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·临床研究·

孟德尔随机化方法在胃癌危险因素研究中的应用

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Mendelian Randomization Analysis of Research on Risk Factors for Gastric Cancer

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Abstract: Objective　To understand the application and research progress of Mendelian randomization (MR) studies related to gastric cancer and provide a scientific basis for gastric cancer prevention. **Methods** Published studies on risk factors of gastric cancer based on MR methods were searched in PubMed, Web of Science, EMBASE, CNKI, and WANFANG DATA from the establishment of each database to November 19th, 2022. Two researchers examined the eligibility of studies, extracted key information, and assessed the research quality independently. **Results**　A total of 30 publications published from 2016 to 2022 were included in the study, and 20 were judged to be of high quality. These studies examined the relationship between behaviors and lifestyle factors, anthropometric characteristics, indicators of biological exposure, and other pathological conditions and gastric cancer, and the results suggest potential causal associations between smoking and other factors and the risk of gastric cancer. **Conclusion**　Previous MR studies extensively investigated the causal association between internal and external exposures or traits and gastric cancer and provided positive evidence of gastric cancer etiology. However, MR studies may be subject to methodological limitations. Interpretation of results needs to be approached with caution, which necessitates the integration with biological plausibility and evidence from observation studies.

Key words: Gastric cancer; Mendelian randomization; Causality

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摘　要：目的　了解胃癌危险因素研究中孟德尔随机化（MR）方法的应用情况，为胃癌的病因学研究和预防策略制定提供依据。**方法**　在PubMed、Web of Science、EMBASE、中国知网和万方数据检索建库至2022年11月19日收录的基于MR方法的胃癌危险因素研究。由两位作者独立筛选文献、摘录信息并进行质量评价。**结果**　共纳入2016—2022年发表的30篇研究报告，其中20篇被判定为高质量研究。这些研究探讨了行为及生活方式、人体测量特征、机体生物暴露指标及其他疾病罹患情况与胃癌的关系，支持吸烟等因素可能与胃癌发生风险存在因果关联。**结论**　既往MR研究广泛探讨了机体内外暴露因素或表型与胃癌发生的因果关联，为胃癌病因学研究提供了积极证据。但MR研究可能受方法学缺陷制约，需结合其他证据，对结果谨慎解读。

关键词：胃癌；孟德尔随机化；因果关系
中图分类号：R735.2
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0　引言

胃癌严重威胁着人类的生命健康。目前，除幽门螺杆菌感染外[1]，我们对胃癌相关危险因素的认知仍明显不足[2]。孟德尔随机化（mendelian randomization, MR）方法应用与暴露因素强相关的遗传变异作为工具变量（instrument variable, IV），以推断暴露与研究结局的因果关系[3]，可提供优于观察性研究的证据。

近年来，胃癌领域已经开展了多项危险因素MR研究[4-33]，但尚无系统整理和汇总。本文对既往胃癌危险因素MR研究进行系统综述，以期为胃癌的病因学研究和防控策略制定提供依据。

1　资料与方法

1.1　文献检索策略

检索PubMed、Web of Science、EMBASE、中国知网和万方数据库，查找应用MR方法的胃癌危险因素研究。语言限定为中文和英文，中文数据库以“孟德尔随机化”为主题词、以全文包含“胃癌”为必要条件进行检索；英文数据库检索策略见表1。检索时间为自数据库建库至2022年11月19日，共检索到100篇相关文献。

1.2　文献筛选和信息提取

将检索到的文献导入至文献管理软件EndNote X9（Bld 12062），由两名研究人员独立阅读、筛选和核对文献。采用的筛选策略、纳入和排除标准，见图1。排除在不同数据库中重复的文献、会议摘要、未正式发表文献、非MR研究文献、非原创性研究文献（综述）和与胃癌无关文献，最终纳入30篇合格文献，其中中文文献1篇[4]。摘录文献的基本信息、暴露特征和工具变量解释的暴露变异比例、结局特征（人群、样本量、数据来源）、研究结果和结论，并进行质量评价。本系统综述所纳入研究的筛选、信息提取和质量评估均由两位研究者独立进行，出现分歧时相互讨论达成共识。

