# Plant-Forward Diets Lower Circulating TMAO in Adults: A Systematic Review and Meta-Analysis

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## Abstract

Diet modulates circulating trimethylamine N-oxide (TMAO), a gut microbiota-derived metabolite linked to cardiovascular risk; whether plant-forward versus animal-based dietary patterns consistently influence TMAO concentrations in adults remains unclear. A PRISMA-2020-compliant systematic review and meta-analysis (PROSPERO: CRD420261326106) was conducted through February 2026 across multiple databases; eligible studies assessed dietary patterns, food groups, or diet-related interventions in relation to circulating TMAO in adults. Random-effects meta-analyses were performed where data were combinable. Thirty-four studies were included; 11 contributed to quantitative synthesis. Eight RCTs showed significantly lower TMAO with plant-forward versus animal-based exposures (pooled MD −1.08 μM, 95% CI −1.52 to −0.65; $I^2$ [a measure of between-study heterogeneity] = 0%), consistent across dietary-pattern (−0.85 μM) and food-group subgroups (−1.24 μM). Three cross-sectional studies linking higher meat intake to higher TMAO showed substantial heterogeneity ($I^2$ = 75%). Plant-forward diets are associated with lower circulating TMAO in adults, with the strongest evidence from RCTs.

## INTRODUCTION

Cardiovascular disease (CVD) rank as leading cause of morbidity and mortality worldwide [1], and diet is one of its most important modifiable determinants [2,3]. Contemporary evidence indicates that the global burden of CVD attributable to diet risk is still substantial and is driven not only by excessive intake of sodium, processed foods, and red meat, but also by insufficient consumption of whole grains, fruits, vegetables, legumes, nuts, and other plant foods [2]. While traditional nutritional epidemiology has often focused on single nutrients, this approach does not fully capture the complexity of human diets or the biological pathways through which diet exposures may influence cardiometabolic health. Increasingly, research has shifted toward dietary patterns and toward mechanistic intermediates that may help explain why certain ways of eating are associated with either higher or lower cardiovascular risk.

Among these mechanistic intermediates, gut microbiota–derived metabolites have attracted growing attention as candidate biomarkers—and, in some cases, possible mediators—of cardiometabolic risk . Trimethylamine N-oxide (TMAO) is the most extensively studied example [4–6]. TMAO is generated when diet precursors such as choline, phosphatidylcholine, and L-carnitine are metabolized by gut microbes into trimethylamine (TMA), which is then oxidized in the liver by flavin monooxygenases. Experimental and human evidence has linked TMAO to several pathways relevant to atherosclerosis and CVD, including altered cholesterol handling [7], vascular inflammation, impaired endothelial function[8], thrombosis potential, and interactions with renal function. In observational settings, higher circulating concentrations of TMAO and related metabolites have also been associated with major adverse cardiovascular events and mortality [9], supporting their relevance as intermediate cardiometabolic risk signals.

Because TMAO is strongly influenced by the availability of diet precursors and by the composition and metabolic capacity of the gut microbiota, it represents a plausible mechanistic link between habitual diet and cardiometabolic risk [5]. This makes dietary pattern analysis particularly relevant, as whole diets may shape TMAO production not only through specific nutrients or foods, but also through broader host–microbe interactions. In this context, comparing plant-forward and animal-based dietary exposures may help clarify whether differences in overall diet quality translate into distinct TMAO profiles[4].

Within this framework, the contrast between plant-forward and animal-based dietary exposures has become relevant. Plant-forward diets, characterized by higher intakes of vegetables, fruits, legumes, nuts, and whole grains and by lower intakes of red and processed meat, are aligned not only with cardiometabolic prevention strategies [10] but also with sustainable dietary models such as the EAT-Lancet planetary health diet [11]. This predominantly plant-based dietary framework has been proposed to support both human and planetary health, and recent evidence suggests that greater adherence is generally associated with lower risk of all-cause mortality, cardiovascular disease, and type 2 diabetes[11].

Despite growing literature, the evidence remains inconsistent. Studies have examined both specific food-group contrasts and broader dietary patterns, while findings vary according to biospecimen matrix, study design, and the potential contribution of preformed TMAO from seafood [6,12]. Moreover, not all plant-based diets appear equally beneficial, with healthier plant-based patterns showing more favorable microbiome features and lower TMAO than less healthy ones.

Against this background, a systematic synthesis of the available human evidence is warranted. We therefore conducted a systematic review and meta-analysis to evaluate whether plant-forward dietary exposures are associated with lower circulating TMAO concentrations compared with animal-based exposures in adults, distinguishing between food-group and dietary-pattern comparisons, and assessing consistency of findings across intervention and observational study designs.

## METHODS

### Study Design and Registration

This systematic review was conducted in accordance with the PRISMA 2020 guidelines [13]. The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420261326106).

### Literature Search Strategy

A systematic literature search was conducted in PubMed, MEDLINE (via Ovid), Embase (via Ovid), and Web of Science Core Collection from inception to February 2026, with no language restrictions. The search strategy combined controlled vocabulary — MeSH terms in PubMed/MEDLINE and Emtree in

Embase — with free-text terms, structured around four conceptual domains: trimethylamine N-oxide (TMAO), the gut milieu and microbiome, metabolites and metabolomics, and dietary exposures. The core query followed the structure: ("trimethylamine n-oxide" OR "TMAO") AND ("gut" OR "intestinal" OR "gut-derived" OR "gut-related") AND ("metabolit*" OR "microbiot*" OR "microbiom*" OR "metabolom*") AND ("association*" OR "relation*" OR "correlation*"). This was expanded with dietary and nutritional keywords to capture both food-group and dietary-pattern exposures, including: diet*, dietary, nutrition*, food*, "dietary pattern*", plant-based, vegetarian*, vegan*, Mediterranean, DASH, animal-based, omnivor*, red meat, processed meat, poultry, egg*, dairy, fish, seafood, whole grain*, fiber, and resistant starch. Database-specific syntax, Boolean operators, truncation symbols, field tags, and proximity operators were applied as appropriate, and search strings were translated across all databases.

To maximize sensitivity, no study-design filters were applied at the search stage. Records were limited to human research using database-appropriate limits, and non-eligible publication types were excluded using publication type filters and/or free-text terms as appropriate, including reviews, meta-analyses, editorials, commentaries, letters, consensus statements, and books or book chapters. Animal-only studies were excluded using validated database limits and exclusion logic to avoid inadvertently removing human studies that might include terms such as “animal-based diet.” Reference lists of included articles and relevant reviews were hand-searched, and forward citation tracking was conducted to identify additional eligible studies. Duplicate records were removed prior to screening. The complete search strategy is reported in **Table 1**, and the study selection process is summarized in **Fig. 1** (PRISMA flow diagram).

