 and 4.0 μmol/L. TMAO concentrations may increase by > 20 fold in patients on renal replacement therapy due to impaired glomerular filtration of TMAO [10,11].

In human observational studies, elevated plasma concentrations of TMAO have been associated with cardiovascular diseases [12–15], type 2 diabetes [16,17], impaired kidney function [18–20], and all-cause mortality [12,21]. Other studies have documented a lack of associations between TMAO and various cardiovascular diseases [22,23] or all-cause mortality, even in people with markedly high TMAO concentrations [11]. Of note, adjustment for renal function may abolish the associations between plasma TMAO and vascular or renal outcomes [24], suggesting that renal dysfunction is a major confounder in studies including adults with significant illnesses.

The basis for postulating a causal role for TMAO in atherosclerosis in humans has mainly been results from animal studies and statistical associations in observational human studies, both of which have inherent limitations with regard to causality conclusions. Some mechanisms that were discussed include vascular inflammation [25], thrombosis [26], macrophage foam cell formation [27], and enhancement of tubulointerstitial fibrosis and collagen deposition that causes renal injury [28]. Suppression of intestinal flora was found to reduce TMAO and abolished some of these changes in animals [27]. Direct extrapolation of these results to humans is not possible.

Interventions to lower plasma TMAO concentrations are not available and their potential health impact is unknown. Measuring TMAO concentrations has currently no application in clinical practice. Statistical associations between circulating TMAO and cardiovascular, cerebral, and renal diseases including mortality have been reported in multiple systematic reviews/meta-analyses with very similar objectives. In the present study, we aimed to conduct a systematic literature search to identify published systematic reviews/meta-analyses on the topic and to critically evaluate the body of evidence they provide.

2. Methods

The present study was conducted according to a priori protocol that was registered in the International Prospective Register of Systematic Reviews (PROSPERO) before starting the search (CRD42024534940). The population, intervention, comparator, and the outcomes of the present review are shown in Table 1. The paper was prepared according to the preferred reporting items for overviews of reviews (PRIOR) [29] **(Supplemental Material).**

Table 1
The population, intervention, comparator, and outcomes (PICO) of the present systematic review.

Population	Human subjects including healthy people (men and women), people with risk factors for vascular diseases, people with impaired kidney function, people recruited after a vascular event, people at risk for any of the study outcomes due to their previous morbidities such as diabetes, hyperlipidemia, hypertension, thrombosis, and anti-coagulants use.
Intervention (exposure)	Elevated concentrations of TMAO in plasma (EDTA or Heparin) or serum as defined by: 1)- a given cutoff (such as per 1 SD or a numerical cut-off) or 2)- an observed data-derived cutoff such as tertiles, quartiles, or quintiles.
Comparator	Concentrations of TMAO below the study-specified cutoff or in the lowest data-driven category.
Outcomes	Cardiovascular events (CVD), heart insufficiency/heart failure, myocardial infarction, stroke (ischemic and small vessel disease), atrial fibrillation, hypertension, other cerebral diseases, renal diseases and kidney dysfunction, composite outcomes often referred to as "major adverse cardiac and cerebrovascular event" (MACCE), major adverse cardiac events (MACEs), stroke- or CVD-specific death, and all-cause mortality.

2.1. Search and selection strategies

The study team with expert knowledge of the literature (including both exposure and outcome) developed and validated the literature search strategy. For the search in MEDLINE (on May 16, 2024), we used the keywords shown in Supplemental Table 1. The search in Web of Science and Cochrane Library is described in Supplemental Table 1. We screened the reference lists of potentially relevant studies and conducted an additional search in PROSPERO website to identify potentially relevant systematic reviews/meta-analyses. We additionally reviewed the study protocols (if available on any public domain) of the relevant systematic reviews/meta-analyses publications and evaluated the consistency in the information between the final publication and the protocol. The search was limited to studies published in English. No time restriction was applied.

Inclusion criteria in the present study were: systematic review articles that included quantitative meta-analyses of primary studies on the association between circulating TMAO concentrations and any of the outcomes specified above. The populations of interest were healthy adults (M and F), people at risk of the outcome at baseline, people with chronic kidney disease, people with a previous vascular or cerebral event (Table 1). The present study was concerned with the outcomes shown in Table 1 either as single or composite outcomes. All reported effect sizes such as relative risk (RR), odds ratio (OR), risk difference, and hazard ratio (HR) were qualified for inclusion in our review. In addition, systematic reviews/meta-analyses reporting mean difference or standardized mean difference of TMAO concentrations between people with and those without the outcomes were eligible for inclusion. The review team developed a list of potential confounders that could affect the associations under investigation in the present study.

We excluded animal and in-vitro studies, narrative reviews, meeting abstracts, and genomic studies. Studies reporting urinary TMAO were not eligible because the diagnostic value of urinary TMAO is not established at present. Studies including infants and pregnant or lactating women were excluded. Systematic reviews without quantitative data analysis were screened to identify primary studies, but they were not eligible for formal evaluation as a source of evidence in the present study.

According to our protocol, we extracted the following data into an excel sheet: first author, year, PMID, country of the corresponding author, study registration (where, when, registration ID), population, exposure, control, primary and secondary outcomes, number of reviewers, searched websites, end date of the search, search filters, inclusion and exclusion criteria, study designs of the primary studies, effect size of interest (document whether adjusted or none-adjusted), number of studies included, statistical model used for quantitative combination of the data (fixed-effect or random-effects model), pooled effect size per outcome and 95% Confidence Intervals (95%CI), heterogeneity results, main subgroup analysis, sensitivity analysis, results of publication bias, tools used to investigate study quality and funding sources/conflict of interest of the systematic reviews/meta-analyses. The results were summarized in descriptive tables that were reviewed to evaluate the body of evidence.

The literature search, screening, data extraction and the risk of bias assessment were conducted independently by 2 reviewers (RO and LM). The results were regularly discussed in the study meetings and disagreements between the reviewers were solved by discussion. Minor amendments to the protocol were documented during the entire review process. We planned to collect all primary studies, run an update search and conduct a robust quantitative meta-analysis focusing on subgroup analysis of adjusted effect sizes. This part of the work is currently in progress.

