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Association between tryptophan concentrations and the risk of developing cardiovascular diseases: a systematic review and meta-analysis

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Abstract

Background Metabolic regulation of various amino acids have been proven to be effective in preventing cardiovascular disease (CVD). The impact of tryptophan, an essential amino acid, on the risk of developing CVD has not been fully elucidated.

Aims The aim of this meta-analysis was to systematically review evidence of the effects of tryptophan on CVD risk.

Methods The PubMed, Embase, Web of Science, Cochrane Library, and China National Knowledge Infrastructure (CNKI) databases were searched to collect relevant trials from inception to August 2024. The means and hazard ratios (HRs) were extracted and pooled. Subgroup analysis was performed to identify pooled effect estimates, and sensitivity analysis was conducted to assess the robustness of the pooled estimates.

Results Data were collected from 34,370 people under follow-up for CVD events in 13 studies, including cohort studies and case-control studies. They were categorized into three groups on the basis of sample type and indicators: the plasma tryptophan level group, the plasma tryptophan CVD hazard group, and the urinary tryptophan CVD hazard group. The CVD included in this study were coronary artery disease, heart failure, and peripheral artery disease. Twelve studies on plasma tryptophan were meta-analyzed. The plasma tryptophan levels in CVD patients were generally lower than those in individuals without CVD (SMD = -8.57, 95%CI (-15.77, -1.37), $P=0.02$). Decreased circulating tryptophan levels are associated with cardiovascular disease risk (HR = 0.85, 95%CI (0.78, 0.92), $P<0.00001$).

Conclusions Decreased circulating tryptophan levels are associated with an increased risk of CVD events. Intervention in circulating tryptophan levels may be indicated to help prevent CVD.

Keywords Tryptophan, Cardiovascular diseases, Epidemiology, Nutritional compounds, Metabolic disorder, Meta-analysis

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Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide and remains a major cause of rising health care costs [1]. In 2019, the number of prevalent cases and deaths attributed to CVD reached 523 million and 18.6 million worldwide, respectively [2]. The internal mechanisms of cardiovascular events are extremely complex and are influenced by a myriad of factors. Micro- and macrovascular functions, including impaired vasodilation capacity and increased vasoconstriction responsiveness, are the main contributing factors to CVD burden [3].

In addition to traditional risk factors, such as hypertension, hyperlipidemia, diabetes, smoking, and obesity, metabolic disturbances are intimately involved in the pathogenesis of CVD [4]. Amino acid metabolism has been reported to be an important participant in the development of CVD [5, 6]. For example, branched-chain AAs promote endothelial cell dysfunction through increased reactive oxygen species generation and inflammation [7]. Aromatic amino acids also have important effects on the natural progression of cardiovascular disease. Similarly, tryptophan (Trp) metabolites have been shown to be closely related to inflammation and are thus suggested to be involved in CVD [8, 9].

Trp is an essential amino acid that plays a crucial role in protein biosynthesis and serves as a precursor for the synthesis of various important bioactive compounds. Trp influences various pathophysiological processes, including neuronal function, metabolism, inflammatory responses, oxidative stress, immune responses, and intestinal homeostasis [10–12]. It is related to various vascular complications and cardiovascular diseases, such as atherosclerosis, endothelial dysfunction, heart disease, and hypertension [13]. An increasing number of studies have investigated the association between Trp and CVD events. An accelerated Trp breakdown rate is associated with inflammation and immune activation [14], which further affects the progression of cardiovascular disease. However, previous studies [15–17] have contradicted the current mainstream results [14, 18] concerning plasma Trp levels in patients with CVD. The overall risk indicators of Trp on cardiovascular events also varied significantly across studies [19–25]. Additionally, it is not clear whether there is an intrinsic association between the latest study of urine Trp and previous studies of plasma Trp [26]. Hence, a meta-analysis may lead to a better conclusion on the association of Trp with CVD risk.

Materials and methods

Eligibility criteria

The present meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27]. The study protocol has been registered on PROSPERO (registration number CRD42024533266).

Search strategy

The PubMed, Embase, Web of Science, Cochrane Library, and CNKI mainstream databases were searched with no language restrictions. Our literature search terms combined all the synonyms for tryptophan and cardiovascular disease. In addition, the studies were limited to those with human subjects. The search time was set from the earliest available online indexing year to August 2024. In addition, manual searches of reference lists compiled from relevant original (or review) articles were conducted.

