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Relationship between trimethylamine N-oxide and the risk of hypertension in patients with cardiovascular disease

A meta-analysis and dose-response relationship analysis

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Abstract

Background: The gut microbiota-dependent metabolite trimethylamine N-oxide (TMAO) has recently been recognized to be one of the risk factors for cardiovascular disease (CVD). However, there is a scarcity of data on the relationship between circulating TMAO levels and hypertension in patients with CVD. Meta analysis and a dose-response relationship were used in this study to assess the relationship between circulating trimethylamine N-oxide levels and the risk of hypertension in patients with CVD.

Methods: CNKI, Wanfang Database, Pubmed, Embase, Cochrane Library, and Web of Science were searched up to June 01, 2023. Meta-analysis and dose-response analysis of relative risk data from prospective cohort studies reporting on the relationship between circulating TMAO levels and hypertension risk in patients with CVD were conducted.

Results: Fifteen studies with a total of 15,498 patients were included in the present meta-analysis. Compared with a lower circulating TMAO level, a higher TMAO level was associated with a higher risk of hypertension in patients with CVD (RR = 1.14,95%CI (1.08, 1.20)). And the higher the TMAO level, the greater the risk of hypertension. The dose-response analysis revealed a linear dose-response relationship between circulating TMAO levels and the risk of hypertension in patients with CVD. The risk of hypertension increased by 1.014% when the circulating TMAO level increased by 1 μ mol/L.

Conclusion: In patients with CVD, the level of circulating TMAO is significantly related to the risk of hypertension. The risk of hypertension increased by 1.014% for every 1 μ mol/L increase in circulating TMAO levels.

Abbreviations: CVD = cardiovascular disease, NOS = Newcastle-Ottawa Quality Assessment Scale, TMAO = trimethylamine N-oxide.

Keyword: cardiovascular disease, dose-response relationship, hypertension, meta-analysis, trimethylamine N-oxide.

1. Introduction

Cardiovascular disease (CVD), as a growing public health issue, has become one of the world diseases with the highest morbidity and mortality rates.[1] Despite the fact that methods for diagnosing and treating CVD are constantly being updated and developed, the mortality rate of patients with CVD remains high. As a result, more research into the pathogenesis and risk factors of CVD is required. A large number of studies in recent years have found a link between the occurrence and progression of CVD and the gut microbiota.[2] The human intestinal tract contains a large number of bacteria, which together form the gut microbiota, which can symbiotically interact with the host and maintain intestinal homeostasis.[3] When the balance of the gut microbiota is disrupted due to dietary habits, environmental factors, drug use, or other factors, the risk of CVD will increase significantly.[4–6] Trimethylamine N-oxide (TMAO), a gut microbiota-dependent metabolite, has been shown to be involved in the occurrence and development of CVD, either directly or indirectly, and is an important risk factor for CVD.[7]

One of the risk factors for CVD is hypertension. The 2017 AHA/ACC hypertension guidelines defined grade 1 hypertension as 130/80mmHg,[8] resulting in a significant increase in hypertension prevalence. People with systolic blood pressure >130mmhg had a significantly higher risk of developing CVD and all-cause mortality when compared to the general population, and this risk increased as systolic blood pressure increased.[9] Long-term hypertension can result in life-threatening complications such as CVD, stroke, renal failure,

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The datasets generated during and/or analyzed during the current study are publicly available.

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

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and fundus lesions. The pathogenesis of hypertension is complicated, with environmental, dietary, mental, and genetic factors all playing a role.[10] Recent research has discovered that the gut microbiota and its metabolites can cause the onset and progression of hypertension in a variety of ways.[11,12] Elevated circulating TMAO levels have been linked to an increased risk of MACE and all-cause death in patients with CVD.[13,14] However, there is a scarcity of data on the relationship between circulating TMAO levels and hypertension in patients with CVD. Therefore, we performed the present dose–response meta-analysis of published articles to examine the relationship between circulating trimethylamine N-oxide levels and the risk of hypertension in patients with CVD.

2. Methods

2.1. Search strategy

We (L.G. and X.C.) searched several electronic databases (CNKI, Wanfang Database, Pubmed, Embase, Cochrane Library, and Web of Science) up to June 01,2023 for prospective cohort studies, reporting on the relationship between circulating TMAO levels and hypertension risk in patients with CVD. Indexing terms included ("Trimethylamine N-oxide" or "TMAO") AND ("cardiovascular disease" OR "coronary heart diseases" OR "heart failure" OR "arrhythmia" OR "hypertension") without language restrictions. At the same time, the references in the retrieved literature are searched for additional information. The study protocol was registered in the PROSPERO database (available from: https://www.crd.york.ac.uk/PROSPERO. ID: CRD42023450026).