**Study Selection**

Two reviewers (FC and RZ) independently screened titles and abstracts for relevance. The full texts of potentially eligible articles were then retrieved and assessed against the predefined inclusion and exclusion criteria. Any disagreements were resolved through discussion, and when consensus could not be reached, a third reviewer (RS) was consulted. The study selection process was conducted in accordance with the PRISMA 2020 framework.

## Eligibility Criteria (PICO Framework)

Eligibility criteria were defined according to the PICO framework (**Table 1**).

**Population (P):** Human participants aged 18 years or older, of either sex, were eligible for inclusion. Studies conducted in healthy adults, as well as in adults with overweight, obesity, cardiometabolic risk factors, or stable chronic conditions, were considered eligible provided that TMAO was assessed in plasma/serum or urine. Animal studies, in vitro studies, pediatric populations, and studies conducted exclusively in pregnant women were excluded.

**Intervention/Exposure (I):** Eligible studies investigated dietary exposures potentially associated with TMAO and other gut-derived metabolites. These included plant-forward dietary patterns, vegetarian or vegan diets, Mediterranean- or DASH-style diets, plant-based substitutions, animal-based dietary patterns, and specific food-group exposures such as red or processed meat, poultry, eggs, dairy products, fish, seafood, fiber-rich foods, whole grains, resistant starch, legumes, and nuts. Both controlled dietary interventions and observational assessments of habitual dietary intake were considered.

**Comparator (C):** Comparators included alternative dietary patterns, different levels of intake of the same food group, plant-forward versus animal-based dietary exposures, omnivorous or usual diets, or, in observational studies, lower versus higher adherence or intake categories. Studies without a formal comparator were also considered if they reported quantitative associations between dietary exposure and TMAO.

**Outcomes (O):** The primary outcome was trimethylamine N-oxide (TMAO), measured in plasma/serum or urine. Studies were eligible if they reported absolute TMAO concentrations, changes in TMAO over time, or quantitative associations between dietary exposures and TMAO. Secondary outcomes, when available, included TMAO-related and other gut-derived metabolites, such as choline, carnitine, betaine, trimethylamine, phenylacetylglutamine (PAGln/PAG), indoxyl sulfate, p-cresyl sulfate (including p-cresol sulfate), and imidazole propionate, as well as inflammatory and cardiometabolic biomarkers.

Eligible study designs included randomized controlled trials, non-randomized dietary interventions, crossover feeding studies, prospective and retrospective cohort studies, case-control studies, and cross-sectional studies. Reviews, meta-analyses, editorials, commentaries, letters, conference abstracts without sufficient data, book chapters, and consensus papers were excluded. For the quantitative synthesis, only studies providing sufficiently comparable numerical data were considered for meta-analysis, whereas all eligible studies were included in the qualitative synthesis.

**Table 1**. Search strategy structured according to the PICO framework.

| PICO domain | Concept | Search terms / keywords |
|---|---|---|
| **P**<br>*Population* | Human adult populations | adults OR humans OR men OR women OR participants OR patients OR "aged 18 and over" OR "18 years and older" OR "adult population" OR "working age" OR "middle aged" OR "older adults" OR "elderly" |
| **I/E**<br>*Intervention / Exposure* | Dietary exposures, food groups, and dietary patterns potentially associated with TMAO and other gut-derived metabolites | diet* OR dietary OR nutrition* OR food* OR "dietary pattern*" OR "plant-based" OR vegetarian* OR vegan* OR Mediterranean OR DASH OR "animal-based" OR omnivor* OR "red meat" OR "processed meat" OR poultry OR egg* OR dairy OR fish OR seafood OR "whole grain*" OR fiber OR "resistant starch" OR legumes OR nuts |
| **C**<br>*Comparator* | Alternative dietary exposures, lower versus higher intake categories, plant-forward versus animal-based patterns, or usual diet | —<br>*Comparator terms were not explicitly required in the search string in order to maximize sensitivity; comparators were addressed during study selection and eligibility assessment.* |
| **O**<br>*Outcomes* | Primary metabolite outcome | "trimethylamine n-oxide" OR TMAO |
| **Excl.**<br>*Exclusion block* | Non-eligible publication types and animal-only studies | NOT (review OR "meta-analysis" OR editorial OR commentary OR letter OR consensus OR "book chapter" OR book OR animal OR pig OR pigs OR rat OR rats OR mice) |

## Quality Assessment

The methodological quality and risk of bias of the included studies were assessed according to study design. Randomized controlled trials, including parallel-group, crossover, and controlled-feeding randomized studies, were evaluated using the Cochrane Risk of Bias 2 (RoB-2) tool, which assesses bias across five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. For crossover trials, the crossover-specific RoB-2 version was applied to account for potential carryover effects, period effects, and washout adequacy [14].

Prospective and longitudinal cohort studies were assessed using the Newcastle–Ottawa Scale (NOS), which evaluates study quality according to the selection of participants, comparability of study groups, and ascertainment of exposure or outcomes. The NOS was applied using the original Ottawa Hospital Research Institute guidance [15].

Analytical cross-sectional studies were appraised using the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies, which focuses on the appropriateness of inclusion criteria, validity and reliability of exposure and outcome measurement, identification and management of confounding, and adequacy of statistical analysis [16].

Uncontrolled pre–post intervention studies and before–after feeding studies without a comparator group were evaluated using the National Institutes of Health (NIH) Quality Assessment Tool for Before–After (Pre–Post) Studies With No Control Group, which examines clarity of study objectives, eligibility criteria, participant representativeness, intervention description, outcome assessment, follow-up, and statistical analysis (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).

### Meta-analysis

The meta-analysis was performed using a random-effects model, with between-study variance ($\tau^2$) estimated by Restricted Maximum Likelihood (REML) [17,18]. Effect sizes were expressed as mean differences (MD) in circulating TMAO concentrations between dietary exposure and comparator groups, with corresponding standard errors. Separate analyses were conducted by study design — randomized controlled trials and cross-sectional studies — and further stratified by exposure type. The variable *Type* distinguished studies evaluating the effect of specific food group substitutions (e.g., animal- versus plant-based foods) from those assessing adherence to broader dietary patterns. This two-level stratification allowed simultaneous accounting for within- and between-study heterogeneity [19], yielding both overall and subgroup-specific pooled estimates.

