INPLASY PROTOCOL

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Support: **None.**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Circulating trimethylamine-N-oxide and all-cause or cardiovascular mortality risk in patients with chronic kidney disease: a systematic review and meta-analysis

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Review question / Objective: **Trimethylamine-N-oxide (TMAO) might act as a novel biomarker for prognostic risk stratification of CKD-related all-cause or cardiovascular mortality. To date, several studies have explored the associations between TMAO and the risk of all-cause or cardiovascular mortality in CKD patients, but these findings are inconsistent. To address this issue, we performed this meta-analysis to summarize the published studies on the relationship of circulating TMAO levels with all-cause or cardiovascular mortality risk in CKD patients.**
Information sources: **The electronic databases including Pubmed, EMBASE, and Web of Science will be searched for the information sources.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 October 2021 and was last updated on 16 October 2021 (registration number INPLASY2021180049).

INTRODUCTION

Review question / Objective: **Trimethylamine-N-oxide (TMAO) might act as a novel biomarker for prognostic risk stratification of CKD-related all-cause or cardiovascular mortality. To date, several studies have explored the associations between TMAO and the risk of all-cause or cardiovascular mortality in CKD patients, but these findings are inconsistent. To address this issue, we performed this meta-analysis to summarize the published studies on the relationship of circulating**

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TMAO levels with all-cause or cardiovascular mortality risk in CKD patients.

Condition being studied: In recent years, the interest in the relationship of the gut microbiome with health and disease is burgeoning, and the relation between intestinal flora and CKD is also a developing research area. Trimethylamine-N-oxide (TMAO), which is a small-molecule bioactive compound derived from intestinal microbial metabolism, has been attracting much attention recently. TMAO is normally present at low levels in circulating blood, and its abnormal or excessive accumulation can cause a wide range of diseases, such as diabetes, hypertension, cardiovascular disease, and CKD. Renal excretion is the primary route for TMAO clearance. When the kidney is diseased or injured, the accumulative TMAO can exacerbate renal inflammation and fibrosis, which further causes renal dysfunction.

METHODS

Participant or population: We will include CKD patients who had been followed up for over 1 years. Patients with acute kidney injury or pre-kidney transplantation would be excluded.

Intervention: Circulating TMAO levels will be main Exposure/Interventions.

Comparator: Comparing the highest versus lowest TMAO levels at baseline.

Study designs to be included: Cohort studies.

Eligibility criteria: The eligibility criteria are as follows: (1) cohort studies that evaluated the relationship of circulating TMAO levels with all-cause or cardiovascular mortality; (2) study populations who were CKD patients with or without undergoing dialysis; (3) CKD patients who had been followed up for over 1 years.

Information sources: The electronic databases including Pubmed, EMBASE, and Web of Science will be searched for the information sources.

Main outcome(s): The multivariable-adjusted hazard ratio (HR) and the corresponding 95% confidence interval (CI) will be pooled to estimate the associations of TMAO with the risk of all-cause and cardiovascular mortality.

Quality assessment / Risk of bias analysis: Study quality of the included studies will be assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies.

Strategy of data synthesis: We will perform random effect model if there is significant heterogeneity, while fixed effect model will be used when the heterogeneity was not significant.

Subgroup analysis: Subgroup analysis will be conducted according to geographic region, sample size, sample types, and follow-up duration.

Sensitivity analysis: Sensitivity analysis will be conducted to assess the stability of the results by sequentially removing one study at a time.

Country(ies) involved: China.

Keywords: Trimethylamine-N-oxide; Chronic kidn disease; all-cause mortality; cardiovascular mortality; meta-analysis.

Contributions of each author:
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