2.2. Study selection

All titles and abstracts were initially screened to ensure they met the eligibility requirements. We (L.G. and X.C.) only included prospective cohort studies with a study population that included patients with CVD (including coronary heart disease, heart failure, and arrhythmia); patients who have higher levels of circulating TMAO as exposure; and incidence of hypertension as outcome. Meanwhile, studies without original data, animal experiment studies, review articles, case reports and commentaries were excluded.

2.3. Data extraction

Two reviewers (L.G. and X.C.) worked independently to extract the data. A third reviewer (Y.M.) was invited to participate in the discussion to reach a consensus. The following information was extracted from each study: the first author name, publication data, country, disease status, sample size, average age, sex ratio, circulating TMAO levels, BMI, proportion of smokers, proportion of hypertension, proportion of diabetes, proportion of dyslipidemia, proportion of aspirin users, proportion of statins users, proportion of β-blockers users, proportion of ACEI or ARB users.

2.4. Assessment of methodological quality

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to evaluate the included studies' quality.[15] The scale assesses the study quality based on the sum of 3 scores: selection, comparability, and outcome. The quality of the included studies was classified as low (scores 1–4), moderate (scores 5–6), or high (scores 7–9) based on the NOS scores. Low-quality studies are excluded from meta-analysis.

2.5. Statistical analysis

All the data were analyzed by STATA17.0 software, and Q and I^2 statistics were used to evaluate the heterogeneity of the included study (Low, moderate, and high heterogeneity were defined as I^2 values of 0 to 25, 25 to 49, and > 50%,

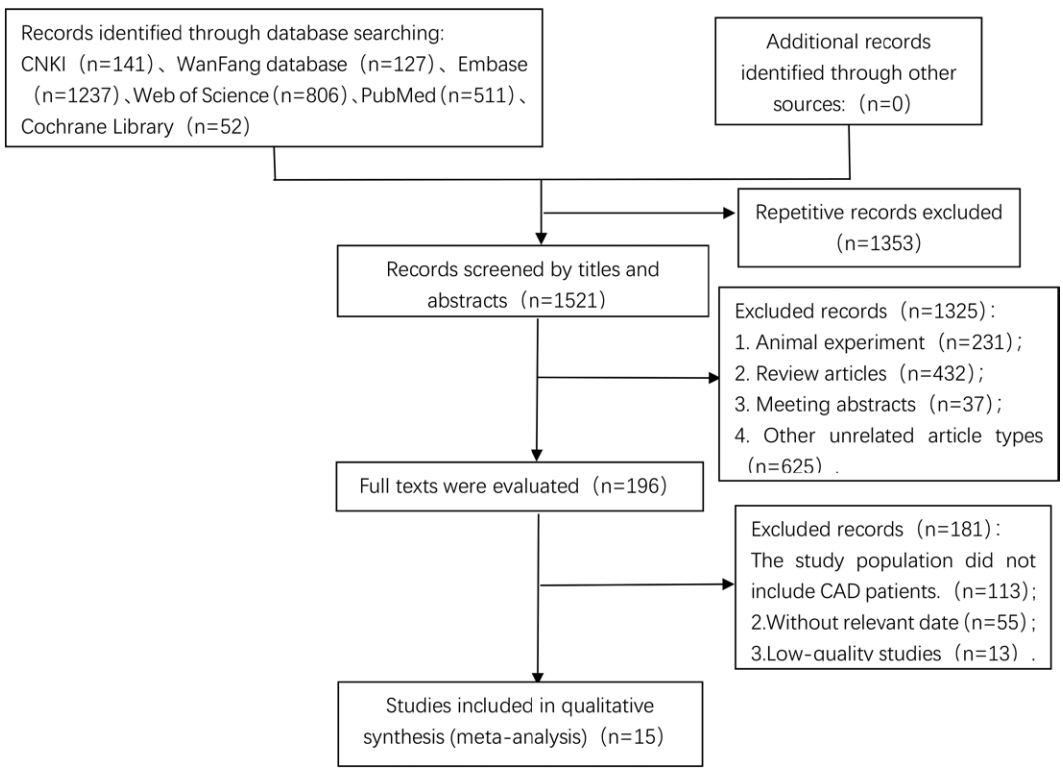

Figure 1. Flow chart of the study selection for the meta-analysis.