2.2. Risk of bias assessment

The risk of bias assessment was performed using individualized

AMSTAR 2 tool (A MeaSurement Tool to Assess systematic Reviews, Supplemental Table 2). The overall evaluation of the confidence in the evidence was conducted using the criteria shown in Supplemental Table 2. A low confidence in the evidence can result from failure to meet goodness criteria of 6 pre-defined critical domains in AMSTAR 2; existing pre-study protocol, search strategy, transparency about excluded studies, risk of bias assessment, methods of statistical combination of the results, and publication bias.

3. Results

3.1. Search results and general evaluation

The initial search identified 92 potentially relevant articles in MEDLINE, 69 in Web of Science, and 313 in Cochrane library. After screening the titles and abstracts, 31 publications were eligible for full text screening. After excluding 4 publications (Supplemental Table 3), we included 27 systematic reviews/meta-analyses investigating the association between TMAO and stroke (n = 7), cardiovascular disease and cause-specific and all-cause mortality (n = 14), and other outcomes (n = 6) (Table 2 and Supplemental Tables 4 and 5). No meta-analyses without systematic reviews were identified in our search. The study flow diagram is shown in Fig. 1.

All systematic reviews/meta-analyses did not report whether a study protocol was prepared prior to conducting the study. Comparing the date of registering the protocol, that of literature search, and submission/publication date suggested that most authors registered the protocols after conducting the search or shortly before publishing. The 27 systematic reviews/meta-analyses included only observational studies on populations with existing clinical conditions that may both cause elevated TMAO and contribute to the etiology of the outcome in question. The systematic reviews/meta-analyses combined data of different study designs and for cohort studies the follow up duration ranged between days and years. Definition of elevated TMAO varied greatly between studies, thus it was not possible to establish a valid threshold for TMAO to define high risk populations.

Dealing with adjusted statistical measures was often unclear and heterogeneous. The majority of the systematic reviews/meta-analyses decided on the statistical combination of the data (fixed-effect or random-effects model) based on the observed heterogeneity (i.e., I^2 statistics), rather than on the hypothesized associations defined in the planning phase (Supplemental Table 5). Moreover, none of the systematic reviews/meta-analyses reported a list of excluded primary studies and justified the exclusions. The assessments of the quality of primary studies were not transparent in several systematic reviews/meta-analyses. The source of funding and conflict of interest statement were reported in 19 systematic reviews/meta-analyses (Supplemental Table 6), while none reported this information in the primary studies.

According to the AMSTAR 2 tool, all available systematic reviews/meta-analyses provided critically low confidence on the association between TMAO and the outcomes addressed in this umbrella review (Supplemental Table 7). Specific flaws in design, conduct and/or reporting are described in Supplemental Table 8.

3.2. Stroke and related outcomes

The association between circulating TMAO concentrations and stroke was studied in 7 systematic reviews/meta-analyses [30–36], of which only 4 were registered in a public domain [31,32,35,36] (Table 2 and Supplemental Tables 4 and 5). Despite similar questions, the studies were heterogeneous in their inclusion and exclusion criteria and search strategies (Supplemental Table 4). The primary studies on stroke were conducted in populations with existing comorbid risk factors for stroke or a previous stroke event (Table 2). All 7 systematic reviews/meta-analyses comprised different study designs and effect size measures (e.g., OR, RR, HR or a mix of those). Subgroup analysis by

Table 2
Description of 27 systematic reviews and meta-analyses identified in the present umbrella review on the association between TMAO and stroke, major adverse cardiac and cerebrovascular events or other related disorders.

Citation, country	Population	Outcome(s)	Designs of the primary studies	Pooled effect size (95%CI) per outcome
Stroke and stroke-related outcomes				
Wang L, 2024, China [36]	People with a stroke event	Prognosis of cerebral infarction (mRS scores at 3 mo); 1st and recurrent stroke; severity of cerebral infarction; stroke mortality; TMAO associations with underlying diseases	CO, CC	mRS score at 3-mo: OR = 1.58 (1.26, 1.99); first stroke OR = 1.21 (1.09, 1.34); recurrent stroke HR = 1.17 (1.08, 1.27); stroke severity OR = 5.19 (1.21, 22.36); history of cerebral infarction RR = 1.12 (1.07, 1.17).
Zhang H, 2024, China [34]	People with stroke and those with/ without risk factors	Risk of stroke; all-cause mortality; risk of MACEs (MI, stroke, need for revascularization and death).	CO, CC	Stroke: OR = 1.83 (1.02, 3.29). HR for all-cause mortality = 1.89 (1.15, 3.08). For MACEs RR (unadjusted) = 2.26 (2.01, 2.54). Risk ratio of MACEs (adjusted) = 1.55 (1.17, 2.05). SMD of TMAO in patients with stoke vs. controls = 2.20 (1.23, 3.16).
Hu X, 2023, China [31]	People with first ischemic stroke and healthy controls	Ischemic stroke; TMAO as a predictor of ischemic stroke incidence? Role (causal) of TMAO in stroke?	CO, CC, MRS	Weighted mean differences of TMAO between patients and controls (95 % CI) = 1.97 (0.87, 3.07).
Hong Y, 2023, China [32]	Adults ≥18 y (not further specified)	Acute ischemic stroke	CC, CO, CS	SMD of TMAO for patients vs. controls (95%CI) = 1.27 (0.94, 1.61); RR (95%CI) = 1.12 (1.07, 1.17) (adjusted) [unclear if OR or RR?]
Tang L, 2023, China [30]	Patients with ischemic stroke	Prognosis of ischemic stroke, including 3-mo mRS, mortality at 3 mo, and major	CO, CC	For mRS at 3-mo RR = 2.76 (1.33, 5.72). Mortality at 3-mo RR = 5.37 (2.63, 10.97).