## RESULTS

### Study selection and characteristics

A total of 34 studies [3–6,12,20–48]met the inclusion criteria. Characteristics of all included studies are summarized in **Table 2**. No time restrictions were set, and the selected publications spanned the period from 2006 to 2024, with a median publication year of 2019 (IQR 2018–2022), indicating a marked increase in interest in this topic in recent years. The included studies were conducted across 11 countries, predominantly in the United States (17/34; 50.0%), followed by the United Kingdom (4/34; 11.8%), and Italy and Norway (3/34; 8.8% each), with additional contributions from Spain, Sweden, Poland, Australia, Denmark, New Zealand, and China. Based on the sample sizes reported in each study, the overall summed study population comprised 8,045 participants. Most included studies were randomized dietary intervention or controlled feeding trials (24/34; 70.6%), including parallel, crossover, and crossover-feeding designs. The remaining studies consisted of 6 cross-sectional studies (17.6%), 2 cohort studies (5.9%), and 2 uncontrolled intervention/pre–post studies (5.9%). The populations were heterogeneous and included healthy adults (16 studies) as well as adults with overweight/obesity, cardiometabolic risk factors, or established clinical conditions (18 studies). Reported mean or median age ranged from approximately

22 to 74 years. Regarding the biological matrix used for TMAO assessment, 25 studies measured TMAO in blood (plasma or serum), 6 studies in urine, and 3 studies in both blood and urine.

To facilitate synthesis of the evidence, exposures were grouped *a priori* into two broad categories: food group (n = 15) and dietary pattern (n = 19). This classification was adopted pragmatically to improve the interpretability of findings, given the wide variability in how dietary exposures were defined across studies. Food group exposures included comparisons focused on specific foods or substitutions, such as meat, plant-based meat alternatives, seafood, or protein sources. Dietary pattern exposures included broader eating patterns or dietary prescriptions, such as Mediterranean, DASH, vegan or vegetarian, Paleolithic, among the others.

For the quantitative synthesis, we extracted or derived, whenever possible, the mean difference (MD) between plant-forward and animal-based dietary exposures, together with the corresponding standard deviation (SD), standard error (SE), 95% confidence intervals (95% CI), and p values. Only 11 study-level comparisons provided sufficiently comparable numerical data for meta-analysis [3,20,22,24–26,35,36,38,43]. These included 8 RCTs and 3 cross-sectional comparisons. Seafood-focused studies were retained in the qualitative synthesis but were not pooled because fish and seafood contain preformed TMAO, which could confound the interpretation of circulating TMAO differences. Likewise, studies reporting only urinary TMAO or non-combinable association measures were not included in the quantitative synthesis. Because of methodological heterogeneity, separate forest plots were generated for RCTs and observational cross-sectional studies.

**Table 2.** Characteristics of included studies (n=34). Study design, population characteristics, dietary exposure, TMAO biospecimen matrix, and key findings, stratified by exposure category (FG: food group; DP: dietary pattern).

| First author, year | Country | Category | Study design | Population | N | Age | Dietary exposure | TMAO matrix | Key finding |
|---|---|---|---|---|---|---|---|---|---|
| Crimarco, 2020 | USA | FG | RCT crossover | Healthy omnivorous adults | 36 | 50 ± 14 y | Plant-based meat vs animal meat (8 wk each) | Plasma or serum | Plant-based meat: 2.7 μM vs animal meat: 4.7 μM; MD −2.0 μM (p=0.012) |
| Farsi, 2023 | UK | FG | RCT crossover | Healthy male adults | 20 | 30.4 ± 7.9 y | Mycoprotein vs red+processed meat (14 d) | Urine | Urinary TMAO not significantly different between phases (p=0.06) |
| Tate, 2023 | USA | FG | RCT parallel | Obese older adults | 28 | 65–84 y | DASH + 3 oz vs 6 oz lean beef/day (12 wk) | Plasma or serum | TMAO increased overall (+26.5%, p<0.001); greater with 6 oz beef (p=0.033) |
| Vázquez-Fresno, 2015 | Spain | FG | RCT parallel | Adults at high CVD risk | 98 | 55–80 y | Mediterranean diet (PREDIMED; 1- and 3-year) | Urine | Urinary TMAO lower with higher MD adherence (ANCOVA; p=0.003–9.56×10⁻⁵) |
| Barrea, 2019 | Italy | FG | Cross-sectional | Healthy normal-weight adults | 144 | 31.6 ± 6.2 y | Mediterranean diet adherence; food groups | Plasma or serum | Higher MD adherence inversely associated with TMAO (r≈−0.50, p<0.001) |
| Krishnan, 2022a | USA | FG | RCT crossover | Overweight/obese adults | 39 | 30–69 y | Mediterranean-style diet: low vs moderate lean red meat (5 wk) | Plasma or serum | Low red meat: 3.1 μM vs moderate: 5.0 μM (p<0.001) |
| Krishnan, 2022b | USA | FG | RCT parallel | Overweight/obese women at cardiometabolic risk | 44 | 20–65 y | Dietary Guidelines for Americans vs Typical American Diet (8 wk) | Plasma or serum | No significant difference in TMAO between diet groups |
| Park JE, 2019 | USA | FG | RCT crossover | Healthy normolipidemic adults | 14 | 30.6 ± 9.6 y | Atkins vs Ornish vs South Beach diets (4 wk each) | Plasma or serum | Atkins vs Ornish: 3.3 vs 1.8 μM (p=0.01); Atkins vs South Beach NS |
| Shen X, 2024 | USA | FG | Cross-sectional | Aging adults (BLSA) | 705 (TMAO n=425) | 71.0 ± 12.8 y | Plant-based diet index (hPDI); food groups | Plasma or serum | Higher hPDI inversely associated with TMAO (q<0.05); fish/seafood positively correlated (ρ=0.12) |
| Costabile, 2021 | Italy | FG | RCT parallel | Adults with metabolic syndrome | 78 / 48 | 53–57 y | Marine LCn3/whole-grain vs refined cereals (8–12 wk) | Plasma or serum | Marine LCn3 and whole-grain diets increased TMAO (p=0.007; p=0.037) |
| Schmedes, 2016 | Norway | FG | RCT crossover | Healthy adults | 20 | ~50 y | Lean-seafood vs non-seafood diet | Plasma or serum + urine | Lean-seafood significantly increased TMAO vs non-seafood |