Table 1

Characteristics of included studies

Study	Yr	Country	Disease status	Sample	Age (y)	Male, %	TMAO, μmol/L	BMI, kg/m²	Smoking, %	Hypertension, %	Diabetes, %	Dyslipidemia, %	Aspirin use, %	Beta-blocker use, %	Statin use, %	ACEI or ARB use, %	NOS
LI[16]	2022	China	Patients with ACS	985	63.0 (54.0–70.0)	77.8	6.7 (4.0–11.7)	25.7 (23.3–27.8)	70.8	66.4	36.3	92.8	94.7	85.3	94.7	69.5	7
Qiu[17]	2022	China	Patients with IHF	189	64 ± 10.5	83.1	4.92 (2.55–6.84)	N/A	28.6	52.4	33.3	60.8	N/A	N/A	N/A	N/A	9
Eyileten[18]	2021	Austria	Patients with ACS	292	59 ± 12	80	2.57 (1.77–3.85)	27.8	7	63	21	57	100	93	93	88	9
Kinugasa[19]	2021	Japan	Patients with AHF	146	80 (73–85)	46.4	20.37 (10.45–38.31)	21.13 (18.44–23.44)	N/A	80.1	40.4	44.5	N/A	76.7	N/A	83.6	8
Gencer[20]	2020	Multiple countries	Patients with SCAD	1803	68 (60–74)	74.4	4.75	28.7 (25.3–33.7)	68.7	80.2	33.9	82.1	99.8	85.8	93.5	79	9
Zhou[21]	2020	China	Patients with ACS	1208	73 (64–80)	68.5	4.5	28.1 (25.4–30.2)	N/A	44.7	28.6	39.7	86.3	76.5	81.5	72.8	8
Matsuzawa[22]	2019	Japan	Patients with ACS	112	63 (56–71)	88	5.63 (3.20–10.38)	24.1 (22.0–26.6)	74	48	29	62	100	86	98	96	8
Svingen[23]	2018	Norway	Patients with SCAD	4141	62 (51–73)	71.9	7.57 (2.2–23.5)	26.3 (24.1–29.1)	31.7	46.7	14	N/A	N/A	N/A	N/A	N/A	8
Zhang[24]	2018	China	Patients with CAD and AF	200	62.7	54.5	5.02	23.1	46	34.5	14	9	N/A	N/A	N/A	N/A	8
Suzuki[25]	2017	UK	Patients with ACS	1079	67 (57–77)	72	3.70 (4.60–6.40)	N/A	42	52	23	N/A	85	81	89	84	7
Tang[26]	2017	USA	Patients with SCAD and T2DM	1216	64.4 ± 10.2	58	4.4 (2.8–7.7)	N/A	63	79	N/A	N/A	75	66	64	59	9
Xu[27]	2017	China	Patients with ACS	200	67.4 ± 12.8	44	5.94 ± 1.93	24.08	41.5	70.5	27.5	N/A	N/A	N/A	N/A	N/A	7
Senthong[28]	2016	USA	Patients with SCAD	2235	63 ± 11	71	3.8 (2.5–6.5)	N/A	70	76	35	N/A	81	70	71	N/A	9
Suzuki[29]	2016	UK	Patients with AHF	972	78 (69–84)	61	5.6 (3.4–10.5)	N/A	9.6	58.3	33.8	24.4	N/A	N/A	N/A	N/A	8
Tang[30]	2014	USA	Patients with CHF	720	66 ± 10	59	5.0 (3.0–8.5)	28.4 (25.1–33.1)	N/A	78	41	N/A	64	69	61	69	9

ACS = acute coronary syndrome, AF = atrial fibrillation, AHF = acute heart failure, BMI = body mass index, CAD = coronary artery disease, CHF = Chronic heart failure, IHF = ischemic heart failure, N/A = no applicable, NOS = Newcastle-Ottawa Scale, SCAD = stable coronary artery disease, T2DM = type 2 diabetes mellitus, TMAO = trimethylamine N-oxide.

