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Relationship between lipid-lowering drugs and gastric cancer: a drug target-mediated Mendelian randomization study

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SUMMARY: *Objective: This study assessed the causal link between lipid traits influenced by lipid-lowering drug targets like HMGCR and PCSK9 and gastric cancer risk. Methods We employed Mendelian randomization with genetic instruments based on genome-wide association study data LDL-C as exposure and gastric cancer as outcome. Analytical approaches included inverse variance weighting as primary method alongside MR-Egger weighted median and mode methods. Sensitivity analyses evaluated result robustness. Results Inverse variance weighting analysis showed HMGCR inhibitor treatment was associated with higher gastric cancer risk OR 1.532 95% CI 1.109-2.118 P 0.010. PCSK9 inhibition similarly elevated risk OR 1.466 95% CI 1.098-1.957 P 0.009. Sensitivity analyses detected no heterogeneity P greater than 0.05. Conclusion In conclusion LDL-C causally affects gastric cancer development. HMGCR and PCSK9 inhibitors appear to raise gastric carcinogenesis risk.*

KEYWORDS: *Lipid-lowering drugs, Gastric cancer, Mendelian randomization, Genome-wide association*

1 Introduction

Gastric cancer ranks among the most prevalent malignant neoplasms of the digestive system. It is characterized by high mortality and recurrence rates, making it the leading primary contributor to global cancer mortality. The etiopathogenesis of gastric cancer is influenced by numerous risk factors, including genetics, environmental factors, and microorganisms like Helicobacter pylori. Early diagnosis and treatment can substantially improve patient prognosis through both pharmaceutical and surgical interventions. Nevertheless, the disease is usually diagnosed at an advanced stage for most patient[1, 2].Therefore, early diagnosis, accurate prognosis assessment, and the development of innovative treatment methods are critical for improving outcomes in gastric cancer patients. Epidemiological evidence indicates a correlation between serum cholesterol and oncogenesis though the causal pathway linking cholesterol to tumorigenesis remains undetermined[3]. Current evidence provides incomplete characterization of lipid-lowering drug associations with gastric cancer necessitating elucidation of causal mechanisms between LDL-C-modulating agents and gastric carcinogenesis.

HMGCR and PCSK9 inhibitors constitute key lipid-modulating therapeutics proven efficacious for cardiovascular disease prevention particularly in hypercholesterolemia and coronary syndromes through targeted pathway modulation[4-6]. It has been reported that these

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drugs demonstrate potential efficacy in cancer treatment, with particular emphasis on the anticancer properties of statins. These drugs are increasingly viewed as repurposable anticancer agents, poised to function asantineoplastic agents in the era of precision medicine[7-9]. However,lipid-lowering medications may not significantly impact the risk of certain cancer types[10]. There is no consensus for retrospective studies and meta-analyses due to biases inherent in observational studies and inadequate sample sizes. In addition, differences in geographical regions, demographic variables and differential follow-up periods may further confound interpretations. Consequently rigorously designed investigations are required to definitively establish causality regarding lipid-lowering pharmacotherapy and gastric cancer risk.

Mendelian randomization provides a pivotal causal inference framework utilizing GWAS-derived SNPs as instrumental variables strongly linked to exposures enabling unbiased exposure-outcome association assessment in clinical epidemiology[11-13]. By mitigating confounding and survival biases plaguing observational designs MR notably enhances causal inference[14]. Drug-targeted MR specifically harnesses target-proximal SNPs as pharmacogenetic instruments to investigate drug-gene pharmacological mechanisms[15]. Drug-targeted MR analysis is a method based on MR principles that utilizes SNPs located at or near a drug target gene as a pharmacogenetic tool to study the relationship between a drug and its target gene[16]. In this study, the drug-targeted MR method was used to investigate the relationship between common lipid-lowering drug targets and cancer risk.The goal is to enhance our understanding of how lipid-modifying drugs affect gastric cancer, thereby providing a scientific foundation for developing relevant prevention and treatment strategies.