(continued on next page)

Table 2 (*continued*)

Citation, country	Population	Outcome(s)	Designs of the primary studies	Pooled effect size (95%CI) per outcome
		ischemic events within 3 mo.		Recurrent event at 3-mo RR = 2.71 (1.68, 4.36).
Chen P, 2022, China [33]	People with or without stroke	Risk of stroke	CC, CO (aimed to include CO studies!)	OR for stroke in highest vs. lowest TMAO category = 1.64 (1.12, 2.41); SMD of TMAO in stroke vs. controls = 1.03 (0.95, 1.11).
Farhangi MA, 2020, Iran [35]	General population and people at risk of stroke (not clearly defined in PICO!)	Risk of stroke and the difference in TMAO between people with and without stroke	CC, nested CC, CS, CO (for CO only baseline data!)	OR for stroke = 1.67 (0.86, 3.24). Weighted mean difference of TMAO between patients and none-patients = 2.20 (1.21, 3.18).
Cardiovascular/cerebral, cause-specific- and all-cause mortality, and/or major adverse cardiovascular events (MACE definition on the study level in Supplemental Table 9)				
Khan QA, 2024, Pakistan [40]	Healthy people and those with established CVD or CKD	MACE (MI, stroke, heart transplant, heart failure, other ischemic cardiovascular events, or death either CV- or all-cause); all-cause mortality.	CO	HR for MACE = 1.41 (1.29, 1.54), n = unclear? (multiple entries for same studies? data analyses on the study level?); HR for all-cause death = 1.55 (1.37, 1.75).
Li Y, 2023, China [18]	Adult patients with CKD	Study a dose-response association between TMAO and all-cause and CVD-mortality; study correlations of TMAO and renal function or inflammatory markers in CKD patients.	CC, CO, CS, nested-CC	TMAO and all-cause mortality: RR = 1.26 (1.03, 1.54) in non-dialysis; RR = 1.21 (0.97, 1.51) in dialysis. TMAO and CVD-mortality: RR = 1.00 (0.87, 1.15) in non-dialysis; RR = 1.35 (0.94, 1.93) in dialysis.
Deam YE, 2023, Lebanon [38]	Patients with CAD and acute coronary syndrome vs. those without any of these conditions	Plasma TMAO (as an outcome variable)	CO, CC, CS	For CAD mean difference (MD) = 1.16 (0.54, 1.78). For acute coronary syndrome MD = 1.33 (0.62, 2.03)
Zhou Z, 2022, China [48]	Patients with CKD	All-cause mortality and CVD-mortality.	CO	HR for all-cause mortality in the upper vs. lower TMAO category = 1.29 (1.11, 1.51); per unit increase in TMAO HR = 1.03 (1.00, 1.06). HR for CVD-mortality = 1.45 (1.01, 2.09). Per unit increase of TMAO on CVD-mortality, n = 2 studies (HR p > 0.05).
Chen G, 2022, China [37]	Elderly people (not further specified). The majority of the participants had co-morbidities at baseline	Risk of CVD-mortality, all-cause mortality, MACE, including congestive HF, MI, death due to cardiac causes, and stroke (not clear whether all-cause mortality and CVD-mortality will be separated from other outcomes?).	CO	All-cause mortality: HR = 1.56 (1.40, 1.75) (? unclear why some studies are listed several times and if the analyses are on the study level). CVD events (? unclear whether this included all-cause mortality or CVD-mortality): HR = 1.52 (1.38, 1.68) (multiple listing of same study?).
Li X, 2022, China [41]	People with heart failure	MACEs (CV-mortality, MI, CV-hospitalization, revascularization (unclear if MACEs include all-cause mortality?). In contrast, the primary outcome. in the registered protocol is all-cause mortality.	CO	MACEs RR = 1.28 (1.17, 1.39) (Ref. 25 participated with 3 time points of follow up; only 3 independent studies); all-cause mortality RR = 1.35 (1.28, 1.42).
Li D, 2022, China [42]		Multiple outcomes (e.g., CVD-mortality, CVD, diabetes, MACE, hypertension, all-cause mortality, stroke).	CO, CC, CS, nested-CC	RR for all-cause mortality = 1.60 (1.43, 1.79); RR for MACE = 1.74 (1.56, 1.95); RR for CVD = 1.50 (1.26, 1.79); RR for CVD-mortality = 2.02 (1.74, 2.34); RR for hypertension

(*continued on next page*)

Table 2 (*continued*)

