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The association between trimethylamine N-oxide levels and ischemic stroke occurrence: a meta-analysis and mendelian randomization study

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 October 2023 and was last updated on 07 October 2023.

INTRODUCTION

Review question / Objective The association between trimethylamine N-oxide levels (TMO) and ischemic stroke (IS) occurrence, and whether TMO plays a causal role in IS.

Condition being studied Stroke is the second leading cause of death nowadays whilst ischemic stroke accounts for 85% of stroke incidences globally. IS is caused by an abrupt blockage of blood flow that results in damage to the central nervous system and thus disability or death of the patients. IS is always an emergent threat to humans.

METHODS

Search strategy Systematic research was performed in PubMed, Web of Science, and Embase for the related studies up until September 2023. Our medical subject heading terms were "(Trimethylamine N-oxide[Title/Abstract] OR TMAO[Title/Abstract]) AND (ischemic stroke[Title/Abstract])" for PubMed, "(TS=(Trimethylamine N-oxide OR TMAO)) AND TS=(Ischemic stroke)" for Web of Science, "((Trimethylamine N-oxide or TMAO) and ischemic stroke).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]" for Embase. The screened references for the articles were manually checked (Table S1). The publications both in English and Chinese were included, and EndNote 21 was used to remove duplicate articles.

Participant or population Studies were included if they were case-control, or cohort studies reported the TMAO levels of both IS patients and healthy controls.

Intervention Not applicable.

Comparator Not applicable.

Study designs to be included Case-control, or cohort studies.

Eligibility criteria The inclusion criteria for the patients in this meta-analysis were: (1) studies including both consecutive patients with first-ever ischemic stroke and controls; (2) symptoms onset less than 24 h; (3) blood sample collected within 24 h post IS onset. The exclusion criteria for this study were: (1) subjects with myocardial infarction, heart failure, malignant tumor, or other systemic diseases; (2) subjects had used antibiotics/ prebiotics or experienced gastrointestinal symptoms in the past 3 months; (3) systematic reviews, meta-analysis articles, and conference abstracts.

Information sources The studies for the meta-analysis were obtained from PubMed, Web of Science, and Embase.
The data for the Mendelian Randomization study were obtained from the IEU GWAS database and the Genotypes and Phenotypes database.

Main outcome(s) First-ever occurrence of ischemic stroke.

Quality assessment / Risk of bias analysis The evidence levels of identified studies were assessed according to the criteria by the Centre for Evidence-Based Medicine in Oxford, UK. The quality of each publication was evaluated by bias analysis using Review Manager 5.3. A funnel plot of all included studies, as well as the Begg's test and the Egger's test, was exploited for assessment of publication bias.

Strategy of data synthesis All the statistical analysis was performed using Review Manager 5.3 and Stata/SE 12.0. Since the obtained data for TMAO levels were continuous, the weighted mean differences with 95% CI were used to compare the difference of TMAO between IS patients and the controls. Statistical heterogeneity among the studies was quantified using the I2 statistic. A random-effect model was used if the studies were heterogeneous, while otherwise, a fix-effect model was adopted.

Subgroup analysis Subgroup analyses were performed to evaluate the effect of race or sample variations.

Sensitivity analysis We performed the sensitivity analyses by excluding one study at a time to estimate the influence of every single study on the overall estimate.

Language restriction The publications both in English and Chinese were included.

Country(ies) involved China.

Keywords trimethylamine-N-oxide, ischemic stroke, meta-analysis, mendelian randomization.

Contributions of each author

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