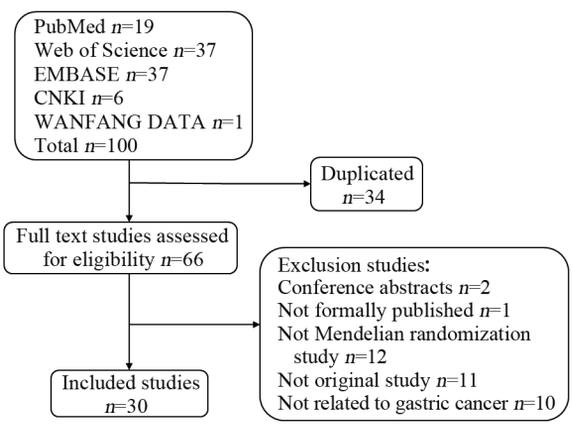

图1　文献检索与筛选流程图

Figure 1　Flow chart of literature search and selection process

1.3　质量评价

Skrivankova等已开发《孟德尔随机化研究的报告规范（Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization, STROBE-MR）》[34]。鉴于该规范并无方法学质量分级的依据，我们在STROBE-MR基础上，参考既往针对MR研究的其他系统综述[35]制定了MR研究质量评价方法，包括是否进行了完整的工具变量分析、对关联性假设的验证、对独立性和排他性假设的验证、开展敏感度分析、考虑人群分层情况、对非线性关联假设的探讨等六部分，各部分的判定原则见表2。

表1　英文数据库文献检索策略汇总

Table 1　Summary of literature search strategies in English databases

Database	Search strategies	Results
PubMed	((mendelian randomization analysis[MeSH Terms]) OR (instrumental variable[Title/Abstract])) AND (neoplasms[MeSH Terms]) AND ((stomach[Title/Abstract])OR (gastric[Title/Abstract]))	19
Web of Science	(TS=(mendelian randomization analysis) OR TS=(instrumental variable)) AND (TS=(gastric cancer) OR TS=(stomach neoplasms) OR TS=(stomach cancer) OR TS=(gastric carcinoma))	37
EMBASE	('instrumental variable analysis'/exp OR 'mendelian randomization analysis'/exp) AND 'stomach tumor'/exp	37

MR研究需要进行完整的IV分析（表2，条目a）以确保质量。IV同时满足关联性（遗传变异与暴露表型相关）、独立性（遗传变异与影响关联的混杂因素独立）和排他性（遗传变异仅通过暴露影响结局）3个核心假设是结果可靠的必要条件。单样本和两样本MR研究通常依托不同方法来验证遗传变异与暴露表型的关联性假设（表2，条目b）。遗传变异的多效性效应普遍存在，如果遗传工具通过感兴趣的暴露以外的因素影响结局，则可能被违反独立性和排他性假设，两个假设一般可以一起检验（表2，条目c）。MR研究通过敏感度分析评估结果的稳健程度[36]（表2，条目d）。鉴于遗传易感性在不同种族间存在异质性[37]，还需关注人群分层的潜在影响（表2，条目e）。此外，我们还关注研究对暴露与结局间潜在非线性关联的探索情况并进行评级（表2，条目f）。鉴于尚无使用汇总统计数据探究非线性关联的MR方法，多数MR研究仅关注暴露因素与结局之间的线性关联情况，因此我们主要依托表2中的条目a~e，将该五项评级均为“良好”的研究判定为高质量MR研究。

2　结果

2.1　文献基本特征

本研究共纳入2016—2022年发表的30篇应用MR方法的研究，见图2。这些研究探讨行为与生活方式、人体测量特征、其他疾病罹患情况及机体生物暴露指标等与胃癌的关系，除一项研究的结局为胃癌死亡风险外，其他均探讨与胃癌发生风险的关联。研究报告的遗传工具解释暴露变异的比例为0.1%~37.6%，其中4项MR分析仅使用1个SNP位点作为工具变量。胃癌结局数据集主要来自英国生物银行（UKB）、日本生物样本库（BBJ）、FinnGen等大型队列，其样本量的中位数为308 908（范围：3 725~456 348），中位胃癌病例数为994（范围：105-6 563）。