Citation, country	Population	Outcome(s)	Designs of the primary studies	Pooled effect size (95%CI) per outcome
				= 1.39 (1.22, 1.57); RR for stroke = 2.88 (1.54, 5.39).
Guasti L, 2021, Italy [39]	Patients at risk of CVD	All-cause mortality; and MACE (as defined in the primary studies).	CO	RR for MACE= 2.05 (1.61, 2.61). RR for all-cause mortality = 3.42 (2.27, 5.15).
Li W, 2020, China [44]	Patients with heart failure	MACEs including all-cause mortality, hospitalization with heart failure, and heart transplantation; and all-cause mortality.	CO	MACEs for TMAO T3 vs. T1: HR = 1.59 (1.30, 1.94); per SD TMAO increment: HR = 1.23 (1.12, 1.35). All-cause mortality (unclear if HR are adjusted or not) for TMAO T3 vs. T1: HR = 1.67 (1.17, 2.38); per SD TMAO increment: HR = 1.26 (1.07, 1.48).
Yao M, 2020, China [47]	People with CHD, including acute coronary syndrome or chronic CHD	Incidence of MACE.	CO	HR for MACE = 1.58 (1.35, 1.84). HR for acute coronary syndrome = 1.87 (1.41, 2.47). HR for chronic CHD = 1.37 (1.11, 1.70).
Qi J, 2018, China [45]	People at risk of CVD	Risk of CVD; all-cause mortality; and MACCE including congestive heart failure (CHF), MI, death due to cardiac causes, stroke and cardiac transplantation.	CO	CVD: HR = 1.23 (1.07, 1.42). All-cause mortality HR = 1.55 (1.19, 2.02).
Farhangi MA, 2020, Iran [49]	healthy and high risk/ not clearly defined	All-cause mortality.	CO, CC, nested-CC, case-CO, CS	All-cause mortality HR = 1.47 (1.29, 1.67).
Schiattarella GG, 2017, Italy [46]	Not clearly defined in PICO, but mostly with CVD and high risk for mortality	All-cause mortality; major adverse cardio and cerebrovascular events (defined as the incidence of death, MI and stroke).	CO	HR for all-cause mortality = 1.91 (1.40, 2.61). HR for MACE = 1.67 (1.33, 2.11).
Heianza Y, 2017, USA [43]	All populations reported in the Primary studies	MACE (MI, stroke, heart transplant, heart failure (HF), other ischemic CV-events, or death (either CV- or all-cause death); and all-cause mortality.	CO	RR for MACE = 1.62 (1.45, 1.80). RR for death (either CV- or all-cause death) = 1.63 (1.36, 1.95).
Other outcomes				
Gui XY, 2023, Canada [53]	People with and without HF	TMAO (HF vs. controls); and TMAO between HF with preserved ejection fraction vs. HF with reduced ejection fraction.	not specified, but included all designs	SMD of TMAO for people with HF with preserved ejection fraction vs. controls = 2.1 (0.35, 3.86). SMD for TMAO in people with HF with reduced ejection fraction vs. controls = 0.89 (0.45, 1.34).
Yang WT, 2021, China [54]	Mixed population (healthy & with co-morbidities)	Atrial fibrillation.	CO, CC, CS	OR for arterial fibrillation = 1.40 (1.23, 1.59).
Farhangi M, 2021, Iran [55]	Healthy and with established diseases	Cardiometabolic risk (as determined by serum lipid levels and blood pressure)	CO, CC, CS	A non-linear relationship between TMAO and OR of hypertension (n = 6, p for non-linearity = 0.049); mean difference of TMAO by systolic blood pressure = 2.16 (1.11, 3.21).
Han JM, 2024, China [50]	Patients with CVD (including CHD, HF, and arrhythmia)	Aimed to study incidence (actually studied prevalence!) of hypertension. Included only prospective cohort studies that contributed with baseline prevalence data!	CO	Risk ratio of hypertension = 1.14 (1.08, 1.20).
Ge X, 2020, China [51]	unclear, but included people with CVD or at risk of CVD (none included healthy individuals)	Prevalence of hypertension in a given population.	Design: not specified, but likely combined all designs	Relative risk of hypertension by TMAO category (high vs. low) RR = 1.12 (1.06, 1.17).
Zeng y, 2021, China [52]	Healthy and people with prevalent co-morbidities	Impaired kidney function (defined as any CKD stage and disturbed kidney function markers).	CO, CC, CS	TMAO mean difference (MD) for patients with advanced CKD vs. healthy subjects = 67.9 (52.7,

(*continued on next page*)

Table 2 (*continued*)

Citation, country	Population	Outcome(s)	Designs of the primary studies	Pooled effect size (95%CI) per outcome
				83.2) μmol/L. GFR ml/(min.1.73m^2) in subjects with high TMAO vs. those with low TMAO MD = 12.9 (16.6, 9.14). Correlations between TMAO and GFR = −0.45 (−0.58, −0.32).

CC, case control study design; CHD, coronary artery disease; CKD, chronic kidney disease; CO, cohort study design; CS, cross sectional study design; CVD, coronary vascular disease; HF, heart failure; HR, hazard ratio; GFR, glomerular filtration rate; MACCE/MACE, major adverse cardiac and cerebrovascular event; MD, mean difference; MI, myocardial infarction; MRS, mendelian randomization studies; OR, odds ratio; mRS, modified Rankin scale; SMD, standardized mean difference.

study design was insufficient to draw any conclusion on temporality due to low number of studies [33].

Higher TMAO showed association with stroke or stroke-related outcomes (based on pooled estimates of OR, RR or HR > 1), while the strength of association varied between the systematic reviews/meta-analyses (Table 2). Publication bias was investigated using appropriate statistical or visual methods in 4 of the 7 systematic reviews/meta-analyses on stroke [31–33,35], of which 2 studies showed evidence for publication bias [32,33] (Supplemental Table 5).

3.3. Cardiovascular/cerebral, cause-specific- and all-cause mortality, and/or major adverse cardiovascular events

We identified 14 systematic reviews/meta-analyses addressing at least one outcome in this category [18,35,37–48] (Table 2, Supplemental Tables 4 and 5). The term "major adverse cardiovascular events (MACE)" was used in 10 studies, but the definitions of MACE were very heterogeneous and often included conditions such as heart transplant and heart failure [40,43–45] that are not considered to be cardiovascular diseases or all-cause mortality that could be due to non-cardiovascular diseases (Supplemental Table 9). The definition of MACE was also used as reported in the primary studies [37,39,42,47] without specifying the original definition of this composite outcome. In the same context, serious discrepancies were detected between the search terms and the intended outcomes of interest (Supplemental Table 9).

Eight of the 14 systematic reviews/meta-analyses were registered in a public domain [18,38,40–43,48,49] (Supplemental Table 4). Ten systematic reviews/meta-analyses included only prospective cohort studies of different follow up time [37,40,41,43–48] whereas; the remaining 4 included multiple study designs (Table 2). The populations in the primary studies were individuals with existing CVDs or CVD-risk factors (Table 2 and Supplemental Table 4). In general, almost all systematic reviews/meta-analyses reported higher HR, RR, or OR for MACE and all-cause mortality when circulating TMAO concentrations were higher. Only 6 of the 14 meta-analyses specified using an adjusted effect size in the data analysis [37,43–46,48], but the associations were generally similar across all studies irrespective of using adjusted estimates. The systematic reviews/meta-analyses were also heterogeneous with regard to their inclusion and exclusion criteria and statistical models used for data combination.