| First author, year | Country | Category | Study design | Population | N | Age | Dietary exposure | TMAO matrix | Key finding |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | (plasma and urine) |
| Schmedes, 2018 | Norway | FG | RCT crossover | Healthy adults | 20 | 50.6 ± 3.4 y | Lean-seafood vs non-seafood diet (4 wk each) | Plasma or serum | Lean-seafood increased postprandial TMAO (diet×time p=0.008) |
| Wang Z, 2019 | USA | FG | RCT crossover | Healthy omnivorous adults | 113 | 21–65 y (median 45) | Red meat vs white meat vs non-meat protein (4 wk each) | Plasma or serum + urine | Red meat: ~3-fold higher plasma TMAO vs non-meat (p<0.0001); median diff −5.9 μM |
| Dhakal, 2022 | USA | FG | RCT crossover | Healthy older adults | 36 | 66 y (mean) | Lean pork vs chicken within DGA-based diet | Plasma or serum | TMAO fold change non-inferior pork vs chicken; p=0.07 (NS) |
| Li J, 2022 | USA | FG | Longitudinal cohort | Healthy free-living men (MLVS/HPFS) | 307 | ~71.4 y | Red meat intake | Plasma or serum | Red meat intake positively associated with circulating TMAO |
| Wang, 2022 | USA | FG | Prospective cohort | Community-dwelling adults ≥65 y (CHS) | 3,931 | ≥65 y | Meat, poultry, fish, processed meat, egg intake | Plasma or serum | Total meat (ρ=0.047) and unprocessed red meat (ρ=0.060) weakly correlated with TMAO (p<0.01) |
| Huang Y, 2024 | China | FG | Cross-sectional | Chinese adults | 754 (TMAO n=333) | NR | Red meat intake | Plasma or serum | Higher red meat intake associated with higher serum TMAO |
| García-Pérez I, 2017 | UK | DP | RCT crossover | Healthy adults (inpatient) | 19 | 55.8 ± 12.6 y | High vs low DASH-score diet (72h inpatient; 4 phases) | Urine | Urinary TMAO higher after high-DASH diet vs low-DASH diet (p<0.0001); driven by fish content |
| De Filippis, 2016 | Italy | DP | Cross-sectional | Healthy adults (omnivore, vegetarian, vegan) | 153 | NR | Mediterranean diet adherence; dietary pattern (omnivore vs veg*n) | Urine | Higher MD adherence and veg*n diet associated with lower urinary TMAO (p<0.0001) |
| Griffin, 2019 | USA | DP | RCT parallel | Adults at risk for colon cancer | 115 (90 completers) | 52 ± 12 y | Mediterranean vs Healthy Eating diet (6 months) | Plasma or serum | No significant change in plasma TMAO after 6-month Mediterranean diet intervention |
| Malinowska AM, 2016 | Poland | DP | Cross-sectional | Elderly women (free-living) | 122 | 68.5 ± 7.4 y | Western vs prudent dietary pattern | Plasma or serum | Western-style pattern associated with higher plasma TMAO across tertiles |
| Argyridou, 2021 | UK | DP | Pre–post (single-arm) | Adults with dysglycemia/obesity | 23 | 57.8 ± 10.0 y | 8-week vegan diet (Plant Your Health trial) | Plasma or serum | TMAO decreased at wk1 and wk8 vs baseline (p=0.004); rebound after |

| First author, year | Country | Category | Study design | Population | N | Age | Dietary exposure | TMAO matrix | Key finding |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | unrestricted diet |
| Landry, 2023 | USA | DP | RCT parallel (twin) | Healthy identical twin pairs | 44 (22 pairs) | 39.6 ± 12.7 y | Healthy vegan vs healthy omnivorous diet (8 wk) | Plasma or serum | Vegan: 2.9 μM vs omnivorous: 4.9 μM; MD −2.1 μM (95% CI −7.7 to 3.6; NS) |
| Djekic, 2020 | Sweden | DP | RCT crossover | Patients with ischemic heart disease | 31 (27 completers) | Median 67 y | Vegetarian vs meat diet (4 wk each) | Plasma or serum | TMAO decreased after vegetarian diet (−1.90 μM vs baseline, p<0.001); between-diet diff NS |
| Heianza Y, 2018 | USA | DP | RCT parallel | Overweight/obese adults (POUNDS Lost) | 504 | NR | Energy-reduced diets varying fat/protein (4 arms) | Plasma or serum | No significant differences in ΔTMAO across macronutrient-varying diet groups |
| Erickson, 2019 | USA | DP | RCT parallel | Obese insulin-resistant older adults | 16 | 66.1 ± 4.4 y | Exercise + hypocaloric vs eucaloric diet (12 wk) | Plasma or serum | Caloric restriction + exercise: TMAO −31% vs +32% with eucaloric (p=0.04) |
| Zhou, 2019 | USA | DP | RCT parallel | Overweight/obese adults (POUNDS Lost) | 264 | 52.3 ± 8.9 y | Energy-reduced diets varying fat/protein (4 arms) | Plasma or serum | Median ΔTMAO = 0.0 μmol/L; no significant differences across diet groups (p=0.70) |
| Schmedes, 2019 | Norway | DP | RCT crossover | Healthy adults | 20 | ~50 y | Lean-seafood vs non-seafood diet (~4 wk each) | Plasma or serum | Lean-seafood significantly increased circulating TMAO vs non-seafood |
| Boutagy, 2015 | USA | DP | Pre–post (single-arm) | Healthy nonobese young men | 10 | 22.1 ± 0.5 y | High-fat diet (5 d) vs eucaloric control | Plasma or serum | Postprandial TMAO increased after high-fat diet; fasting TMAO unchanged |
| Genoni A, 2020 | Australia | DP | Cross-sectional | Paleolithic followers vs controls | 91 | 39–45 y (mean) | Long-term Paleolithic diet | Plasma or serum | Strict Paleo: 9.53 μM vs controls: 3.93 μM (p=0.008); red meat positively associated (r=0.357) |
| Rasmussen LG, 2012 | Denmark | DP | RCT parallel | Overweight non-diabetic adults | 77 | 42–44 y | High-protein vs low-protein diet (6 months) | Urine | Tendency toward higher urinary TMAO with high-protein diet (NMR metabolomics) |
| Mitchell, 2019 | New Zealand | DP | RCT parallel | Healthy older men | 29 | 74.2 ± 3.6 y | Protein at 2×RDA vs RDA (10 wk) | Plasma or serum + urine | Plasma TMAO increased with 2×RDA protein (p=0.004; time×diet p=0.002) |

| First author, year | Country | Category | Study design | Population | N | Age | Dietary exposure | TMAO matrix | Key finding |
|---|---|---|---|---|---|---|---|---|---|
| Starr KNP, 2019 | USA | DP | RCT parallel | Obese middle-aged/older adults | 80 | ~64 ± 8 y | Higher-protein + lean red meat vs RDA protein (6 months) | Plasma or serum | No significant increase in plasma TMAO with higher-protein lean red meat diet |
| Stella C, 2006 | UK | DP | RCT crossover | Healthy male adults | 12 | 25–74 y | High-meat vs low-meat vs vegetarian diet (15 d each) | Urine | Urinary TMAO elevated during high-meat vs low-meat and vegetarian periods (NMR) |