2 Materials and Methods

2.1 Study design

Open-access GWAS data were employed for two-sample and drug-target Mendelian randomization analyses conducted per STROBE-MR guidelines [17]. LDL-C served as exposure and gastric cancer as outcome with exposure-associated SNPs sourced from GWAS repositories serving as instrumental variables for causality inference. Analyses adhered to core MR postulates requiring SNP-exposure relevance SNP-confounding independence and exposure-restricted SNP-outcome effects as depicted in Figure1 [18].

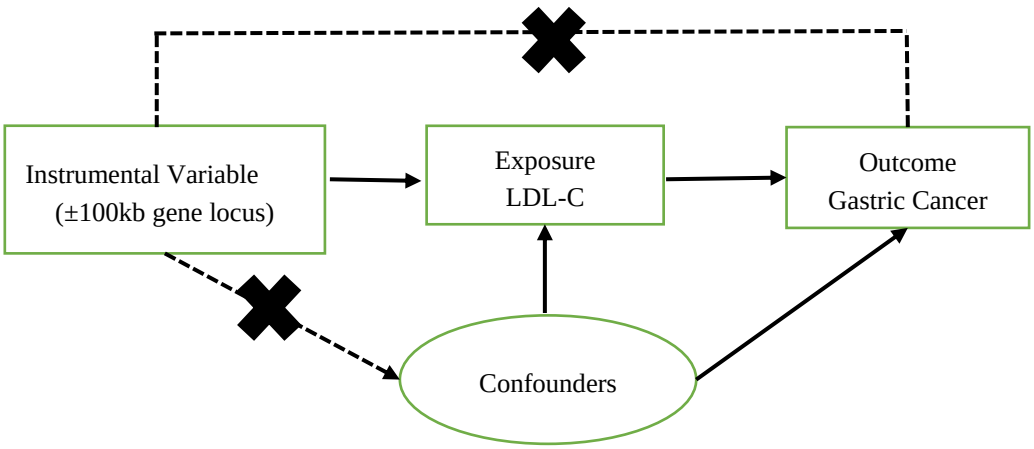


Figure 1. Research design schematic diagram

2.2 Data source

LDL-C-related GWAS statistics were sourced from ieu-b-110 (https://gwas.mrcieu.ac.uk/) comprising 440,546 European samples and 12,321,875 SNPs. Additionally, genetic data concerning gastric cancer were obtained from the GWAS statistics database, and were identified as ebi-a-GCST90018849. This dataset encompasses 476,116 samples from European populations, including 24,188,662 SNPs.

2.3 Selection of instrumental variables

Instrumental variable SNPs demonstrating genome-wide significance for lipid traits ($P < 0.05$) were selected. To ensure the robustness and validity of these IVs, our selection was confined to SNPs located within a 100 kilobase (kb) window surrounding the target locus. Additionally, an r^2 threshold was set at less than 0.3 and an effect allele frequency exceeding 0.01 was required[19, 20]. To address potential weak instrument bias F-statistics exceeding 10 were required for all SNPs. Computed with values exceeding 10 serving as an indicator of reduced bias risk[21]. Further, gene loci associated with lipid-lowering medications were identified using data from public databases (https://www.ncbi.nlm.nih.gov/gene). For statins, the target gene identified is HMGCR, located on chromosome5 (GRCh37.p13: 74,632,993–74,657,941), while for evolocumab, the target genes PCSK9, situated on chromosome1 (GRCh37.p13: 55,505,221–55,530,525).

2.4 MR analyses

This study's central objective assessed gastric cancer incidence causality for lipid-lowering drug targets through multiple MR approaches. To achieve this, five distinct MR statistical regression techniques were applied: five MR estimators were implemented IVW [22] MR-Egger [23] weighted median [24] and simple/weighted modes [25]. IVW was designated the primary estimator owing to maximal statistical power [26].

2.5 Statistical analysis

Cochran's Q test evaluated SNP heterogeneity with $P>0.05$ indicating homogeneity [27]. Horizontal pleiotropy was assessed via MR-Egger intercept ($P>0.05$ implying absence)[28]. MR-PRESSO excluded outlier SNPs to reduce heterogeneity [29]. Leave-one-out analysis tested result robustness. Analyses used R v4.4.1 with TwoSampleMR [30] and MRPRESSO [31]packages. Forest plots visualized ORs with 95% CIs.