Literature selection

Two independent reviewers (JZ and CMZ) adhered to the following inclusion criteria: (1) participants: patients with cardiovascular-related diseases; (2) exposure: circulating Trp concentrations, as a continuous variable; (3) comparison: people without cardiovascular disease or study was self-controlled; (4) outcome: cardiovascular disease events (coronary artery disease, ischemic heart disease, myocardial infarction, heart failure, stroke, peripheral artery disease); (5) study design: a cohort, a case–cohort, a case–control or a nested case–control study; (6) means with standard deviations and hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were provided for Trp or could be back-calculated using the provided data. Exclusion criteria: (1) duplicate publications; (2) animal experiments, cell experiments, reviews, conference abstracts and other literatures without available data; (3) literatures with poor quality and obvious statistical errors.

Data extraction

After removing duplicates, titles, and abstracts, the entire manuscript was independently screened by two reviewers. Data extraction was conducted independently. The author, year, country, sources of participants, population characteristics, sample type (serum or urine), method of assessment, association estimates per concentration of Trp, adjustment factors and other basic information were extracted. Discrepancies in the process of study selection and data extraction were resolved through discussion and consensus between the two abovementioned researchers. If discrepancies could not be resolved, a senior researcher joined and decided whether studies should be included. If multiple outcomes are reported in the paper, the outcome with the largest number of participants would be extracted for meta-analysis.

Quality assessment, risk of bias assessment and sensitivity analysis

The Newcastle–Ottawa scale (NOS) was used to assess the quality of the included studies. Each study was assessed from three perspectives, including the selection of study groups, which provided a score between 0 and 4 points, comparability of groups (0–2 points), and ascertainment of outcomes (0–3 points). Studies with more than six points were considered high quality. The risk of bias was assessed using the Cochrane handbook. Funnel plots were plotted for publication bias. Statistical assessment of the asymmetry in the funnel plot was performed via Egger's regression asymmetry test and Begg's adjusted rank correlation test. Sensitivity analysis plots were plotted to examine the effect of each trial on the pooled effect size. For all analyses, P values <0.05 were considered statistically significant.

Data analysis

Statistical meta-analyses were performed using the RevMan5.3 software. Standardized mean difference (SMD) and multivariable adjusted effect estimates (HRs with 95% CIs) were meta-analyzed to obtain pooled effect estimates. $P<0.05$ was considered statistically significant. Stata12.0 software was used to detect publication bias, Egger and Begg methods were mainly used, $P>0.05$ indicates no significant publication bias. Heterogeneity among studies was assessed by means of the Cochrane Q statistic and I^2 statistic. The random-effects model (DerSimonian and Laird method) was adopted for meta-analysis.

Results

Literature search results

The flow chart of the literature search and study selection is shown in Fig. 1. A total of 1,029 publications were initially identified; after duplicates were removed, 1,007 records remained for title and abstract screening. Among these studies, 970 records were excluded because they were animal studies, review articles or nonrelated experimental studies. Finally, thirteen studies were included and categorized into three groups on the basis of sample type and indicators: the plasma tryptophan level group, the plasma tryptophan CVD hazard group, and the urinary tryptophan CVD hazard group. The characteristics of the studies included are provided in Table 1. Owing to the limited research available on this topic, only a systematic review of the urinary tryptophan CVD hazard group was performed. This group's data were not included in the meta-analysis. We categorised studies with a low risk of bias in three key domains (random sequence generation, allocation concealment, and missing participant outcome data) as having low overall risk of bias.

Qualitative analysis

The characteristics of the studies included in the review are shown in Table 1 and include a variety of cardiovascular diseases and 34,370 patients. The cardiovascular diseases included in this study were coronary artery disease, heart failure, and peripheral artery disease. There are a total of 5 research papers reporting plasma levels of Trp in cardiovascular patients, and these studies were published many years ago. Four studies reported that, compared with healthy controls, cardiovascular patients had varying degrees of decreased levels of Trp. Only one study did not support the abovementioned results. Recent studies have reported the hazard ratio of cardiovascular events to plasma Trp, with a total of 7 studies included. These studies all indicated that plasma Trp is a protective factor against the development of CVD. However, one study revealed a positive association between urinary Trp concentrations and incident CVD.