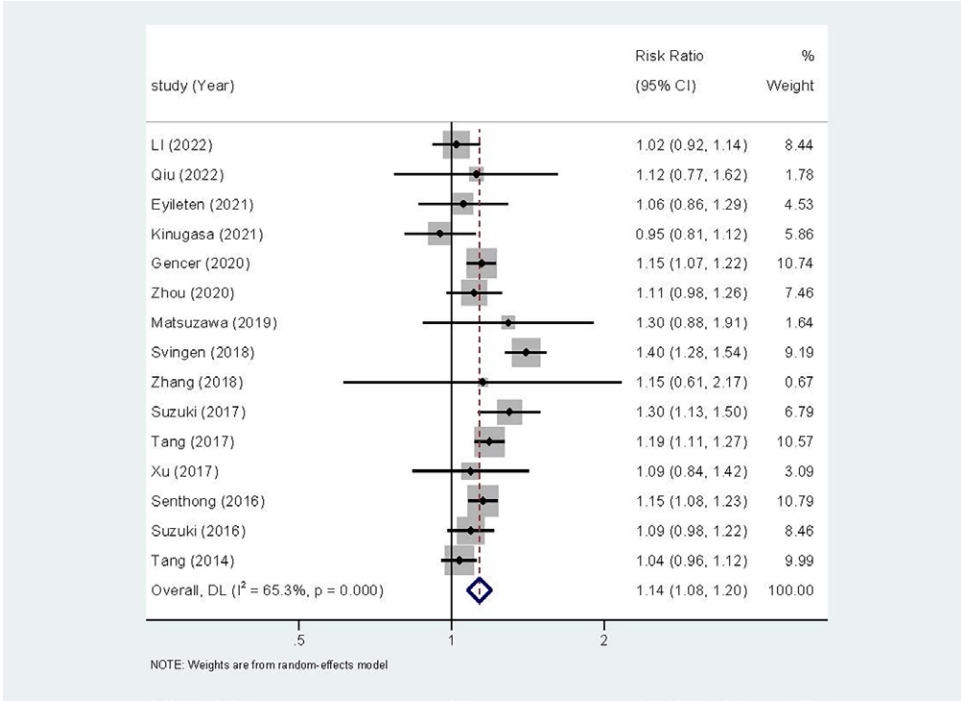

Figure 2. Forest plot of the relationship between circulating TMAO levels and the risk of hypertension in patients with cardiovascular disease. TMAO = trimethylamine N-oxide.

respectively.). If $I^2 < 50\%$, a fixed-effects model would be used to compute the pooled RR estimates. Otherwise, the pooled RR estimates would be calculated using a random-effects model. To investigate the source of heterogeneity, the following variables were used: country, disease status, sample size, average age, sex ratio, circulating TMAO concentration, BMI, proportion of smokers, proportion of hypertension, proportion of diabetes, proportion of dyslipidemia, proportion of aspirin users, proportion of statins users, proportion of β-blockers users, proportion of ACEI or ARB users. Begg and Egger tests were used to determine whether there was publication bias, and a sensitivity analysis was performed to test the results' reliability by eliminating each of the included studies sequentially.

The dose-response relationship between circulating TMAO levels and the risk of hypertension was evaluated by collecting the following data from the study: the average circulating TMAO level in each group; the total number of cases in each group; the total number of hypertension cases in each group. When the mean value of TMAO is not reported in the study, the average of the upper and lower intervals is used; when the TMAO level is an open interval, the interval lowest limit is multiplied by 1.5. The dose-response relationship between circulating TMAO level and the risk of hypertension was analyzed using the data presented above, and a dose-response diagram was created.

3. Result

3.1. Characteristics of the included studies

A total of 2874 potentially relevant publications were identified, including CNKI (n = 141), WanFang database (n = 127), Embase (n = 1237), PubMed (n = 511), Web of science (n = 806), Cochrane library (n = 52). After screening the titles and abstracts, our meta-analysis included 15 studies with a total of 15,498 participants.[16–30] (the flow chart for the study selection is shown in Figure 1).

The average age of the included studies' participants ranged from 59 to 80 years, the average TMAO level ranged from 2.57 to 20.37 μ mol/L, and the proportion of men ranged from 44 to 88 percent. A total of twelve studies on the dose-response relationship between circulating TMAO levels and the risk of hypertension in patients with CVD were included.[16–18,20–23,25,26,28–30] The results of study quality revealed that the NOS scores of 3 studies were 7,[16,25,27] 6 studies had NOS scores of 8,[19,21–24,29] and 6 studies had NOS scores of 9.[17,18,20,26,28,30] (the general characteristics of the included studies are illustrated in Table 1).