3 Results

3.1 Instrumental variable selection

The methods enabled the identification of genetic instruments to reduce LDL-C via the HMGCR and PCSK9 pathways. Specifically we identified 19 HMGCR-linked and 33 PCSK9-linked SNPs all yielding F-statistics >10 validating robust weak-instrument bias minimization. As a result, instrument bias was effectively minimized within this Mendelian randomization study.

3.2 Mendelian Randomization Outcomes

IVW analysis demonstrated causality between HMGCR expression and elevated gastric cancer risk (OR 1.532, 95%CI 1.109-2.118; P=0.010; Figure2). This finding was further corroborated by the WME and WM methods, indicating a robustness with p<0.05. As shown in Figure 3A, the regression line for genetically predicted HMGCR-mediated genetically predicted LDL-C levels corresponded to gastric cancer risk. Concurrently PCSK9 elevation conferred elevated gastric cancer risk (OR 1.466, 95%CI 1.098-1.957; P=0.009). The robustness of this association was supported by the WME and WM methods (P<0.05). Scatter plot (Figure 4A) confirmed dose-response concordance between PCSK9-mediated LDL-C levels and gastric cancer risk.

Disease	Gene	nsnp	method	pval	OR(95% CI)
Gastric cancer	HMGCR	19	MR Egger	0.917	0.940 (0.298 to 2.962)
		19	Weighted median	**0.040**	1.495 (1.018 to 2.194)
		19	Inverse variance weighted	**0.010**	1.532 (1.109 to 2.118)
		19	Simple mode	0.179	1.578 (0.833 to 2.989)
		19	Weighted mode	**0.030**	1.433 (1.061 to 1.935)
	PCSK9	33	MR Egger	0.089	1.670 (0.942 to 2.961)
		33	Weighted median	**0.024**	1.631 (1.067 to 2.493)
		33	Inverse variance weighted	**0.009**	1.466 (1.098 to 1.957)
		33	Simple mode	0.122	1.686 (0.886 to 3.212)
		33	Weighted mode	**0.043**	1.573 (1.031 to 2.400)

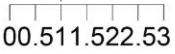


Figure 2: Association of lipid-lowering drug targets with gastric cancer risk

3.3 Validation Analyses

Heterogeneity was evaluated by Cochrane's Q test (P>0.05 indicating homogeneity); horizontal pleiotropy assessed via MR-Egger regression and MR-PRESSO global tests. It can be seen that both heterogeneity and horizontal pleiotropy had no potential impact on the outcomes (Table 1). Consequently, the associations identified in the sensitivity analyses between lipid-lowering drug targets and lipid phenotypes concerning gastric cancer are regarded as reliable. Funnel plot analysis demonstrated that the SNPs associated with LDL-C, mediated by HMGCR and PCSK9, were symmetrically distributed, suggesting the absence of bias (Figures 3B and 4B). Forest plots from Mendelian randomization (MR) analyses are also provided, illustrating the causal relationship between HMGCR- and PCSK9-mediated LDL-C levels and cancer risk (Figures 3C and 4C). Omission of one analysis confirmed that MR results remained consistent even when single SNPs were excluded (Figures 3D and 4D).

Table 1: Heterogeneity test and horizontal pleiotropy of lipid-lowering drugs corresponding to targets in gastric cancer

Drug target	outcome	Cochran's Q P	MR-Egger P	MR-PRESSO P
LDL-C				
HMGCR	GC	0.268	0.258	0.396
PCSK9	GC	0.699	0.666	0.609