Analysis of the risk of bias

As shown in Table 1, only one study had an NOS score lower than 6 points, indicating an overall medium to high quality of research. Visual inspection of the funnel plot (Fig. 2) revealed no potential publication bias. In addition, bias testing revealed that the P values for the plasma tryptophan level group ($P=0.35$) and plasma tryptophan CVD hazard group ($P=0.968$) indicated no apparent bias in the literature of this review. Sensitivity analysis was performed on 5 subjects from the plasma tryptophan level group and 7 subjects from the plasma tryptophan CVD hazard group. The results indicated that none of the articles had a strong impact on the research results (Fig. 2).

Quantitative analysis

The data for the plasma tryptophan level group was available in 5 trials, including 1,451 cases. The random-effects model was used for analyses. The results revealed that the plasma Trp levels in CVD patients were generally lower than those in individuals without CVD (SMD = -8.57, 95%CI (-15.77, -1.37), $P=0.02$). The I^2 index was 93% and the Cochran Q test was significant at $P<0.00001$. The sample size and type of disease included in the study vary greatly, which may lead to some heterogeneity. The random-effects model was used for analysis. The results from seven studies involving a total of 30,625 individuals indicated that decreased circulating Trp levels are associated with cardiovascular disease risk (HR=0.85, 95%CI (0.78, 0.92), $P<0.00001$). The I^2 index was 34% and the Cochran Q test was not statistically significant with $P=0.17$. The forest plots of the above two groups was shown in Fig. 3.

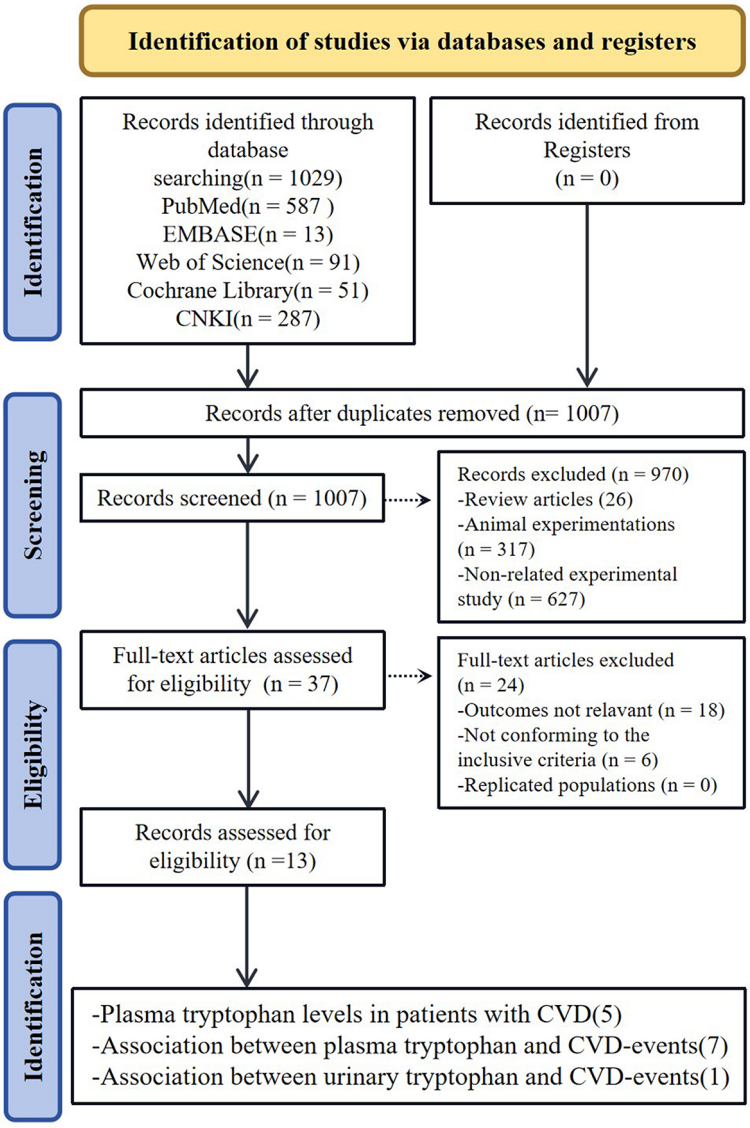

Fig. 1 Flow chart of the literature search and study selection

Discussion

In this systematic review and meta-analysis, data from studies reporting the relationship between Trp and CVD over the past 21 years were pooled. It included 34,370 individuals. The cardiovascular diseases included in this study were coronary artery disease, heart failure, and peripheral artery disease. Current evidence suggests that there is a decrease in the plasma Trp concentration in CVD patients. Moreover, plasma Trp is negatively associated with cardiovascular events. A reduction in circulating Trp levels may serve as a significant predictor of adverse outcomes in patients with CVD.