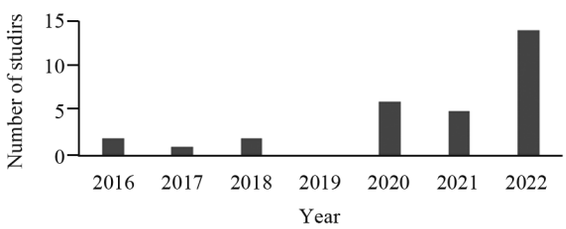

图2　2016-2022年胃癌危险因素孟德尔随机化研究数量

Figure 2　Number of Mendelian randomization studies related to risk factors of gastric cancer published from 2016 to 2022

2.2　文献质量评价

30项研究中，27项研究（90.0%）进行了完整的IV分析，23项研究（76.7%）验证了MR研究的3个核心假设，26项研究（86.7%）进行了敏感度分析，23项研究（76.7%）不存在人群分层问题，最终有20项研究（60.7%）的研究判定为高质量MR研究，见图3。

2.3　胃癌危险因素MR研究进展

本研究共汇总20项高质量MR研究的研究进展，见表3。

2.3.1　行为与生活方式　MR研究支持吸烟是

表2　孟德尔随机化研究质量评价方法

Table 2　Methods for assessing the quality of MR study

Item	Grade	Criteria
a. Full IV analysis	Good	Full IV analyses, such as two-stage least-squares regression for one-sample MR study and inverse-variance weighted method for two-sample MR study.
	Poor	Without full IV analyses; only uses other approaches, such as an association analysis between the genetic variant and outcome.
b. Relevance assumption	Good	For one-sample MR study, the assumption is tested by reporting an F-statistic (F>10); for two-sample MR study, strongly and robustly associated SNPs from GWAS are selected (P<5×10-8).
	Moderate	Associated SNPs are selected using a P value threshold not satisfying Bonferroni correction.
	Poor	Failure to describe whether the assumption is satisfied.
c. Independence assumption and exclusion restriction assumption	Good	Assumption is tested using MR-Egger regression, MR-Pleiotropy Residual Sum and Outlier, and other novel methods.
	Moderate	Full IV analysis is selected based on literature research and without testing the assumption.
	Poor	Failure to describe whether the assumption is satisfied.
d. Sensitivity analysis	Good	Sensitivity analysis is conducted, and results that are consistent with primary analyses are reported.
	Poor	Failed sensitivity analysis or inconsistent results are reported.
e. Population stratification	Good	Absence of population stratification.
	Poor	Presence of population stratification or failure to report population information.
f. Non-linearity correlation	Good	Potential non-linearity correlations of exposure and outcome variables are explored.
	Poor	Failure to describe potential non-linearity correlations.

Notes: GWAS: genome-wide association studies, IV: instrument variable, MR: mendelian randomization, SNPs: single-nucleotide polymorphisms.

胃癌的危险因素（*OR*=1.46, 95%*CI*: 1.05~2.03, *P*=0.024），未发现饮酒是胃癌的危险因素[5]。在睡眠方面，倾向于早起者的胃癌发病风险比“夜猫子”型显著降低（*OR*=0.84, 95%*CI*: 0.73~0.97）[6]，但睡眠时长并未发现与胃癌有关[7]。此外，既往MR研究也不支持咖啡[8]、加工肉类及红肉[9]摄入量改变胃癌发生风险。

2.3.2 人体测量特征 多项研究探讨了人体测量指征与胃癌之间的因果关联。研究表明，脂肪质量指数、非脂肪质量指数和身高均与胃癌发生无关[10]。既往基于欧洲人群[10]（*OR*=1.13, 95%*CI*: 1.06~1.21, *P*<0.001）和中国人群[11]（*OR*=1.07, 95%*CI*: 1.02~1.13, *P*=4.94×10^{-3}）的两项研究报告较高的体质指数（body mass index, BMI）是胃癌发生的危险因素，但另一项基于日本人群的MR研究得到不一致结论[12]。此外，既往基于欧洲人群的MR研究也不支持BMI与胃癌死亡风险相关[13]。