*Abbreviations: FG, food group; DP, dietary pattern; RCT, randomized controlled trial; TMAO, trimethylamine N-oxide; MD, mean difference; NMR, nuclear magnetic resonance; DGA, Dietary Guidelines for Americans; DASH, Dietary Approaches to Stop Hypertension; hPDI, healthful plant-based diet index; LCn3, long-chain omega-3 fatty acids; NS, not significant; NR, not reported*

#### Quality assessment

Among the 24 RCTs, 23 were judged as having some concerns and 1 as high risk of bias (**Fig. 2**). Concerns were mainly related to the randomization process, deviations from intended interventions, and selection of the reported result, whereas outcome measurement was consistently rated at low risk across all studies. **Fig. 3** summarizes the quality assessment of non-randomized studies. Both cohort studies (panel A) were rated as good quality using the NOS. Among the six cross-sectional studies (panel B), five were judged as low risk/high quality, whereas De Filippis [34] showed some concerns related mainly to confounding. The two before–after studies without controls (panel C) were rated as fair [37] and poor [42], reflecting the limitations inherent to uncontrolled pre–post designs.

#### Meta-analysis

The quantitative synthesis included 11 study-level comparisons, comprising 8 randomized controlled trials and 3 observational cross-sectional studies. In the RCT meta-analysis (**Fig. 4**), plant-forward dietary exposures were associated with significantly lower serum TMAO concentrations than animal-based exposures, with a pooled random-effects mean difference of −1.08 μM (95% CI −1.52 to −0.65; I²=0%). Subgroup analyses showed consistent results for both dietary-pattern interventions (−0.85 μM, 95% CI −1.52 to −0.17; I²=0%) and food-group interventions (−1.24 μM, 95% CI −1.86 to −0.62; I²=10%), with no significant subgroup differences. In contrast, the meta-analysis of cross-sectional studies (**Fig. 5**), comparing high versus low meat intake, showed substantial heterogeneity (I²=75%). The pooled random-effects estimate was 2.35 (95% CI −0.20 to 4.90), whereas the fixed-effect estimate was 1.30 (95% CI 0.54 to 2.05). Because this comparison was defined as higher versus lower meat intake, the positive effect estimate indicates higher serum TMAO concentrations among participants with greater meat consumption. Overall, the meta-analysis supports a consistent TMAO-lowering effect of plant-forward dietary exposures in intervention studies, while observational findings point in the same direction but are less precise because of between-study heterogeneity.

## DISCUSSION

The aim of this systematic review and meta-analysis was to evaluate whether plant-forward diet exposure is associated with lower circulating TMAO concentrations than animal-based diet in adults, while distinguishing between food-group and dietary-pattern. Across 34 studies included in the qualitative synthesis, the overall evidence suggested a consistent directional pattern: plant-forward exposures tended to be associated with lower TMAO, whereas animal-based exposures—particularly higher meat intake—tended to be associated with higher TMAO. In the quantitative synthesis, 11 study-level comparisons were meta-analyzed. Among the 8 RCTs, plant-forward interventions were associated with significantly lower serum/plasma TMAO concentrations than animal-based interventions, with a pooled mean difference of −1.08 μM (95% CI −1.52 to −0.65). This pattern remained consistent in subgroup analyses of both dietary-pattern interventions and food-group interventions. In contrast, the 3 cross-sectional studies comparing high versus low meat intake suggested higher TMAO with greater meat consumption, but with substantial heterogeneity, indicating that observational evidence was directionally supportive but methodologically less stable.

From a clinical perspective, these findings are relevant because TMAO is well-acknowledged as a gut microbiota–related marker linked to cardiometabolic risk, atherosclerotic disease, and adverse cardiovascular outcomes, although causal role remains debated [5,6]. The present results suggest that diets emphasizing plant foods and reducing animal source—especially red and processed meat—may shift the circulating TMAO profile in a more favorable direction. Importantly, the consistency of the pooled RCT estimate strengthens the interpretation that this association is not purely observational but is at least partly diet-responsive under controlled conditions.

This interpretation is biologically plausible. Plant-forward diets generally reduce exposure to dietary precursors of TMAO, including L-carnitine and choline-rich animal foods, while at the same time providing more fiber and plant substrates that may favourably shape gut microbial ecology. Several intervention studies included in this review support this framework. In the SWAP-MEAT trial, replacing animal meat with plant-based meat alternatives significantly lowered circulating TMAO [20]. Similarly, an 8-week randomized trial in identical twins found lower TMAO under a healthy vegan diet compared with a healthy omnivorous diet [3]. In overweight or obese adults, a Mediterranean-style dietary pattern with lowered meat intake reduced fasting TMAO, whereas a similar pattern with moderate red meat intake did not, suggesting that the overall healthfulness of the diet may not fully offset the effect of animal-source precursor load [24]. Likewise, chronic red meat intake has been shown to increase plasma and urinary TMAO compared with non-meat protein sources under controlled feeding conditions [30].

The observational findings were directionally concordant with the intervention evidence. Higher meat intake was associated with higher TMAO, although heterogeneity was substantial, likely reflecting differences in study populations, exposure assessment, background diets, renal function, microbiome composition, and biospecimen handling. This variability is not surprising, because TMAO is not merely a readout of food intake; it reflects a dynamic interaction between dietary precursors, gut microbial metabolic capacity, and host metabolism [5]. For this reason, the clinical significance of a given TMAO concentration should be interpreted in context, rather than as a stand-alone nutritional target.

Another clinically important point is that not all animal-source foods behave similarly. Seafood-focused studies were deliberately excluded from the pooled meta-analysis because fish and seafood contain preformed TMAO, which may elevate circulating concentrations through a mechanism distinct from endogenous microbial generation from meat-derived precursors. Controlled studies have shown that lean-seafood diets can increase fasting or postprandial TMAO despite otherwise favorable cardiometabolic features [29]. This reinforces the idea that TMAO should not be interpreted simplistically as a universal marker of “healthy” or “unhealthy” eating, but rather as a context-dependent metabolite whose meaning depends on food source, microbiome function, and cardiometabolic background.

