L-carnitine and cardiovascular disease: a Mendelian randomisation study (abridged secondary publication)

J Zhao *, S Burgess, BH Fan, CM Schooling

KEY MESSAGES

1. Our findings do not support a beneficial association between L-carnitine and cardiovascular disease or its risk factors but suggest potential harm.
2. Sex differences in cardiovascular effects of L-carnitine remain to be confirmed.
3. Our findings highlight concerns about dietary factors that increase carnitine levels (ie, red meat), with implications for dietary recommendations.

Hong Kong Med J 2025;31(Suppl 1):S41-4
HMRF project number: 16172921

[1] J Zhao, [2] S Burgess, [1] BH Fan, [1] CM Schooling

[1] *School of Public Health, The University of Hong Kong, Hong Kong SAR, China*
[2] *Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, United Kingdom*

* Principal applicant and corresponding author: janezhao@hku.hk

Introduction

Cardiovascular disease (CVD) is a leading cause of death worldwide. Effective interventions, especially daily dietary measures, are valuable for primary prevention and care. Red meat and its associated metabolites, such as trimethylamine-N-oxide (TMAO), are important for human and planetary health.[1] L-carnitine, the active form of dietary carnitine and a precursor to TMAO, is considered a target in CVD prevention and treatment. L-carnitine is abundant in animal products, especially red meat; it also serves as a nutrient supplement to increase endurance in athletes.

Evidence is contradictory regarding effectiveness and safety of L-carnitine in CVD. In a systematic review and meta-analysis of 13 controlled trials involving 3629 patients with acute myocardial infarction, L-carnitine is beneficial for angina but had no effect on heart failure or myocardial infarction outcomes.[2] These findings may be partly explained by short follow-up periods, variable L-carnitine dosage, and the inclusion of low-quality trials that lacked randomisation and blinding.[2] Additionally, there is speculation that dietary carnitine can accelerate atherosclerosis through metabolites from gut microbiota.[3]

In the absence of conclusive evidence from high-quality randomised controlled trails, naturally occurring L-carnitine-related genetic variants can be used to predict serum carnitine in Mendelian randomisation studies, thereby examining the role of L-carnitine without potentially harmful interventions.[4] Genetic variants are established at conception, making them less susceptible to confounders (eg, socioeconomic position) that can bias conventional observational studies. In this study, we used Mendelian randomisation to examine the associations of genetically predicted L-carnitine levels with CVD and its risk factors. We also assessed the association between red meat consumption and CVD by conducting a systematic review and meta-analysis of observational studies.

Methods

A two-sample Mendelian randomisation study was conducted based on large, well-established cohorts and consortia. Specifically, genetic proxies for L-carnitine were used in genome-wide association studies (GWAS) of CVD and its risk factors. The association of red meat consumption (including both unprocessed and processed red meat) with CVD was assessed through a systematic review and meta-analysis of observational studies.

Eight independent genome-wide significant single nucleotide polymorphisms (SNPs) associated with L-carnitine were identified from a GWAS meta-analysis involving 23 658 people of European ancestry, with adjustments for age, sex, and study-specific covariates.[5]

Primary outcome measures included fatal and non-fatal CVD events such as coronary artery disease (CAD), ischaemic stroke, heart failure, and atrial fibrillation (AF). Secondary outcome measures included type 2 diabetes, levels of glucose, glycated haemoglobin, and insulin, lipid profile (low- and high-density lipoprotein cholesterol, triglycerides, and apolipoprotein B), systolic and diastolic blood pressures, and body mass index, all of which constitute risk factors for CVD.

The Wald estimate (ie, the genetic association with CVD and its risk factors divided by the genetic association with L-carnitine) was calculated for