3.2. The association between circulating TMAO levels and hypertension risk in patients with cardiovascular disease

The relationship between circulating TMAO levels and the risk of hypertension in patients with CVD was reported in fifteen of the included studies. A random effect model was used for Meta analysis due to the statistical heterogeneity among the studies ($I^2 = 65.3\%$ $P < .001$). The results revealed that circulating TMAO levels were associated with the risk of hypertension in patients with CVD (RR = 1.14, 95%CI (1.08, 1.20))(Fig. 2). And the higher the level of TMAO in the patient, the greater the risk of developing hypertension.

Subgroup analysis is required to identify the source of heterogeneity in studies on the relationship between circulating TMAO levels and the risk of hypertension in patients with CVD due to statistical heterogeneity ($I^2 = 65.3\%$ $P < .001$). To investigate the source of heterogeneity, the following variables were used: country, disease status, sample size, average age, sex ratio, circulating TMAO concentration, BMI, proportion of smokers, proportion of hypertension, proportion of diabetes, proportion of dyslipidemia, proportion of aspirin users, proportion of statins users, proportion of β-blockers users, proportion of ACEI or ARB users. Following the subgroup analysis, the results revealed that no significant source of heterogeneity was discovered, indicating that additional sensitivity analysis is required (Table 2).

Table 2

Subgroup analysis of the relationship between circulating TMAO levels and the risk of hypertension in patients with cardiovascular disease

		Overall effect		Heterogeneity	
Subgroups	**Studies, (n)**	**RR (95% CI)**	***P* value**	**I^2, %**	***P* value**
All	15	1.14 (1.08, 1.20)	<.001	65.3	<.001
Study location					
Asia	7	1.05 (0.98, 1.12)	.156	0	.698
Europe	5	1.20 (1.08, 1.33)	.001	78.4	.001
North America	3	1.13 (1.04, 1.22)	.002	71.9	.028
Disease status					
Patients with CAD	11	1.16 (1.09, 1.23)	<.001	70.7	<.001
Patients with HF	3	1.05 (0.96, 1.15)	.305	5.4	.348
Patients with arrhythmia	1	1.15 (0.61, 2.17)	.657	—	—
Year of publication					
≥2019	7	1.09 (1.02, 1.15)	.005	18.8	.287
<2019	8	1.18 (1.09, 1.27)	<.001	75.1	<.001
Participants, n					
≥1000	6	1.21 (1.13, 1.29)	<.001	70.3	.005
<1000	9	1.05 (1.00, 1.10)	.072	0	.883
Male, %					
≥70%	8	1.18 (1.09, 1.28)	<.001	71.6	<.001
<70%	7	1.09 (1.02, 1.16)	.007	42	.111
Mean/median, yr					
≥65	7	1.10 (1.04, 1.17)	.002	51.8	.052
<65	8	1.17 (1.08, 1.28)	<.001	68.3	.002
Mean circulating TMAO, μ mol/L					
≥5	8	1.11 (0.99, 1.24)	.074	79.2	<.001
<5	7	1.16 (1.12, 1.20)	<.001	0	.6
Smoking, %					
≥50	5	1.14 (1.09, 1.20)	<.001	31.8	.209
<50	7	1.19 (1.07, 1.34)	.002	63.3	.012
N/A	3	1.04 (0.97, 1.11)	.251	10	.329
BMI (kg/m^2)					
≥26	4	1.19 (1.05, 1.34)	.007	80.9	.001
<26	6	1.03 (0.97, 1.09)	.31	0	.754
N/A	5	1.17 (1.12, 1.22)	<.001	5.7	.374
Hypertension, %					
≥60	8	1.10 (1.04, 1.16)	<.001	53.6	.035
<60	7	1.22 (1.09, 1.35)	<.001	62.5	.014
Diabetes, %					
≥30	7	1.09 (1.03, 1.14)	.001	45	.091
<30	7	1.22 (1.09, 1.35)	<.001	55.5	.036
N/A	1	1.19 (1.11, 1.27)	<.001	—	—
Dyslipidemia, %					
≥60	4	1.11 (1.03, 1.19)	.008	21.1	.283
<60	5	1.07 (1.00, 1.14)	.061	0	.626
N/A	6	1.19 (1.09, 1.30)	<.001	81	<.001
Aspirin use, %					
≥90	4	1.10 (1.02, 1.19)	.012	26.4	.253
<90	5	1.15 (1.07, 1.22)	<.001	62.9	.029
N/A	6	1.13 (0.97, 1.33)	.125	77.7	<.001
Beta-blocker use, %					
≥80	5	1.14 (1.04, 1.24)	.005	52.1	.08
<80	5	1.10 (1.03, 1.18)	.005	65.1	.022
N/A	5	1.19 (1.02, 1.40)	.032	70.2	.009
Statin use, %					
≥90	4	1.10 (1.02, 1.19)	.012	26.4	.253
<90	5	1.15 (1.07, 1.22)	<.001	62.9	.029
N/A	6	1.13 (0.97, 1.33)	.125	77.7	<.001
ACEI or ARB use, %					
≥80	4	1.12 (0.94, 1.34)	.191	67.5	.026
<80	5	1.11 (1.04, 1.17)	.001	59.6	.042
N/A	6	1.19 (1.07, 1.32)	.002	68.5	.007
NOS					
≥8	12	1.14 (1.07, 1.21)	<.001	66.4	.001
<8	3	1.13 (0.95, 1.35)	.154	72.2	.027