Three systematic reviews/meta-analyses did not investigate publication bias. Several systematic reviews/meta-analyses showed evidence suggesting significant publication bias [37,41,44,45], but only 2 systematic reviews/meta-analyses accounted for this bias (e.g., by performing trim-and-fill modelling) [41,45]. Only 9 systematic

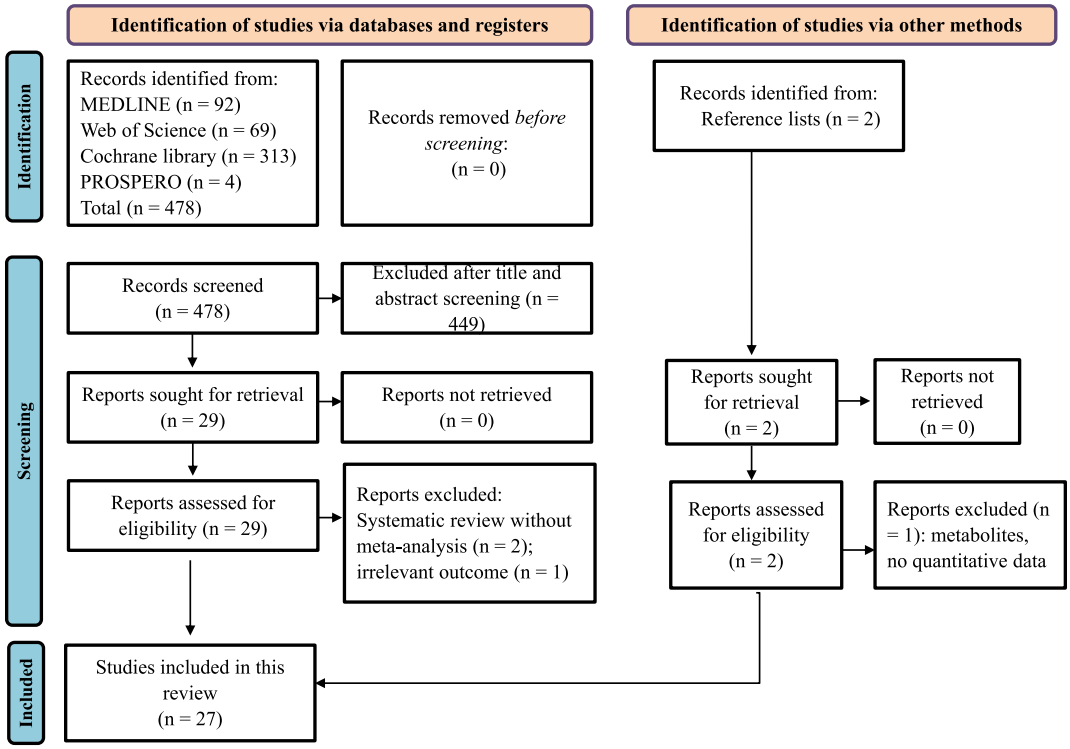

Fig. 1. Study flow diagram.

reviews/meta-analyses conducted subgroup analyses to identify sources of heterogeneity between the primary studies (Supplemental Table 5).

3.4. Other outcomes

Six additional systematic reviews/meta-analyses dealt with the associations between TMAO concentrations and hypertension [50], chronic kidney disease [51,52], heart failure [53], arterial fibrillation [54], or cardiometabolic risk [55]. Five of the 6 systematic reviews/meta-analyses were registered [50–52,54,55]. The primary studies were conducted among people with established illnesses.

Meta-analysis of 13 primary studies reported a moderate correlation between circulating TMAO and GFR [correlation coefficient (95%CI) = −0.45 (−0.58, −0.32)] [52]. This correlation was markedly weak in studies among individuals without chronic kidney disease [56,57] compared to studies among people with chronic kidney disease [52], confirming that renal function is an important determinant of TMAO and a confounder in the association between TMAO and the investigated clinical outcomes.

4. Discussion

The association between TMAO and clinical outcomes related to vascular, cerebral, or renal diseases was addressed in 27 systematic reviews/meta-analyses of human observational studies. Careful evaluation of the systematic reviews/meta-analyses indicated a low confidence in the evidence due to issues related to design or conduct of the studies. All primary studies included populations with prevalent risk factors for future outcomes. The systematic reviews/meta-analyses combined data from different study designs (cohort, case-control, and cross sectional) and measures of associations, and applied different inclusion and exclusion criteria for similar questions. The low quality of systematic reviews/meta-analyses was due to methodological flaws and low quality of the included primary studies.

Elevated plasma concentration of TMAO has emerged as a potential predictive marker of disease outcomes in precision medicine, similar to eGFR. TMAO could also have an etiological role in some diseases as suggested by animal studies [25,26,28]. In clinical practice, the implications and interpretation of TMAO concentrations depend on whether TMAO is a cause of or a marker for the disease. If elevated plasma TMAO concentration in people at risk would predict disease outcomes, TMAO measurement would offer the possibility of intensifying the therapies to delay or prevent disease progression. In terms of hierarchy of evidence, a causal role of TMAO in diseases is not evident, as no randomized control trials have shown that lowering TMAO may reduce the risk of clinical outcomes. Lowering TMAO concentrations can be theoretically achieved by eliminating the gut bacterial strains that produce TMA, turning off the FMO3 enzyme and thereby, reducing the conversion of TMA to TMAO, or cutting all dietary sources of TMA precursor such as choline, betaine and carnitine (including food supplements). Whether interventions to lower TMAO show protective or deleterious health effects in humans is currently unknown. On the one hand, interventions with probiotics [58,59] or symbiotics [60] (that aimed to cause a beneficial shift in the microbiome) failed to lower TMAO. On the other hand, trials that found a minor reduction of plasma TMAO concentrations failed to show improvements in surrogate markers of atherosclerosis such as blood lipids [61,62].

In the absence of randomized controlled trials of suitable design and duration, observational studies on biomarkers such as TMAO are insufficient to establish a causal relationship due to inherent limitations [63]. First, elevated TMAO concentrations could be caused by the outcome (reverse causality), e.g., poor kidney function resulting in reduced TMAO clearance and higher circulating concentrations. Second, confounding by shared causes of elevated TMAO and the outcome could exist (e.g., meat consumption or kidney dysfunction). Third, the criteria of including/excluding participants into the study (selection bias) could bias observed effects. Fourth, imprecision in assessments of the outcome, the confounding factors, or TMAO concentrations can lower confidence in the associations. Almost all primary studies measured plasma TMAO concentrations only once and mostly in people with acute or chronic diseases. Studies on patients with ischemic stroke collected blood samples for measuring TMAO in the acute phase of the disease (i.e., within 24 h of hospital admission) [64,65]. However, repeated-measurement studies have shown that TMAO concentrations decline a few days after ischemic stroke [66,67], thus questioning the relevance of the baseline TMAO measurement as a determinant of the clinical outcome in people admitted to the hospital with stroke.