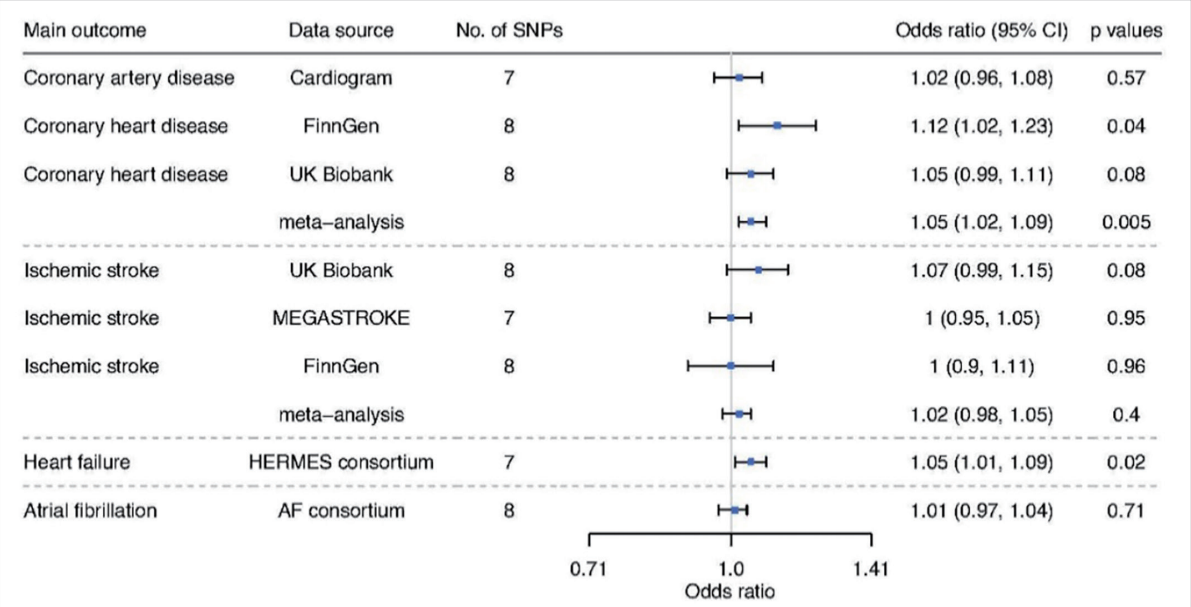

FIG 1. Odds ratios for cardiovascular diseases per standard deviation increase in genetically predicted L-carnitine level associated with eight independent genome-wide significant single nucleotide polymorphisms (SNPs)

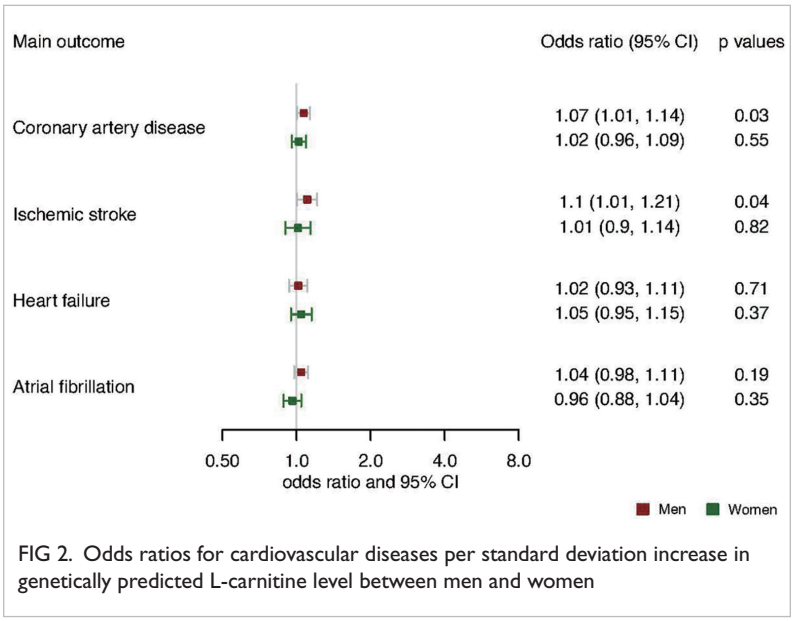

FIG 2. Odds ratios for cardiovascular diseases per standard deviation increase in genetically predicted L-carnitine level between men and women

each SNP. SNP-specific estimates were combined using inverse variance weighting with multiplicative random effects. Estimates from different data sources were meta-analysed. A Mendelian randomisation pleiotropy residual sum and outlier analysis, which uses the 'leave-one-out' approach, was conducted to identify outliers and provide a corrected estimate after outlier removal. The adjusted estimates served as the primary results if outliers were detected; otherwise, the inverse variance–weighted estimates were used. The analysis was repeated after sex stratification, with a heterogeneity test to assess differences between estimates.