Previous studies on the reduction in Trp levels in patients with CVD have focused predominantly on Trp metabolism. The metabolic pathways of Trp include the kynurenine pathway, the 5-hydroxyindole pathway, and the gut microbial metabolism pathway [28]. The kynurenine pathway accounts for more than 95% of these genes [29]. Studies on the kynurenine/tryptophan pathway have shown that an increase in the plasma kynurenine/tryptophan ratio is positively associated with the risk of developing CVD and atherosclerosis [20, 25, 30, 31]. Furthermore, inflammation is also a potential factor contributing to decreased levels of Trp in patients with cardiovascular diseases [32]. In CVD patients, the Th1-type cytokine IFN-γ causes increased 2,3-dioxygenase activity, which ultimately decreases the serum levels of Trp [33]. A recent prospective cohort study suggested that increased dietary intake of aromatic amino acids is associated with a reduced risk of CVD mortality over 20 years of follow-up [34]. In this study, the intake of tyrosine was independently associated with a reduced risk of CVD

Table 1 Characteristics of studies included in the review

Grouping	Reference	Country	Study design	NOS score	Average age	*N*, follow-up(year)	Male (%)	Case/ Outcome
Plasma tryptophan level group	Aquilani [16]	Italy	Case-control	7	(69.7 ± 11.4)~(71 ± 4.5)	46 (38, 8), NR	83	Stroke
	Murr [14]	Austria	Nested case-control	5	NR	1196, 10.7	NR	CAD
	Ormstad [15]	Norway	Case-control	8	(67.7 ± 11.8)~(59.1 ± 5.7)	85 (45, 40), NR	53	AIS
	Ozkan [18]	Turkey	Case-control	7	(62.6 ± 8.4)~(54.3 ± 10.7)	54 (36, 18), NR	67	CAD
	Wirleitner [17]	Latvia	Case-control	7	(60.8 ± 9.5)~(42.1 ± 10.4)	70 (35, 35), NR	50	CAD
Plasma tryptophan CVD hazard group	Hu [19]	USA	Cohort, prospective	7	(71.2 ± 4.1)~(72.2 ± 4.5)	13,669, NR	NR	CAD
	Li [24]	China	Cohort, prospective	6	(61.72 ± 11.21)~(70.23 ± 9.73)	1829 (424, 1405), 9.2	23	CAD
	Qi [25]	USA	Cohort, prospective	6	42(38–46) ~ 47(45–54)	737 (112, 625), 7	15	CVD
	Razquin [20]	Spain	Cohort, prospective	6	(68.2 ± 6.1)~(70.3 ± 5.8)	1046 (502, 544), NR	48	HF
	Razquin [21]	Spain	Case-control, prospective	6	(67.6 ± 6.8)~(68 ± 6.8)	417 (167, 250), 4.8	40	PAD
	Teunis [22]	UK	Cohort, prospective	7	(56.6 ± 8.8)~(62.0 ± 8.4)	11,972 (6989, 4983), 22.1	58	CAD
	Yu [23]	USA	Cohort, prospective	7	69.06 ± 5.7	955 (231, 724), 4.7	24	CVD
Urinary tryptophan CVD hazard group	Hs [22]	China	Cohort, prospective	6	61.9 ± 10.6	2294 (1374, 920), > 20	60	CAD

Note NR = Not reported, CAD = Coronary artery disease, CVD = Cardiovascular disease, AIS = Acute ischemic stroke, HF = Heart failure, PAD = Peripheral artery disease