Several confirmatory systematic reviews/meta-analyses on TMAO overlap with regard to the aim, outcomes, populations, methods and results. In contrast, there is a lack of systematic reviews/meta-analyses on TMAO precursors such as choline, betaine and carnitine since they are considered analogue exposures, and might be expected to show the same associations with the outcomes as with TMAO.

In conclusion, the associations between TMAO and the outcomes of this umbrella review were investigated in 27 systematic reviews/meta-analyses, but the evidence remains insufficient to determine the nature of the association, due to low quality of the studies, variability in adjustment for critical confounding factors, inclusion of participants at high risk for the outcome of interest, variability of follow up time in cohort studies, and lack of a biological threshold for TMAO to define high risk populations. Due to lack of randomized controlled trials, it remains unclear if elevated TMAO is the result of renal dysfunction, a proxy for other causal predictors of the clinical outcomes of interest, or whether it plays an etiological role in the progression of the disease.

Data availability statement

Data was extracted from the original systematic reviews/meta-analyses and summarized in the present article and therefore, data will not be shared beyond this publication.

Disclosures

RO has served on advisory board for Balchem Corporation. LM, BAW, GH, IE, JG, and RCC have no conflict of interest to declare.

Funding

Financial support was provided by a grant from Balchem Corporation, US (granted for RO). Balchem Corporation had no role in study design, the collection, analysis and interpretation of data, the writing of the report; or in the decision to submit the article for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2025.103908.

References

[1] Rebouche CJ. Kinetics, pharmacokinetics, and regulation of L-carnitine and acetyl-L-carnitine metabolism. Ann N Y Acad Sci 2004;1033:30–41.
[2] Kruger R, Merz B, Rist MJ, Ferrario PG, Bub A, Kulling SE, et al. Associations of current diet with plasma and urine TMAO in the KarMeN study: direct and indirect contributions. Mol Nutr Food Res 2017;61.
[3] Schmedes M, Aadland EK, Sundekilde UK, Jacques H, Lavigne C, Graff IE, et al. Lean-seafood intake decreases urinary markers of mitochondrial lipid and energy metabolism in healthy subjects: metabolomics results from a randomized crossover intervention study. Mol Nutr Food Res 2016;60:1661–72.
[4] Cheung W, Keski-Rahkonen P, Assi N, Ferrari P, Freisling H, Rinaldi S, et al. A metabolomic study of biomarkers of meat and fish intake. Am J Clin Nutr 2017;105:600–8.
[5] West AA, Shih Y, Wang W, Oda K, Jaceldo-Siegl K, Sabate J, et al. Egg n-3 fatty acid composition modulates biomarkers of choline metabolism in free-living lacto-ovo-vegetarian women of reproductive age. J Acad Nutr Diet 2014;114:1594–600.