Taken together, the present findings may have practical implications for dietary counseling, particularly in individuals with overweight, obesity, insulin resistance, dyslipidemia, or established cardiovascular disease. While TMAO should not replace established clinical outcomes, it may provide a useful intermediate biomarker through which plant-forward dietary strategies could exert cardiometabolic benefit. In this sense, our results are consistent with a broader movement toward dietary models that combine metabolic and environmental relevance, including Mediterranean-style and other plant-forward eating patterns.

## Strengths and limitations

This study has several strengths. First, to our knowledge, it provides one of the most focused syntheses of the literature comparing plant-forward versus animal-based dietary exposures in relation to circulating TMAO. Second, we separated food-group and dietary-pattern comparisons, which improved interpretability and allowed us to show that the overall direction of effect was consistent across both exposure types. Third, we analyzed RCTs and observational cross-sectional studies separately, thereby avoiding inappropriate pooling across fundamentally different study designs. Fourth, we deliberately excluded seafood-focused studies from the quantitative synthesis to minimize confounding by preformed TMAO, which strengthens the internal coherence of the pooled estimates.

This study has also several limitations. The total number of studies that could be quantitatively pooled was relatively small, especially for the observational meta-analysis. Reporting formats were highly heterogeneous: some studies presented means and standard deviations, whereas others reported medians, relative intensities, p-value contrasts, or graphical data only. Several crossover trials required careful handling because paired variance estimates were not always fully available. In addition, exposures were diverse, ranging from whole dietary patterns to single food substitutions, which may limit direct comparability. TMAO was measured in different biological matrices, although the meta-analysis was restricted to serum/plasma studies whenever possible. Another important limitation is that the gut microbiota was not systematically incorporated into the quantitative synthesis, despite its central role in TMAO generation. Although several studies acknowledged or explored microbiome-related mechanisms, the available data were still too limited, heterogeneous, and inconsistently reported to allow a methodologically robust synthesis of microbiota-related findings. As a result, the present review could not adequately address how inter-individual differences in microbial composition or function may modify the association between diet and circulating TMAO. Finally, because TMAO is an intermediate biomarker rather than a hard clinical endpoint, its interpretation should remain cautious and embedded within the broader cardiometabolic, dietary, and host–microbiome context.

## Conclusion

This systematic review and meta-analysis demonstrate that plant-forward dietary exposures are associated with lower circulating TMAO concentrations compared with animal-based exposures in adults, with the most consistent evidence derived from RCTs. Observational data were directionally concordant, linking greater meat intake to higher TMAO concentrations, albeit with substantial between-study heterogeneity. Collectively, the available evidence suggests that shifting toward plant-forward dietary strategies may beneficially modulate circulating TMAO; however, larger, well-standardized human studies with harmonized exposure definitions, standardized biospecimen protocols, and consistent outcome reporting are needed to establish the clinical relevance of these findings and their translation into dietary recommendations.

## Declarations

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## Figures

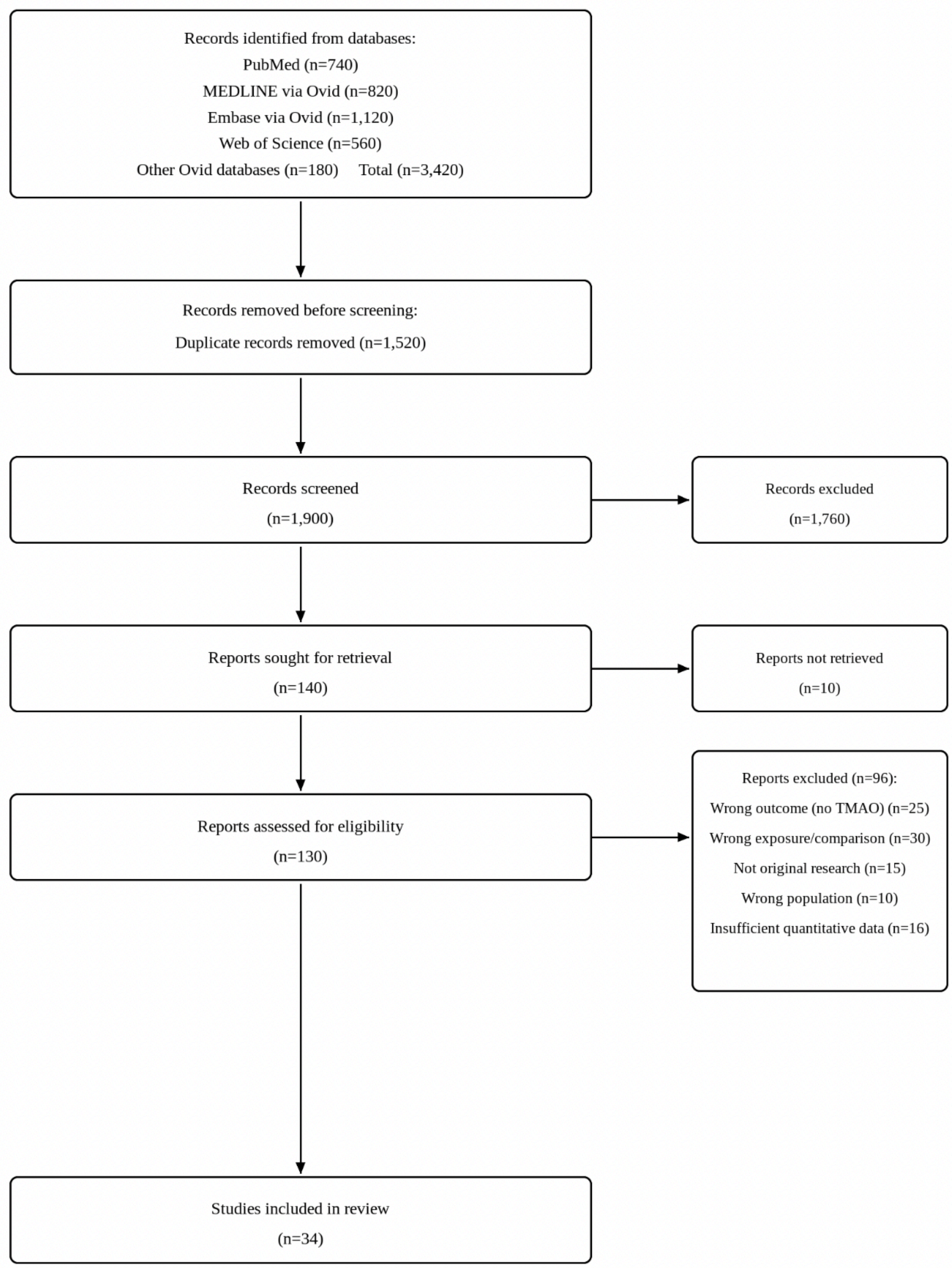


**Figure 1**

PRISMA 2020 flow diagram of study selection. Records identified through database searching (PubMed, MEDLINE, Embase, and Web of Science) and additional sources are shown in the top boxes. Numbers of records excluded at each stage, with reasons, are indicated in the right-hand boxes. The bottom box shows the total number of studies included in qualitative synthesis (n = 34) and quantitative synthesis (n = 11).