2.3.3 生物暴露指标 共有9项MR研究探讨生

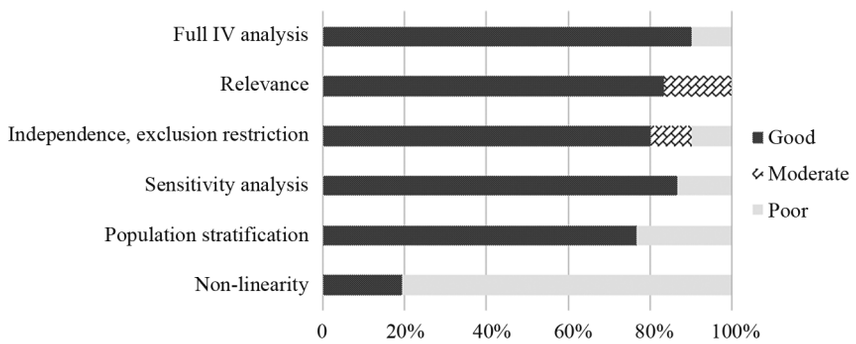

图3 胃癌危险因素孟德尔随机化研究方法学质量评价结果

Figure 3 Methodological quality assessment of the included MR studies related to risk factors of gastric cancer

表3 20篇高质量胃癌危险因素孟德尔随机化研究的主要信息

Table 3 Key information of 20 high-quality MR studies related to risk factors of gastric cancer

Author, Year	Exposure			Outcome				Main methods	Primary findings
	Exposure/trait	SNPs	R^2	Population	Cases	Controls	Sources		
Behaviors and lifestyle factors									
Larsson, 2020[5]	Smoking initiation	75	2.30%	European	736	366,907	UKB	IVW	Smoking may be a risk factor for GC (*OR*: 1.46, 95%*CI*: 1.05-2.03)
	Alcohol consumption	19-29	0.2%-0.3%						No significant association.
Yuan, 2022[6]	Chronotype	317	NR	European	1,086	366,456	UKB		Morning chronotype was associated with a decreased risk of GC (*OR*: 0.84, 95%*CI*: 0.73-0.97)
					889	204,070	FinnGen		
Titova, 2021[7]	Short-sleep duration	27	NR	European	736	366,907	UKB	IVW	No significant association.
		26	NR		329	120,006	FinnGen		
	Long sleep	8	NR		736	366,907	UKB		No significant association.
	Continuous sleep duration	77	NR		736	366,907	UKB		No significant association.
Carter, 2022[8]	Coffee consumption	12	NR	European	994	366,567	UKB	IVW	No significant association.
	Caffeine consumption	2	NR						No significant association.
Wu, 2022[9]	Processed meat intake	23	NR	European	633	174,006	FinnGen	IVW	No significant association.
	Pork intake	14	NR						No significant association.
	Beef intake	17	NR						No significant association.
	Mutton intake	32	NR						No significant association.
Anthropometric characteristics									
Vithayathil, 2021[10]	BMI	312	4.05%	European	994	366,567	UKB	IVW	Elevated BMI was positively associated with GC (per 1 kg/m^2, *OR*: 1.13, 95%*CI*: 1.06-1.21)
	FMI	577	3.15%						No significant association.
	FFMI	577	2.27%						No significant association.
	Height	293	5.50%						No significant association.
Mao, 2017[11]	BMI	37	NR	Chinese	2,631	4,373	Nanjing-GWAS, Beijing-GWAS, and NCI-GWAS	wGRS	High BMI was associated with increased GC risk (per SD in the wGRS, *OR*: 1.07, 95%*CI*: 1.02-1.13)
Zang, 2022[12]	BMI	57	<1%	East Asians	6,563	195,745	BBJ	IVW	No significant association.
Wade, 2018[13]	BMI	77	NR	White British	144[a]	NR	UKB	IVW	No significant association.
				White British male	105[a]	NR	UKB		