[6] Miller CA, Corbin KD, da Costa KA, Zhang S, Zhao X, Galanko JA, et al. Effect of egg ingestion on trimethylamine-N-oxide production in humans: a randomized, controlled, dose-response study. Am J Clin Nutr 2014;100:778–86.
[7] Samulak JJ, Sawicka AK, Samborowska E, Olek RA. Plasma trimethylamine-N-oxide following cessation of L-carnitine supplementation in healthy aged women. Nutrients 2019;11.
[8] Wilcox J, Skye SM, Graham B, Zabell A, Li XS, Li L, et al. Dietary choline supplements, but not eggs, raise fasting TMAO levels in participants with normal renal function: a randomized clinical trial. Am J Med 2021;134:1160–9.
[9] Rohrmann S, Linseisen J, Allenspach M, von EA, Muller D. Plasma concentrations of trimethylamine-N-oxide are directly associated with dairy food consumption and low-grade inflammation in a German adult population. J Nutr 2016;146:283–9.
[10] Pelletier CC, Croyal M, Ene L, Aguesse A, Billon-Crossouard S, Krempf M, et al. Elevation of trimethylamine-N-oxide in chronic kidney disease: contribution of decreased glomerular filtration rate. Toxins (Basel) 2019;11.
[11] Kaysen GA, Johansen KL, Chertow GM, Dalrymple LS, Kornak J, Grimes B, et al. Associations of trimethylamine N-oxide with nutritional and inflammatory biomarkers and cardiovascular outcomes in patients new to dialysis. J Ren Nutr 2015;25:351–6.
[12] Zhang P, Zou JZ, Chen J, Tan X, Xiang FF, Shen B, et al. Association of trimethylamine N-Oxide with cardiovascular and all-cause mortality in hemodialysis patients. Ren Fail 2020;42:1004–14.
[13] Wang Z, Tang WH, Buffa JA, Fu X, Britt EB, Koeth RA, et al. Prognostic value of choline and betaine depends on intestinal microbiota-generated metabolite trimethylamine-N-oxide. Eur Heart J 2014;35:904–10.
[14] Mente A, Chalcraft K, Ak H, Davis AD, Lonn E, Miller R, et al. The relationship between trimethylamine-N-oxide and prevalent cardiovascular disease in a multiethnic population living in Canada. Can J Cardiol 2015;31:1189–94.
[15] Tang WH, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med 2013;368:1575–84.
[16] Kalagi NA, Thota RN, Stojanovski E, Alburikan KA, Garg ML. Association between plasma trimethylamine N-oxide levels and type 2 diabetes: a case control study. Nutrients 2022;14.
[17] Dong Z, Liang Z, Guo M, Hu S, Shen Z, Hai X. The Association between plasma levels of trimethylamine N-oxide and the risk of coronary heart disease in Chinese patients with or without type 2 diabetes mellitus. Dis Markers 2018;2018:1578320.
[18] Li Y, Lu H, Guo J, Zhang M, Zheng H, Liu Y, et al. Gut microbiota-derived trimethylamine N-oxide is associated with the risk of all-cause and cardiovascular mortality in patients with chronic kidney disease: a systematic review and dose-response meta-analysis. Ann Med 2023;55:2215542.
[19] Kalagi NA, Thota RN, Stojanovski E, Alburikan KA, Garg ML. Plasma trimethylamine N-oxide levels are associated with poor kidney function in people with type 2 diabetes. Nutrients 2023;15.
[20] Xu KY, Xia GH, Lu JQ, Chen MX, Zhen X, Wang S, et al. Impaired renal function and dysbiosis of gut microbiota contribute to increased trimethylamine-N-oxide in chronic kidney disease patients. Sci Rep 2017;7:1445.
[21] Shafi T, Powe NR, Meyer TW, Hwang S, Hai X, Melamed ML, et al. Trimethylamine N-oxide and cardiovascular events in hemodialysis patients. J Am Soc Nephrol 2017;28:321–31.
[22] Skagen K, Troseid M, Ueland T, Holm S, Abbas A, Gregersen I, et al. The carnitine-butyrobetaine-trimethylamine-N-oxide pathway and its association with cardiovascular mortality in patients with carotid atherosclerosis. Atherosclerosis 2016;247:64–9.
[23] Canyelles M, Plaza M, Rotllan N, Llobet D, Julve J, Mojal S, et al. TMAO and gut microbial-derived metabolites TML and gammaBB are not associated with thrombotic risk in patients with venous thromboembolism. J Clin Med 2022;11:1425.
[24] Obeid R, Awwad H, Heine GH, Emrich IE, Fliser D, Zawada AM, et al. Plasma concentrations of trimethylamine-N-oxide, choline, and betaine in patients with moderate to advanced chronic kidney disease and their relation to cardiovascular and renal outcomes. J Ren Nutr 2024;34:530–8.
[25] Chen ML, Zhu XH, Ran L, Lang HD, Yi L, Mi MT. Trimethylamine-N-oxide induces vascular inflammation by activating the NLRP3 inflammasome through the SIRT3-SOD2-mtROS signaling pathway. J Am Heart Assoc 2017;6:e006347.
[26] Witkowski M, Witkowski M, Friebel J, Buffa JA, Li XS, Wang Z, et al. Vascular endothelial tissue factor contributes to trimethylamine N-oxide-enhanced arterial thrombosis. Cardiovasc Res 2022;118:2367–84.
[27] Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 2011;472:57–63.
[28] Tang WH, Wang Z, Kennedy DJ, Wu Y, Buffa JA, Agatisa-Boyle B, et al. Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. Circ Res 2015;116:448–55.
[29] Gates M, Gates A, Pieper D, Fernandes RM, Tricco AC, Moher D, et al. Reporting guideline for overviews of reviews of healthcare interventions: development of the PRIOR statement. BMJ 2022;378:e070849.
[30] Tang L, Zhang L, Zeng Y, Li S, Li Y. Prognostic value of gut microbiota-derived trimethylamine N-oxide in patients with ischemic stroke: a meta-analysis. Neurol Asia 2023;28:55–63.
[31] Hu X, Ren H, Cao Y. The association between trimethylamine N-oxide levels and ischemic stroke occurrence: a meta-analysis and Mendelian randomization study. BMC Neurol 2023;23:413.
[32] Hong Y, Sun Z, Liu N, Yang K, Li Y, Xu Q, et al. The relationship between trimethylamine-N-oxide and the risk of acute ischemic stroke: a doseâ€'response meta-analysis. PLoS One 2023;18:e0293275.
[33] Chen P, Guo Z. Plasmatic trimethylamine N-oxide and its relation to stroke: a systematic review and dose-response meta-analysis. Medicine (Baltim) 2022;101:e29512.
[34] Zhang H, Yao G. Significant correlation between the gut microbiota-derived metabolite trimethylamine-N-oxide and the risk of stroke: evidence based on 23 observational studies. Eur J Clin Nutr 2023;77:731–40.
[35] Farhangi MA, Vajdi M, Asghari-Jafarabadi M. Gut microbiota-associated metabolite trimethylamine N-oxide and the risk of stroke: a systematic review and dose-response meta-analysis. Nutr J 2020;19:76.
[36] Wang L, Nan Y, Zhu W, Wang S. Effect of TMAO on the incidence and prognosis of cerebral infarction: a systematic review and meta-analysis. Front Neurol 2023;14:1287928.
[37] Chen G, He L, Dou X, Liu T. Association of trimethylamine-N-oxide levels with risk of cardiovascular disease and mortality among elderly subjects: a systematic review and meta-analysis. Cardiorenal Med 2022;12:39–54.
[38] Dean YE, Rouzan SS, Loayza Pintado JJ, Talat NE, Mohamed ARH, Verma S, et al. Serum trimethylamine N-oxide levels among coronary artery disease and acute coronary syndrome patients: a systematic review and meta-analysis. Ann Med Surg (Lond) 2023;85:6123–33.
[39] Guasti L, Galliazzo S, Molaro M, Visconti E, Pennella B, Gaudio GV, et al. TMAO as a biomarker of cardiovascular events: a systematic review and meta-analysis. Intern Emerg Med 2021;16:201–7.
[40] Khan QA, Asad M, Ali AH, Farrukh AM, Naseem U, Semakieh A. others. Gut microbiota metabolites and risk of major adverse cardiovascular events and death: a systematic review and meta-analysis. Medicine 2024;103:e37825.
[41] Li X, Fan Z, Cui J, Li D, Lu J, Cui X, et al. Trimethylamine N-oxide in heart failure: a meta-analysis of prognostic value. Front Cardiovasc Med 2022;9:817396.
[42] Li D, Lu Y, Yuan S, Cai X, He Y, Chen J, et al. Gut microbiota-derived metabolite trimethylamine-N-oxide and multiple health outcomes: an umbrella review and updated meta-analysis. Am J Clin Nutr 2022;116:230–43.
[43] Heianza Y, Ma W, Manson JE, Rexrode KM, Qi L. Gut microbiota metabolites and risk of major adverse cardiovascular disease events and death: a systematic review and meta-analysis of prospective studies. J Am Heart Assoc 2017;6:e004947.
[44] Li W, Huang A, Zhu H, Liu X, Huang X, Huang Y, et al. Gut microbiota-derived trimethylamine N-oxide is associated with poor prognosis in patients with heart failure. Med J Aust 2020;213:374–9.
[45] Qi J, You T, Li J, Pan T, Xiang L, Han Y, et al. Circulating trimethylamine N-oxide and the risk of cardiovascular diseases: a systematic review and meta-analysis of 11 prospective cohort studies. J Cell Mol Med 2018;22:185–94.
[46] Schiattarella GG, Sannino A, Toscano E, Giugliano G, Gargiulo G, Franzone A, et al. Gut microbe-generated metabolite trimethylamine-N-oxide as cardiovascular risk biomarker: a systematic review and dose-response meta-analysis. Eur Heart J 2017;38:2948–56.
[47] Yao ME, Liao PD, Zhao XJ, Wang L. Trimethylamine-N-oxide has prognostic value in coronary heart disease: a meta-analysis and dose-response analysis. BMC Cardiovasc Disord 2020;20:7.
[48] Zhou Z, Jin H, Ju H, Sun M, Chen H, Li L. Circulating trimethylamine-N-oxide and risk of all-cause and cardiovascular mortality in patients with chronic kidney disease: a systematic review and meta-analysis. Front Med (Lausanne) 2022;9:828343.
[49] Farhangi MA. Gut microbiota-dependent trimethylamine N-oxide and all-cause mortality: findings from an updated systematic review and meta-analysis. Nutrition 2020;78:110856.
[50] Han JM, Guo L, Chen XH, Xie Q, Song XY, Ma YL. Relationship between trimethylamine N-oxide and the risk of hypertension in patients with cardiovascular disease: a meta-analysis and dose-response relationship analysis. Medicine (Baltim) 2024;103:e36784.
[51] Ge X, Zheng L, Zhuang R, Yu P, Xu Z, Liu G, et al. The gut microbial metabolite trimethylamine N-oxide and hypertension risk: a systematic review and dose-response meta-analysis. Adv Nutr 2020;11:66–76.
[52] Zeng Y, Guo M, Fang X, Teng F, Tan X, Li X, et al. Gut microbiota-derived trimethylamine N-oxide and kidney function: a systematic review and meta-analysis. Adv Nutr 2021;12:1286–304.
[53] Gui XY, Rabkin SW. C-reactive protein, interleukin-6, trimethylamine-N-oxide, syndecan-1, nitric oxide, and tumor necrosis factor receptor-1 in heart failure with preserved versus reduced ejection fraction: a meta-analysis. Curr Heart Fail Rep 2023;20:1–11.
[54] Yang WT, Yang R, Zhao Q, Li XD, Wang YT. A systematic review and meta-analysis of the gut microbiota-dependent metabolite trimethylamine N-oxide with the incidence of atrial fibrillation. Ann Palliat Med 2021;10:11512–23.
[55] Abbasalizad FM, Vajdi M. Gut microbiota-associated trimethylamine N-oxide and increased cardiometabolic risk in adults: a systematic review and dose-response meta-analysis. Nutr Rev 2021;79:1022–42.
[56] Randrianarisoa E, Lehn-Stefan A, Wang X, Hoene M, Peter A, Heinzmann SS, et al. Relationship of serum trimethylamine N-oxide (TMAO) levels with early atherosclerosis in humans. Sci Rep 2016;6:26745.
[57] Gruppen EG, Garcia E, Connelly MA, Jeyarajah EJ, Otvos JD, Bakker SJL, et al. TMAO is associated with mortality: impact of modestly impaired renal function. Sci Rep 2017;7:13781.
[58] Malik M, Suboc TM, Tyagi S, Salzman N, Wang J, Ying R, et al. Lactobacillus plantarum 299v supplementation improves vascular endothelial function and reduces inflammatory biomarkers in men with stable coronary artery disease. Circ Res 2018;123:1091–102.