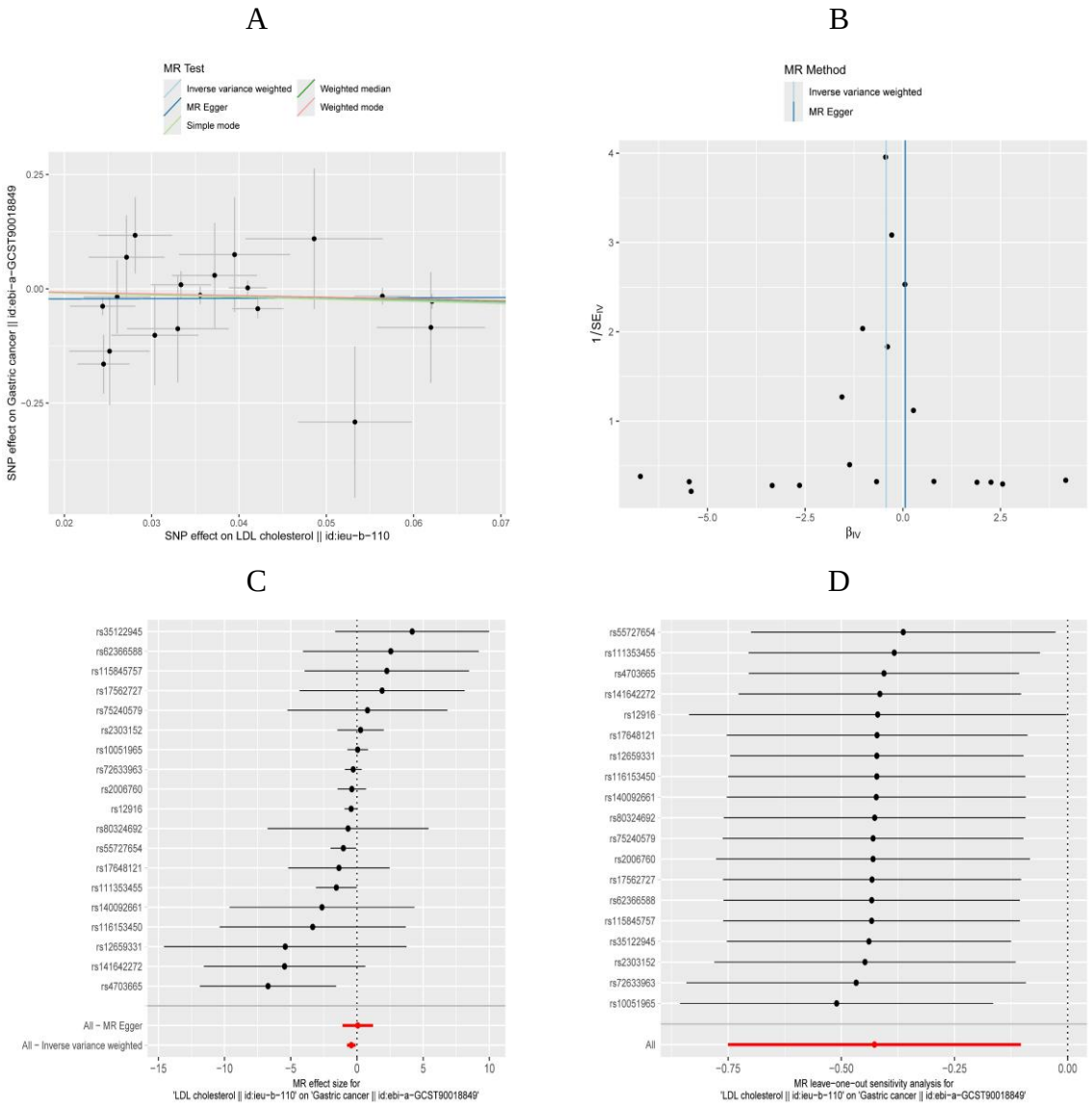
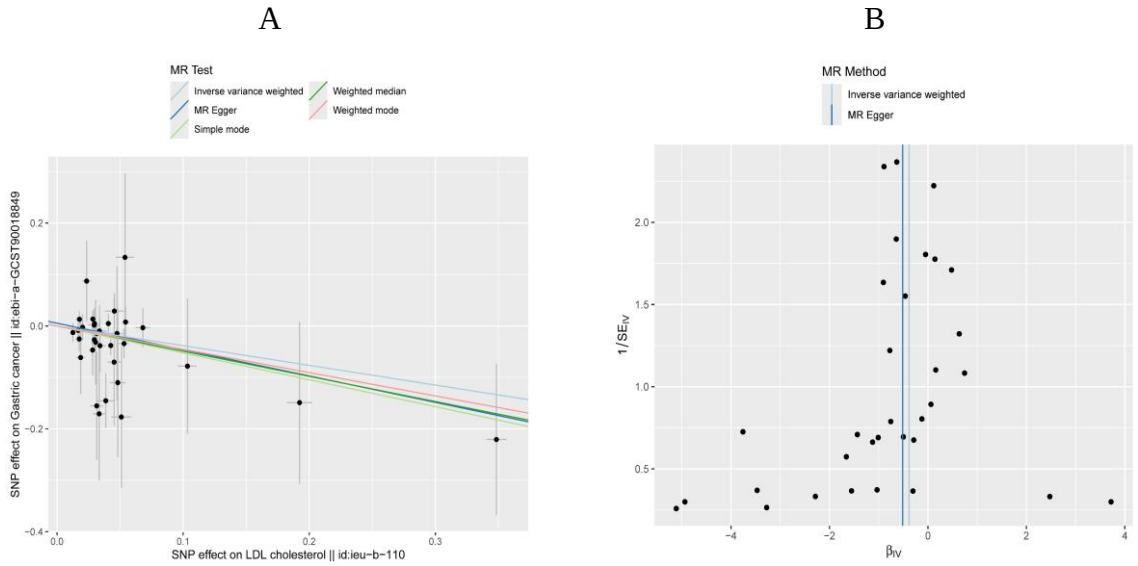