### RoB 2 — Randomized controlled trials

| Study | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Costabile 2021 | ? | ? | ? | ✓ | ? | ? |
| Crimarco 2020 | ✓ | ? | ✓ | ✓ | ? | ✕ |
| Dhakal 2022 | ? | ? | ✓ | ✓ | ? | ? |
| Djekic 2020 | ? | ? | ✓ | ✓ | ? | ? |
| Erickson 2019 | ? | ? | ✓ | ✓ | ? | ? |
| Farsi 2023 | ? | ? | ✓ | ✓ | ? | ? |
| García-Pérez 2017 | ? | ? | ✓ | ✓ | ? | ? |
| Griffin 2019 | ? | ? | ? | ✓ | ? | ? |
| Heianza 2018 | ? | ? | ? | ✓ | ? | ? |
| Krishnan 2022 | ? | ? | ✓ | ✓ | ? | ? |
| Krishnan 2022 | ? | ? | ✓ | ✓ | ? | ? |
| Landry 2023 | ✓ | ? | ✓ | ✓ | ✓ | ? |
| Mitchell 2019 | ? | ? | ? | ✓ | ? | ? |
| Park 2019 | ? | ? | ✓ | ✓ | ? | ? |
| Rasmussen 2012 | ? | ? | ? | ✓ | ? | ? |
| Schmedes 2016 | ? | ? | ✓ | ✓ | ? | ? |
| Schmedes 2018 | ? | ? | ✓ | ✓ | ? | ? |
| Schmedes 2019 | ? | ? | ✓ | ✓ | ? | ? |
| Starr 2019 | ? | ? | ? | ✓ | ? | ? |
| Stella 2006 | ? | ? | ✓ | ✓ | ? | ? |
| Tate 2023 | ? | ? | ✓ | ✓ | ? | ? |
| Vázquez-Fresno 2015 | ? | ? | ✓ | ✓ | ? | ? |
| Wang 2019 | ? | ? | ✓ | ✓ | ? | ? |
| Zhou 2019 | ? | ? | ? | ✓ | ? | ? |

*Overall: 23 some concerns, 1 high risk*

**D1** — Randomization process
**D2** — Deviations from intended interventions
**D3** — Missing outcome data
**D4** — Measurement of the outcome
**D5** — Selection of the reported result

✓ Low risk ? Some concerns ✕ High risk

**Figure 2**

Risk of bias assessment of randomized controlled trials (n = 24) using the Cochrane Risk of Bias 2 (RoB 2) tool. Each row represents one RCT; columns correspond to the five RoB 2 domains: D1, randomization process; D2, deviations from intended interventions; D3, missing outcome data; D4, measurement of the outcome; D5, selection of the reported result. Colours indicate the risk-of-bias judgement: green, low risk; yellow, some concerns; red, high risk. The rightmost column shows the overall risk-of-bias judgement for each study.

### A. NOS cohort studies

| Study | S1 | S2 | S3 | S4 | C1 | C2 | O1 | O2 | O3 |
|---|---|---|---|---|---|---|---|---|---|
| Li 2022 | ✓ | ✓ | ✓ | ? | ✓ | ✓ | ✓ | ✓ | × |
| Wang 2022 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

*Overall: Good*

### B. JBI cross-sectional studies

| Study | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 |
|---|---|---|---|---|---|---|---|---|
| Huang 2024 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| De Filippis 2016 | ✓ | ✓ | ? | ✓ | × | × | ✓ | ✓ |
| Malinowska 2016 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Genoni 2020 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Barrea 2019 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Shen 2024 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

*Overall: Low risk / Some concerns*

### C. NIH before-after studies

| Study | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Q11 | Q12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Argyridou 2021 | ✓ | ? | ✓ | ✓ | × | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| Boutagy 2015 | ✓ | ✓ | × | ? | × | ? | ✓ | × | ✓ | ✓ | ✓ | – |

*Overall: Fair / Poor*

✓ Yes / criterion met   ? Unclear / cannot determine   × No / criterion not met   – Not applicable

**Figure 3**

Quality assessment of non-randomized studies (n = 10) using design-specific appraisal tools. Panel A: cohort studies (n = 2) assessed with the Newcastle–Ottawa Scale (NOS). Panel B: cross-sectional studies (n = 6) assessed with the JBI critical appraisal checklist. Panel C: uncontrolled before–after studies (n = 2) assessed with the NIH Quality Assessment Tool for Before–After (Pre–Post) Studies With No Control Group. Green, low risk or high quality; yellow, some concerns or fair quality; red, high risk or poor quality.