NOS = Newcastle-Ottawa Scale, TMAO = trimethylamine N-oxide.

3.3. Publication bias and sensitivity analysis

The Egger test (t = -0.36, P = .724) and Begg test (Z = 0.20, P = .843) indicated no statistically significant publication bias in this meta-analysis (Fig. 3). The funnel diagram depicts a roughly symmetrical distribution. The sensitivity analysis revealed that the consolidated results were all stable (Fig. 4).

3.4. Dose-response analysis

The dose-response relationship between circulating TMAO levels and the incidence of hypertension was studied using 12 studies and 14,952 patients.[16–18,20–23,25,26,28–30] The results revealed a linear dose-response relationship between circulating TMAO levels and the risk of hypertension in patients with CVD. The risk of hypertension increased by 1.014% when the circulating TMAO level increased by 1 μ mol/L. The risk of hypertension increased by 7.34% when the circulating TMAO level was 5 μ mol/L, and by 15.22% when the circulating TMAO level was 10 μ mol/L (Fig. 5).

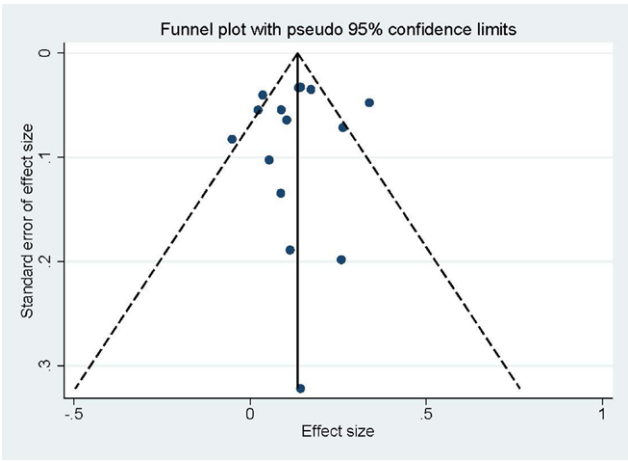

Figure 3. Funnel diagram of the relationship between circulating TMAO levels and risk of hypertension in patients with cardiovascular disease. TMAO = trimethylamine N-oxide.

4. Discussion

The results of this study show a direct link between circulating TMAO concentration and an increased risk of hypertension in CVD patients. CVD patients with high TMAO concentrations had a 14% increased risk of developing hypertension compared to CVD patients with low TMAO concentrations. Simultaneously, there was a linear dose-response relationship between circulating TMAO concentration and hypertension risk in CVD patients. The risk of hypertension increased by 1.014% for every 1 μ mol/L increase in circulating TMAO concentration