续表3

Author, Year	Exposure			Outcome				Main methods	Primary findings
	Exposure/trait	SNPs	R^2	Population	Cases	Controls	Sources		
Indicators of biological exposure									
Jiang, 2022[14]	Adiponectin	8	2.65%	East Asians	6,563	195,745	BBJ	IVW	High level of adiponectin may have a causal effect on GC (per 10% increase in log-transformed adiponectin level, *OR*: 0.88, 95%*CI*: 0.81-0.96)
Song, 2022[15]	Circulating IL-17	2	NR	European	569	455,779	UKB	IVW	Circulating levels of IL-17 and the risk of stomach cancer using the IVW method (per 1 SD increase, *OR*: 0.15, 95%*CI*: 0.07-0.36)
	Other circulating levels of cytokines	224	NR						No significant association.
Gao, 2020[16]	LTL	17	1.37%	European	155	420,318	UKB	IVW	No significant association.
Yuan, 2020c[17]	FI	17	1.20%	European	736	367,643	UKB	IVW	No significant association.
	FG	35	4.80%					IVW	No significant association.
Zhang, 2022[18]	FI	35	0.80%	European	1,091[b]	410,350	UKB, GERA	IVW	No significant association.
Zhu, 2022[19]	CRP	52	2.60%	European	335	386,319	UKB	wGRS	No significant association.
Wu, 2022[20]	HDL	81	NR	European	554	393,372	UKB	IVW	No significant association.
		84	NR	Japanese	6,563	195,745	BBJ		
		72	NR	Chinese	1,625	2,100	Shanxi, and NIT		
	LDL	71	NR	European	554	393,372	UKB		No significant association.
		62	NR	Japanese	6,563	195,745	BBJ		
		56	NR	Chinese	1,625	2,100	Shanxi, and NIT		
	TG	48	NR	European	554	393,372	UKB		TG involved in GC etiology in Japanese (*OR*: 1.11, 95%*CI*: 1.01-1.22)
		48	NR	Japanese	6,563	195,745	BBJ		
		42	NR	Chinese	1,625	2,100	Shanxi, and NIT		
Yuan, 2021[21]	Folate	2	1%	European	994	307,914	UKB	IVW	No significant association.
					506	147,282	FinnGen		
	Vitamin B6	1	2.80%		994	307,914	UKB		No significant association.
					506	147,282	FinnGen		
	Vitamin B12	14	6.30%		994	307,914	UKB		No significant association.
					506	147,282	FinnGen		
Larsson, 2022[22]	Vitamin C	10	1.90%	European	1,054	308,100	FinnGen	IVW	No significant association.
					1,086	366,456	UKB		
Other pathological conditions									
Yuan, 2020c[17]	T2DM	399	17.40%	European	736	367,643	UKB	IVW	No significant association.
Gu, 2022[23]	PBC	5	11.30%	East Asians	6,563	195,745	BBJ	IVW	An inverse association was observed between PBC and risk of GC (*OR*: 0.96, 95%*CI*: 0.93-0.99)
Kamiza, 2022[24]	Chronic HBV infection	4	NR	East Asians	6,563	195,745	BBJ	IVW	Chronic HBV infection is causally associated with GC (*OR*: 1.12, 95%*CI*: 1.05-1.19)

Notes: BBJ: BioBank Japan; BMI: body mass index; CI: confidence interval; CRP: C-reactive protein; FFMI: fat-free mass index; FG: fasting glucose; FI: fasting insulin; FMI: fat mass index; GC: gastric cancer; GERA: Kaiser Permanente Genetic Epidemiology Research on Adult Health and Aging; GRS: genetic risk score; GWAS: genome-wide association studies; HBV: Hepatitis B virus; HDL: high-density lipoprotein; IL: interleukin; IVW: inverse-variance weighted; LDL: low-density lipoprotein; LTL: leukocyte telomere length; NCI: United States National Cancer Institute; NIT: Linxian Nutrition Intervention Trial; NR: not reported; OR: odds ratio; PBC: primary biliary cholangitis; SD: standard deviation; Shanxi: Shanxi Upper Gastrointestinal Cancer Genetics Project; SNP: single-nucleotide polymorphism; T2DM: type 2 diabetes mellitus; TG: triglyceride; UKB: UK Biobank; a: number of stomach cancer deaths; b: number of esophagus and stomach cancer cases; c: the study investigated causal associations of T2DM, FG and FI with gastric cancer.