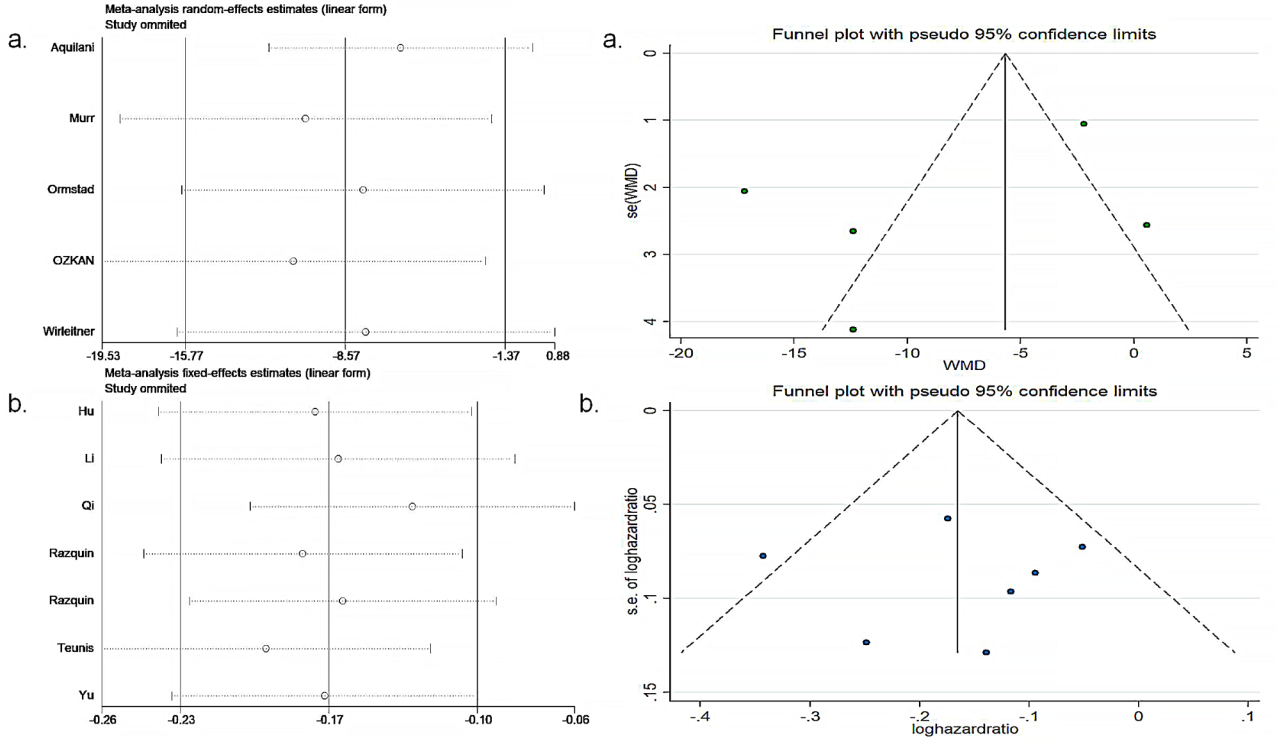

Fig. 2 Sensitivity analysis and funnel plot based on visual inspection (**a**. the plasma tryptophan level group, **b**. the plasma tryptophan CVD hazard group)

mortality. The precise mechanisms by which increased levels of exogenous Trp exert cardiovascular protective effects remain unclear.

However, urinary Trp has been reported to be positively associated with CVD [26]. Consistent with previous studies on plasma Trp, an increase in urinary Trp loss may further exacerbate the reduction in circulating Trp levels. Currently, research on urinary Trp is limited and focused on tyrosine metabolites [35, 36], with only one study meeting the inclusion criteria for this study, elucidating the impact of urinary Trp levels on the risk of developing CVD. In contrast to plasma Trp levels,