TMAO is a small molecular organic compound (75.11g/mol) produced primarily by the oxidation of trimethylamine (TMA) in the gut microbiota. When the human body consumes foods containing L-carnitine, choline, and betaine, these substances are converted into TMA by various enzymes in the gut microbiota. The majority of TMA is passively absorbed into the portal circulation and oxidized to TMAO in the liver by flavin-containing monooxygenases (FMOS).[31] The high concentration of TMAO in the bloodstream increases the risk of MACE and all-cause death in CVD patients. First, TMAO inhibits cholesterol reverse transport and increases cholesterol accumulation in macrophages, resulting in increased foam cell formation and dyslipidemia, as well as atherosclerotic plaques[32,33]; Furthermore, TMAO can impair endothelial function and cause vascular inflammation, leading to vascular dysfunction.[34–36] According to the latest research, TMAO also promotes platelet aggregation, which increases the risk of blood clots and makes atherosclerotic plaques more likely to rupture.[37,38] In addition, circulating TMAO concentration have been independently associated with subclinical myocardial damage.[39]

The latest evidence suggests that the gut-brain-bone marrow (BM) axis, which includes gut microbiota, gut epithelial wall permeability, increased production of pro-inflammatory BM cells, and neuroinflammation, plays an important role in hypertension. Hypertension can cause an imbalance in the gut microbiota, a weakening of the intestinal barrier, and inflammation. Inflammatory mediators produced in the intestine can easily

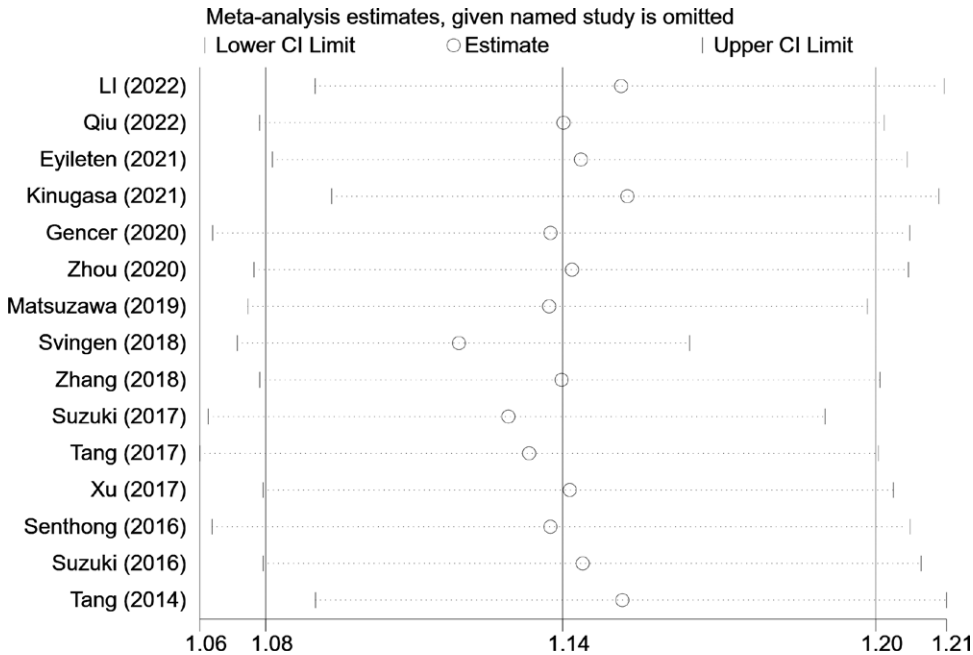

Figure 4. Sensitivity analysis of the relationship between circulating TMAO levels and the risk of hypertension in patients with cardiovascular disease. TMAO = trimethylamine N-oxide.

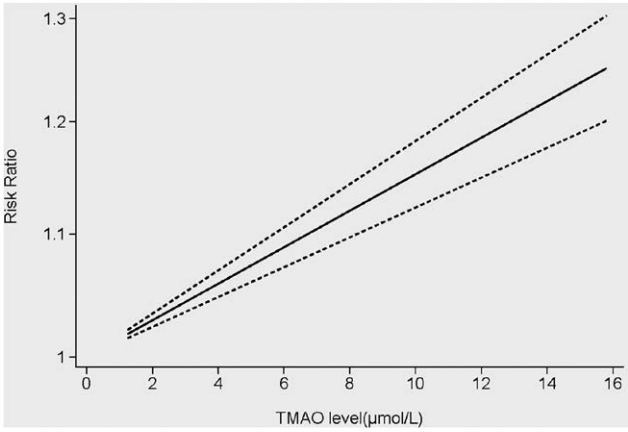

Figure 5. Dose-response relationship between circulating TMAO levels and the risk of hypertension in patients with cardiovascular disease. TMAO = trimethylamine N-oxide.