Figure 3: (A) Scatter plot; (B) Funnel plot; (C) Forest plot; (D) Leave-one-out plot.



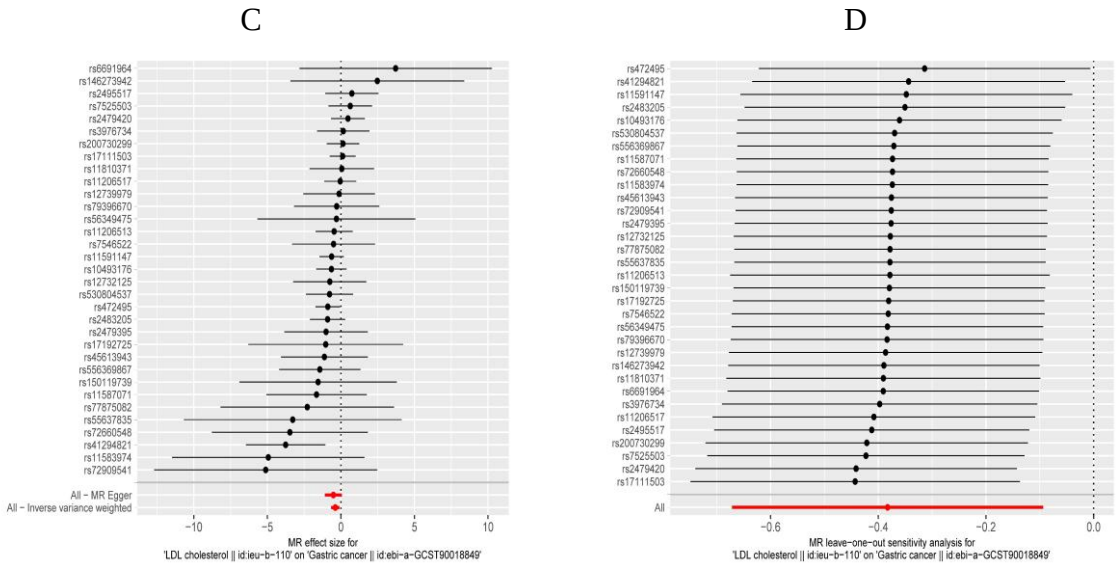


Figure 4: Sensitivity analysis of HMGCR-mediated LDL-C levels with gastric cancer (A) Scatter plot of Mendelian randomization analysis;(B) Funnel plot of Mendelian randomization analysis; (C) Forest plot of Mendelian randomization analysis; (D) Leave-one-out plot of Mendelian randomization analysis.