PubMed, Web of Science, Embase, and the Cochrane Library were searched for studies regarding associations between red meat consumption and CVD. The search terms included synonyms and combinations of terms for red meat and CVD. Only observational studies (cohort studies, cross-sectional, and case-control) with available full texts were included. When multiple studies analysed the same population, only the most recent study was used. Relative risks and 95% confidence intervals were calculated using inverse variance-weighted meta-analysis. Heterogeneity between studies was evaluated using I^2. High heterogeneity was defined using thresholds of I^2 >50% and P values of <0.10; in these cases, a random-effects model was used. Otherwise, a fixed-effects model was used. Subgroup analyses according to sex and region (Western and Eastern populations) also were conducted.

Results

Each standard deviation increase in genetically predicted L-carnitine level was associated with a higher risk of CAD (odds ratio [OR]=1.05) and heart failure (OR=1.05); however, it was not associated with ischaemic stroke (OR=1.02) or AF (OR=1.01) [Fig 1]. Specifically, it was associated with a higher risk of CAD in men (OR=1.07) but not in women (OR=1.02), although this sex difference was not significant (P=0.31) [Fig 2].

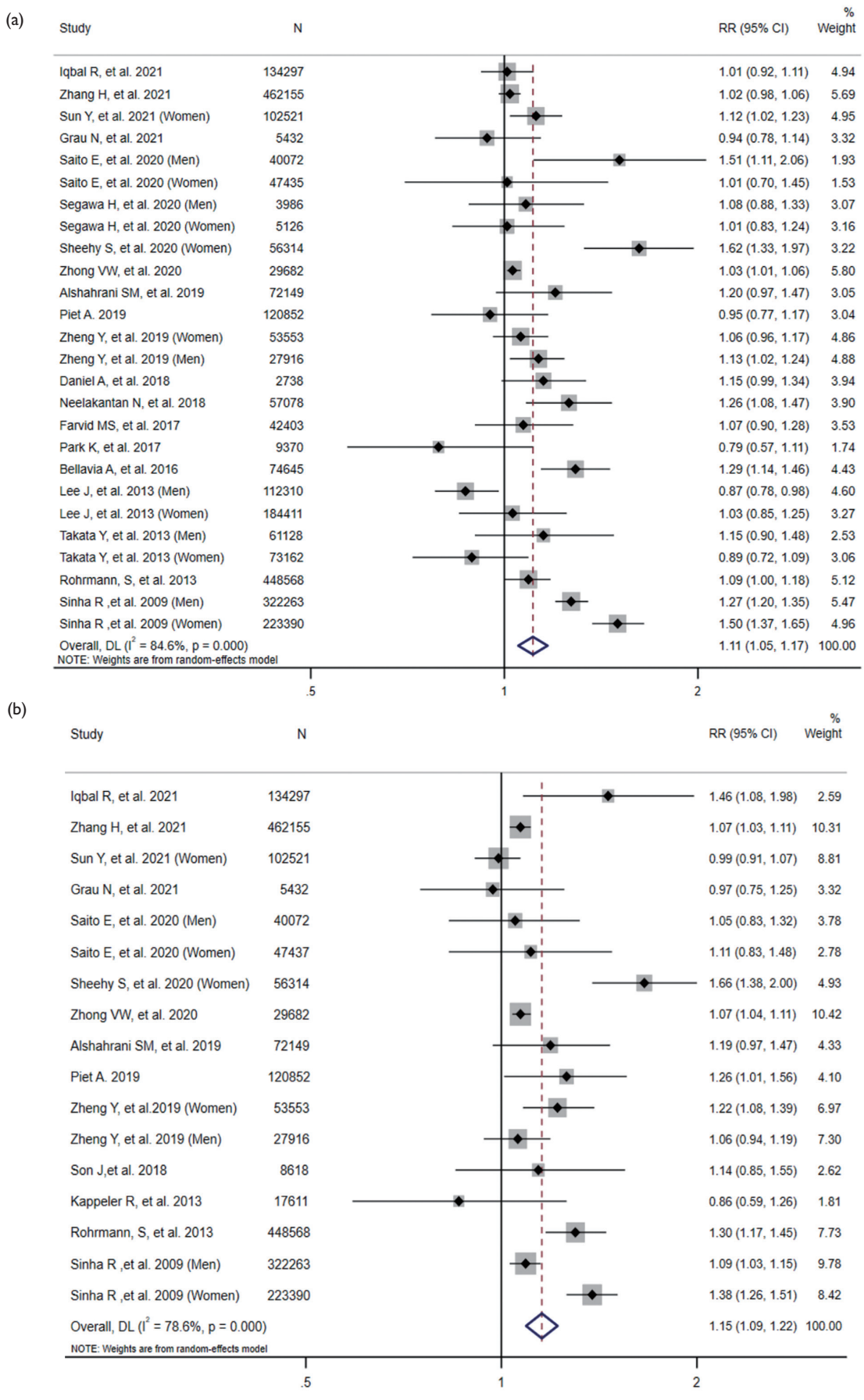

FIG 3. Meta-analysis of the associations of (a) unprocessed and (b) processed red meat consumption with cardiovascular disease risk