cross the weakened intestinal barrier and circulate to the brain, causing neuroinflammation and mild systemic inflammation. The interaction of these 3 organs strengthens their individual responses, resulting in hypertension maintenance and increase, creating a vicious circle.[40] A proven triangle exists between salt, high blood pressure, and gut microbiota. The gut microbiota produces 2 major products: short-chain fatty acids (SCFAs) and TMAO. SCFAs play an important role in blood pressure regulation, while TMAO is also involved in the development of atherosclerosis and hypertension. High salt consumption can cause an increase in TMAO and a decrease in SCFAs in the intestine, causing intestinal disorders and promoting the onset and progression of hypertension.[41] TMAO may also play a role in the pathogenesis of hypertension in a variety of ways and can help predict the severity of hypertension.[42] The renin-angiotensin-aldosterone system (RAAS) impacts cardiovascular homeostasis via direct actions on peripheral blood vessels and via modulation of the autonomic nervous system. Angiotensin (Ang) II is the main effect substance of RAAS, which increases blood pressure through various pathways.[43] TMAO can prolong the hypertensive effect of Ang II, lengthen the duration of hypertension, and increase susceptibility to hypertension.[44] Furthermore, TMAO promotes Ang II-induced vasoconstriction, which promotes Ang II-induced hypertension and damages glomerular filtration rate via the PERK/ROS/CaMKII/PLC3 axis.[45] According to the findings of a recent animal experimental study, an increase in TMAO levels can lead to higher plasma osmotic pressure and trigger the regulation of the "TMAO-AVP-AQP-2" axis in rats, which causes increased water reabsorption and eventually leads to hypertension.[46] It is well known that the risk of CVD increases exponentially with age, and the level of circulating TMAO has also been shown to increase with age. High levels of TMAO can cause oxidative stress, which can lead to endothelial dysfunction and eventually lead to hypertension.[47] Furthermore, an increase in TMAO could be a new mechanism causing aortic stiffness. When the aorta hardens, its elasticity weakens and the velocity of blood flow in the blood vessels increases, resulting in an increase in blood pressure and eventually lead to hypertension.[48] TMAO-induced advanced glycation end-products (AGEs) accumulation, as well as superoxide-related oxidative stress, which causes aortic hardening and increases systolic blood pressure.[49]

The studies discussed above reveal a link between TMAO and hypertension and provide preliminary evidence that circulating TMAO levels can predict the risk of hypertension in CVD patients. However, there are some unanswered questions about the relationship between circulating TMAO levels and hypertension. First, there is a lack of long-term monitoring of TMAO concentration in CVD patients, which makes it impossible to determine the long-term average concentration and source of TMAO in CVD patients, and it is impossible to determine whether high levels of TMAO cause hypertension. Second, while the strategy for reducing TMAO levels through dietary intervention to reduce the risk of CVD has been confirmed,[50] the intervention for TMAO is still in the animal experimental stage, and there is no effective treatment in clinic. As a result, more research is needed to investigate the link between circulating TMAO concentrations and hypertension in CVD patients.

5. Study limitations

When interpreting the results, many potential limitations of our study must be considered. First, there are some differences between research groups, such as research objects, countries, regions, races, and eating habits, which may cause results to differ. Second, there is no systematic correction of various factors of the research objects for the study of hypertension, and the results may be influenced by multiple factors. Third, the setting of the boundary value of the TMAO level interval varies greatly between research cohorts, which may have an effect on the results. Given these limitations, additional research is needed to validate our finding of a link between circulating TMAO levels and hypertension in patients with CVD.

6. Conclusions

The results of this study show that circulating TMAO levels are associated with the incidence of hypertension in patients with CVD. In patients with CVD, there is a linear dose-response relationship between circulating TMAO levels and the risk of hypertension. The risk of hypertension increased by 1.014% when the circulating TMAO level increased by 1 μ mol/L. Elevated circulating TMAO levels may indicate an increased risk of hypertension in patients with CVD.

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The authors' contributions were as follows. Y.M.: Devised the study; L.G., X.C.: contributed to data collection, analysis, and interpretation of data; X.S., Y.M.: carried out the quality assessment; J.H.: wrote the initial draft of the manuscript; J.H., L.G., X.C., Q.X., X.S., Y.M.: participated in the discussion and approved the final manuscript.

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