物暴露指标（激素、细胞因子、脂蛋白、循环维生素水平等）与胃癌发生风险的因果关联。有研究表明，具有较高的脂联素（*OR*=0.88, 95%*CI*: 0.81~0.96, *P*=0.009）[14]或白细胞介素-17（*OR*=0.15, 95%*CI*: 0.07~0.36, $P=1.25\times10^{-5}$）[15]水平者胃癌发生的风险显著降低。而白细胞端粒长度[16]、空腹血糖[17]、空腹胰岛素水平[17-18]、C-反应蛋白[19]及其他细胞因子[15]与胃癌的发生风险无关。

基于日本人群的MR研究还报告血清甘油三酯水平与胃癌发生的因果关联（*OR*=1.11, 95%*CI*:

1.01~1.22, *P*=0.034），但基于中国和欧洲人群的研究则不然[20]。此外，血清高密度脂蛋白[20]、低密度脂蛋白[20]、循环B族维生素[21]和维生素C[22]水平等也与胃癌的发生风险无关。

2.3.4 其他疾病罹患情况 原发性胆汁性胆管炎（*OR*=0.96, 95%*CI*: 0.93~0.99, *P*=0.02）[23]和慢性乙型肝炎病毒感染（*OR*=1.12, 95%*CI*: 1.05~1.19, *P*=0.0001）[24]可能是胃癌的病因学因素。2型糖尿病与胃癌的发生风险无关[17]。

3 讨论

基于观察性研究探究危险因素时可能受到混杂因素或反向因果偏误等干扰，导致因果推断能力受限[38]。随机对照试验虽是确证因果关联的金标准，但常受限于外部条件。鉴于遗传变异不受环境等混杂因素的影响，且与结局之间具有时序合理性，MR方法可为评估暴露与结局之间的因果关系提供重要证据[39]。本文对MR方法在胃癌危险因素研究中的应用现状进行了系统的文献整理、信息提取和质量评价，总结了既往胃癌危险因素MR研究的主要研究结果。

胃癌危险因素MR研究结果的质量受诸多因素的影响。在设计严谨和工具变量满足核心假设的前提下，MR研究可以为暴露与胃癌结局之间是否具有因果关联提供一定的线索，也为基础实验室研究和机制探索提供理论依据。例如，既往基于不同人种的前瞻性研究表明，吸烟显著增加胃癌的发生风险[40]，对贲门癌和非贲门癌均如此[41]。前期MR研究同样提示吸烟是胃癌发生的危险因素，支持吸烟可能与胃癌发生风险存在因果关联。然而，该研究仅涵盖了欧洲人群，目前尚无针对亚洲人群的相关MR研究。BMI是超重和肥胖最常用的衡量标准。纳入22项队列研究的meta分析显示，超重和肥胖显著增加食管或贲门胃癌的发生风险[42]，但针对非贲门胃癌的研究仍缺少此类证据。汇总既往MR研究，两项分别基于欧洲人群[10]和中国人群[11]的MR研究支持高BMI增加胃癌风险，但一项基于日本人群的MR研究结论并不一致[12]。一般认为欧洲人群中贲门胃癌比例高，而亚洲人群非贲门胃癌比例高。这三项MR研究均未区分贲门或非贲门胃癌，因而BMI与不同胃癌亚型的关系仍有待后续研究探讨。

应用MR研究进行因果推断还受到方法学局限性的影响：第一，当选择的工具变量只能解释一小部分暴露时，弱工具变量偏倚的存在可能导致MR分析不足以检测因果效应[37]；第二，鉴于人群分层的广泛存在，工具变量的选择如源自具有遗传异质性的群体，则产生有偏的效应估计[43]；第三，多数MR分析尚无能力评估暴露与结局之间可能的非线性关系；第四，MR研究对样本量有较高的要求。即便依托具有大样本量的BBJ汇总数据（病例：6 563例，对照：195 754例）作为结局样本来源，选择可解释1%暴露的遗传工具探究与疾病之间的关联时，也仅能对关联效应OR≥1.4的遗传位点达到80%以上的统计学把握度；第五，与观察性研究一样，MR研究虽然可提示危险因素与胃癌发生的潜在因果关系，但增加或降低胃癌风险的潜在机制并不清楚。

目前，诸多胃癌危险因素MR研究存在报告不规范的问题，MR分析本身也受到方法学局限性的制约。研究者应致力于开展高质量的MR研究，并结合既往观察性队列研究、生物学合理性等多方面证据对潜在的因果关系进行综合解读，以为胃癌的病因学研究和预防策略制定提供科学依据。

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