Each standard deviation increase in genetically predicted L-carnitine level was associated with higher triglyceride levels (effect size was 0.04 overall, 0.05 in men, and 0.03 in women; no significant sex difference) and lower high-density lipoprotein cholesterol levels (effect size was -0.02 overall, -0.04 in men, and 0.004 in women [P=0.88]). It also was associated with a higher risk of diabetes (P=0.04) but not with other glycaemic traits (levels of glucose, glycated haemoglobin, or insulin).

Of the 5743 studies identified, 22 met the inclusion criteria for meta-analysis. Higher red meat consumption was associated with increased CVD risk (relative risk was 1.11 for unprocessed red meat and 1.15 for processed red meat) [Fig 3]. There were no significant differences according to sex or region.

Discussion

Our Mendelian randomisation study indicated that L-carnitine does not have beneficial effects on CVD or its risk factors and instead may be harmful. The meta-analysis of observational studies suggested that higher red meat consumption is associated with increased CVD risk.

Endogenous L-carnitine may not fully reflect the effects of exogenous carnitine supplementation. However, L-carnitine can be readily obtained from dietary sources, and the highest content is present in red meat. L-carnitine levels rise after red meat consumption, and higher red meat consumption is associated with increased CVD risk. The absence of detectable sex differences might be due to the limited number of studies that examine men and women separately. The lack of regional differences could reflect lower levels of red meat consumption in Eastern populations or the effects of confounders, particularly socio-economic status, which strongly influences both diet and health outcomes.

Our study had several limitations. First, although Mendelian randomisation estimates are less susceptible to confounding than conventional observational studies, they are less precise because genetic variants only explain a small proportion of the variance in exposure. Replication in larger samples, especially for nominal associations, is therefore warranted. Second, the role of L-carnitine might be influenced by interactions with microbiota, but information about microbiota is not available in UK Biobank data. Third, the genetic instruments for L-carnitine were derived from GWAS of metabolites; replication via GWAS focused on L-carnitine is needed. Fourth, observational studies included in the meta-analysis are susceptible to confounding and selection biases. Finally, few studies provided subgroup analyses stratified by sex, making it difficult to identify sex-specific differences. Future studies should explore the benefits of lower red meat consumption on CVD risk through randomised controlled trials. Our findings highlight concerns about dietary factors that increase L-carnitine levels, such as red meat, with implications for dietary recommendations. Sex differences in the effects of L-carnitine remain to be confirmed, and the underlying mechanisms warrant further investigation.

Conclusion

Our findings do not support a beneficial association between L-carnitine and CVD or its risk factors but suggest potential harm. Lower red meat consumption is recommended; this also contributes to an environmentally friendly lifestyle.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#16172921). The full report is available from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

Disclosure

The results of this research have been previously published in:

1. Zhao JV, Burgess S, Fan B, et al. L-carnitine, a friend or foe for cardiovascular disease? A Mendelian randomization study. BMC Med 2022;20:272.
2. Shi W, Huang X, Schooling CM, Zhao JV. Red meat consumption, cardiovascular diseases, and diabetes: a systematic review and meta-analysis. Eur Heart J 2023;44:2626-35.

References

1. Abbasi J. TMAO and Heart Disease: The new red meat Risk? JAMA 2019;321:2149-51.
2. DiNicolantonio JJ, Lavie CJ, Fares H, Menezes AR, O'Keefe JH. L-carnitine in the secondary prevention of cardiovascular disease: systematic review and meta-analysis. Mayo Clin Proceed 2013;88:544-51.
3. Johri AM, Heyland DK, Hetu MF, Crawford B, Spence JD. Carnitine therapy for the treatment of metabolic syndrome and cardiovascular disease: evidence and controversies. Nutr Metab Cardiovasc Dis 2014;24:808-14.
4. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. Stat Med 2008;27:1133-63.
5. Lotta LA, Pietzner M, Stewart ID, et al. A cross-platform approach identifies genetic regulators of human metabolism and health. Nat Genetics 2021;53:54-64.