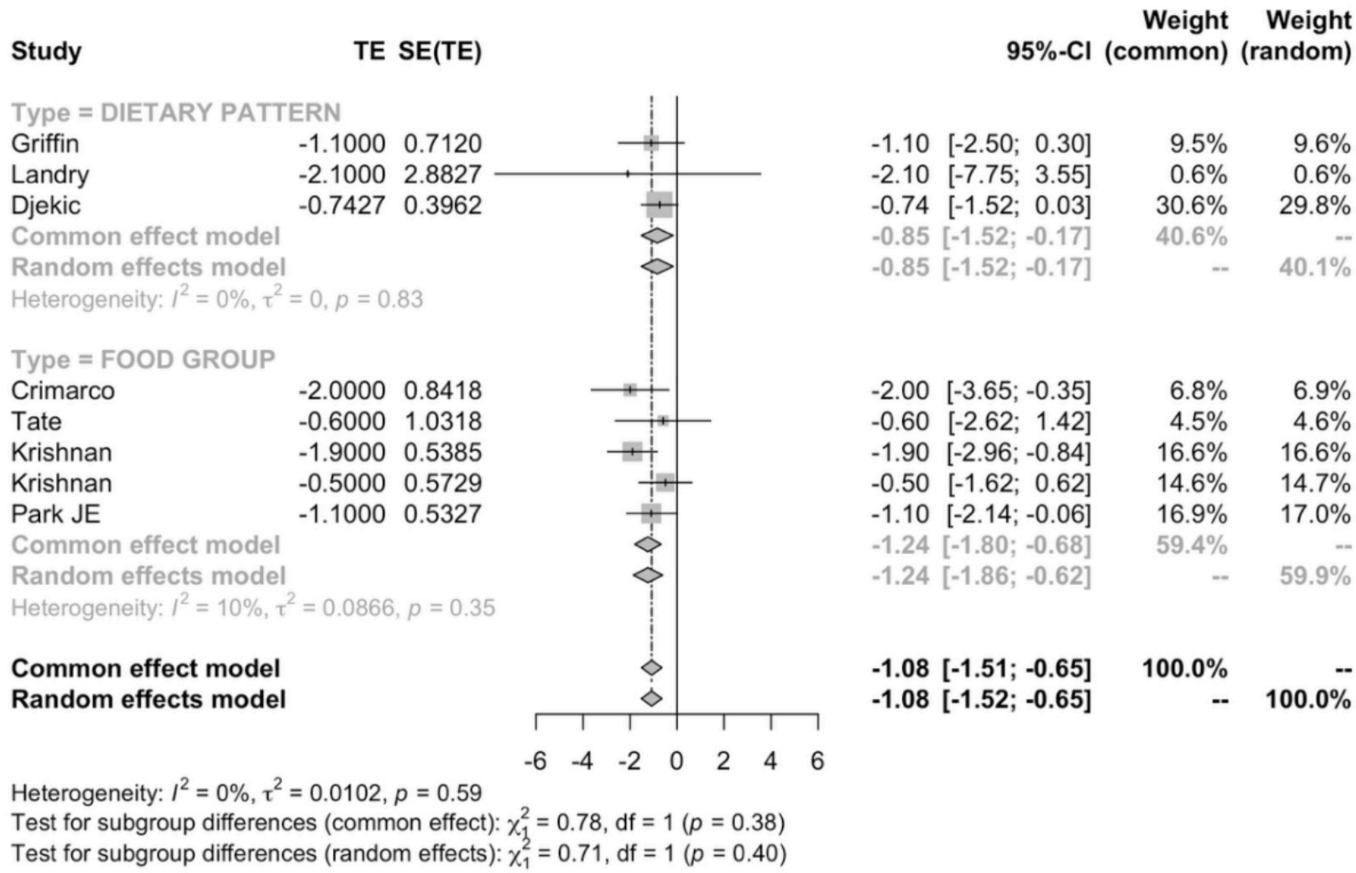


**Figure 4**

Forest plot of randomized controlled trials (n = 8 studies; 8 comparisons; total n = 477 participants) comparing circulating TMAO concentrations between plant-forward and animal-based dietary exposures. Effect sizes are expressed as mean differences (MD) in serum or plasma TMAO (μM); horizontal bars represent 95% confidence intervals. The overall pooled estimate (random-effects model, REML) is shown as a filled diamond; individual study estimates are shown as filled squares sized proportionally to study weight. Subgroup analyses are stratified by exposure type (dietary-pattern interventions and food-group interventions). $I^2 = 0\%$ for the overall analysis and dietary-pattern subgroup; $I^2 = 10\%$ for the food-group subgroup, indicating negligible between-study heterogeneity.

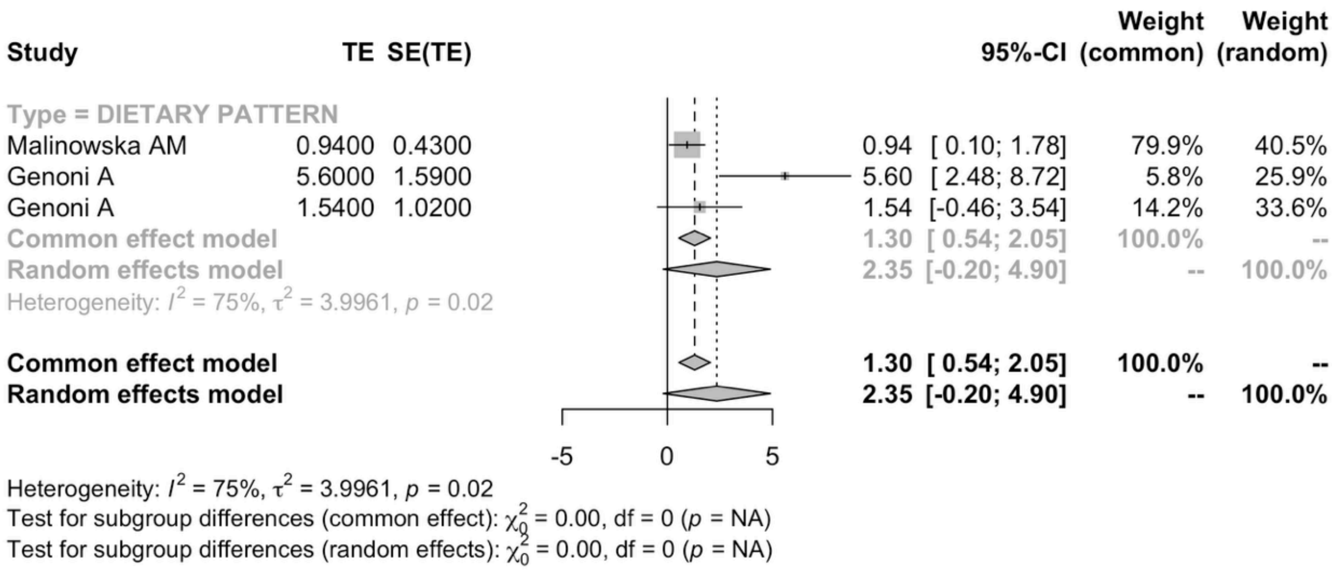


**Figure 5**

Forest plot of observational cross-sectional studies (n = 3 studies; 3 comparisons; total n = 891 participants) comparing circulating TMAO concentrations between high and low meat intake groups. Effect sizes are expressed as mean differences in serum or plasma TMAO (μM); horizontal bars represent 95% confidence intervals. Individual study estimates are shown as filled squares sized proportionally to study weight. The random-effects pooled estimate is shown as a filled diamond (MD 2.35 μM, 95% CI −0.20 to 4.90); the fixed-effect estimate is shown as an open diamond (MD 1.30 μM, 95% CI 0.54 to 2.05). $I^2$ = 75%, indicating substantial between-study heterogeneity.