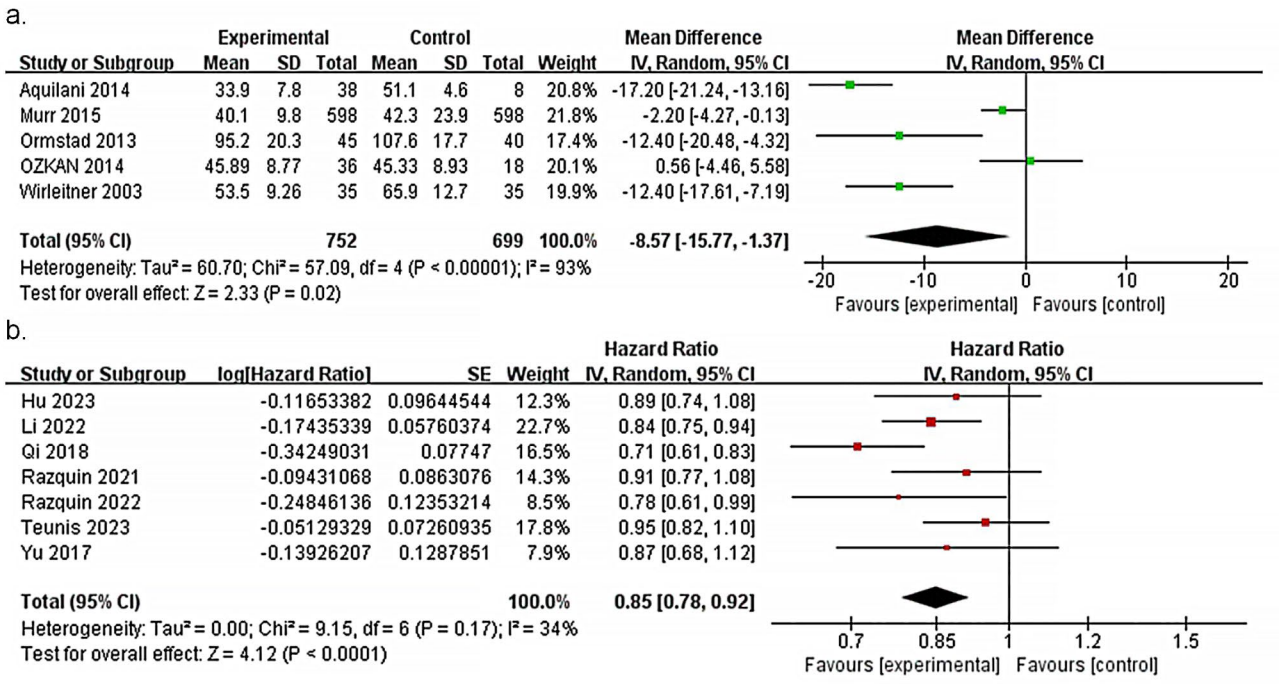

Fig. 3 Forest plot (**a**. the plasma tryptophan level group, **b**. the plasma tryptophan CVD hazard group)

elevated urinary Trp levels may be associated with the risk of coronary heart disease in Chinese adults [26]. Elevated Trp levels in urine may be one of the underlying causes of reduced plasma Trp levels. This phenomenon was previously unrecognized. Hence, in addition to augmenting exogenous intake, reducing renal Trp loss may represent a potential intervention mechanism for modulating circulating Trp levels. In addition, potential racial/ethnic differences may have contributed to the controversial results. Most of the previous studies were conducted among Western Caucasian populations, and there were also differences between different races/ethnicities [34]. This correlation may be reversed in non-Caucasian populations [37, 38]. Further studies are needed to elucidate the effect of Trp on the development of CVD in diverse populations.

In the sensitivity analysis, none of the articles had a strong impact on the research results; this finding supports the robustness of our findings. Additionally, on the basis of the NOS scores, most of the included studies were of high quality in terms of methodology. With respect to limitations, we included only 13 studies in this meta-analysis, and the number of studies included in each group was relatively small. Second, our findings remain at the macroscopic level, and only reveals that decreased circulating Trp levels are associated with an increased risk of CVD events. The mechanism of Trp's impact on different cardiovascular diseases is unknown. Third, only one study in a non-Caucasian population was included in our meta-analysis, making a full analysis of the impact of Trp levels on cardiovascular events in different ethnic groups incomplete. Fourth, the reported case data of specific cardiovascular diseases (e.g.: IDH, MI, Stroke, AIS, and PAD) are limited, an outcome-specific meta-analysis has not been clarified.

In conclusion, this study provides evidence that decreased circulating Trp levels are associated with an increased risk of CVD events. Intervention in circulating Trp levels may be useful to help prevent the development of CVD. Hopefully, these findings will provide interesting new research directions for preventing the progression of CVD.

Abbreviations

CVD Cardiovascular disease
Trp Tryptophan

Author contributions

Conceptualization: JZ, CMZData curation: JZ, TDZ, BYW, XJ, BP, DYLFormal and statistical analysis: JZ, LHZ, CMZ, LFKWriting-original draft: JZ, TDZ, XJWriting-review & editing: CMZ, LZFinal approval of the article: LZAll the authors read and approved the manuscript.

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Data availability

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Declarations

Consent for publication
This manuscript does not contain data from any individual person.

Eligibility criteria
The study protocol has been registered on PROSPERO (registration number CRD42024533266).

Competing interests
The authors declare no competing interests.

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