4 Discussion

Recent years witnessed substantial progress in gastric cancer early detection through clinical and basic research globally with multimodal interventions like surgery chemotherapy radiotherapy and immunotherapy reducing cancer risk. Despite chemotherapy improving advanced-stage prognosis chemoresistance and adverse effects remain challenges [32-34]. In current study, mendelian randomization analysis was conducted to explore the relationship between lipid-lowering drug targets and gastric cancer risk, specifically examining the effects of HMGCR and PCSK9 on this risk. The findings suggest a correlation between HMGCR and PCSK9 and an increased risk of gastric cancer.

A retrospective cohort study involving gastrointestinal cancer patients in South Korea indicated that lipid-lowering drugs demonstrated chemopreventive properties against gastric carcinogenesis, thereby reducing the risk of gastrointestinal malignancies [35]. Recent studies further supported this notion and highlighted lipid-modulating agents' potential in mitigating gastric cancer susceptibility [36]. A meta-analysis confirmed statins favorably modulate gastric cancer risk and prognosis [37]. MR evidence suggests PCSK9 and HMGCR inhibitors confer modest gastric cancer protection [38]. Conversely HDL-C showed inverse association with gastric cancer risk whereas LDL-C demonstrated no association [39]. Prospective cohort data suggested elevated LDL-C may reduce gastric cancer susceptibility [40]. Contrastingly PCSK9 inhibitors elevated gastric cancer risk [41] while another MR study found no drug-cancer association [42].

HMGCR upregulation in gastric tumors promotes cancer cell growth and migration [43]. PCSK9 mechanisms remain incompletely characterized though proposed to upregulate tumor MHC-II expression enabling immunotherapeutic targeting [44]. In syngeneic models PCSK9 inhibition enhanced DC infiltration boosting CD8+ T-cell activation and tumor suppression [44]. Alternatively integrated experimental models showed PCSK9 promotes invasion and inhibits apoptosis via MAPK pathway activation driving metastasis and survival [45].

Exploring PCSK9's therapeutic potential thus offers novel oncology strategies [46]. Clarifying lipid-drug/cancer relationships remains imperative necessitating large-scale clinical trials to define clinical impacts.

First drug-target MR constitutes a hypothesis-generating framework requiring clinical trial validation to confirm lipid-drug/cancer causality. Second, our dataset primarily comprises data from European populations, which may introduce bias in estimates and diminish the credibility of the findings due to the summary data utilized in GWAS.Additionally, Mendelian randomization estimates primarily focus on the effects of long-term exposure, while the accuracy of analyses regarding the short-term therapeutic effects of drugs remains insufficient. Finally absent demographic/clinical stratification in GWAS data constrains detailed exploration necessitating larger cohorts. Future causal investigations must incorporate ethnically diverse samples to enhance generalizability.

5 Conclusions

Collectively LDL-C exerts a causal effect on gastric carcinogenesis susceptibility. HMGCR and PCSK9 inhibitors demonstrate elevated gastric cancer risk.

6 Patents

This section is not mandatory but may be added if there are patents resulting from the work reported in this manuscript.

Supplementary Materials

The following supporting information can be downloaded at: https://www.mdpi.com/article/doi/s1, Figure 1: Research design schematic diagram; Figure 2. Association of lipid-lowering drug targets with gastric cancer risk; Figure 3. (A) Scatter plot; (B) Funnel plot; (C) Forest plot; (D) Leave-one-out plot. Figure 4: Sensitivity analysis of HMGCR-mediated LDL-C levels with gastric cancer.

Author Contributions

CP wrote the manuscript and conducted quality evaluation. LTY conceived the study and performed statistical analysis. LTY and JYD contributed to manuscript revision and interpreted findings. Conceptualization: LTY and JYD. Methodology: CP. Software: LTY. Validation: LTY. Formal analysis: CP. Investigation: CP. Resources: LTY. Data curation: JYD. Writing—original draft preparation: CP. Writing—review and editing: JYD. Visualization: LTY. Supervision: JYD. Funding acquisition: LTY. All authors approved the final version.

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Institutional Review Board Statement

This reanalysis used publicly available GWAS summary data. Original studies obtained ethical approval; additional review was waived.

Informed Consent Statement

Not applicable.

Data Availability Statement

Data are contained within the manuscript/supplementary material.

Acknowledgments

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Conflicts of Interest

The authors declare no conflicts.

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