[59] Borges NA, Stenvinkel P, Bergman P, Qureshi AR, Lindholm B, Moraes C, et al. Effects of probiotic supplementation on trimethylamine-N-oxide plasma levels in hemodialysis patients: a pilot study. Probiotics Antimicrob Proteins 2019;11:648–54.
[60] Mitrovic M, Stankovic-Popovic V, Tolinacki M, Golic N, Sokovic BS, Veljovic K, et al. The impact of synbiotic treatment on the levels of gut-derived uremic toxins, inflammation, and gut microbiome of chronic kidney disease patients; a randomized trial. J Ren Nutr 2023;33:278–88.
[61] Tsutsumi R, Yamasaki Y, Takeo J, Miyahara H, Sebe M, Bando M, et al. Long-chain monounsaturated fatty acids improve endothelial function with altering microbial flora. Transl Res 2021;237:16–30.
[62] Tenore GC, Caruso D, Buonomo G, D'Avino M, Ciampaglia R, Maisto M, et al. Lactofermented annurca apple puree as a functional food indicated for the control of plasma lipid and oxidative amine levels: results from a randomised clinical trial. Nutrients 2019;11.
[63] Zoccali C, Tripepi G, Stel V, Fu EL, Mallamaci F, Dekker F, et al. Biomarkers in clinical epidemiology studies. Clin Kidney J 2024;17:sfae130.
[64] Sun T, Zhang Y, Yin J, Peng X, Zhou L, Huang S, et al. Association of gut microbiota-dependent metabolite trimethylamine N-oxide with first ischemic stroke. J Atherosclerosis Thromb 2021;28:320–8.
[65] Xu J, Cheng A, Song B, Zhao M, Xue J, Wang A, et al. Trimethylamine N-oxide and stroke recurrence depends on ischemic stroke subtypes. Stroke 2022;53:1207–15.
[66] Tan C, Wang H, Gao X, Xu R, Zeng X, Cui Z, et al. Dynamic changes and prognostic value of gut microbiota-dependent trimethylamine-N-oxide in acute ischemic stroke. Front Neurol 2020;11:29.
[67] Schneider C, Okun JG, Schwarz KV, Hauke J, Zorn M, Nurnberg C, et al. Trimethylamine-N-oxide is elevated in the acute phase after ischaemic stroke and decreases within the first days. Eur J Neurol 2020;27:1596–603.