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Estimation of Peptic Ulcer Risk Through Mendelian Randomization Analyses Using Genetically Predicted Circulating Levels of Cytokines

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ABSTRACT

Background: The relationship between inflammatory cytokines and peptic ulcer disease (PUD) has been reported in several observational studies, but causal inference remains uncertain. This study aimed to investigate the causal association between 41 circulating cytokines and PUD using Mendelian randomization (MR) analysis.

Methods: We performed a two-sample MR analysis using genetic variation data from a large genome-wide association study (GWAS) of peptic ulcer (130 European cases and 189,695 controls) and cytokine-related GWAS data from 8,293 healthy individuals. The inverse variance weighted (IVW) method was used as the primary analysis, supported by sensitivity analyses including MR-Egger, weighted median, simple model, weighted model, and MR-PRESSO.

Results: Our findings suggest that platelet-derived growth factor-BB (PDGF-BB), stromal cell-derived factor-1α (SDF-1A), and macrophage inflammatory protein-1α (MIP-1A) are associated with PUD risk. Specifically, genetically predicted PDGF-BB was positively associated with ulcer risk (ORIVW = 4.15; 95% CI: 1.74–9.87; P = 0.0013), while higher levels of MIP-1A (ORIVW = 0.20; 95% CI: 0.07–0.59; P = 0.0037) and SDF-1A (ORIVW = 0.32; 95% CI: 0.12–0.87; P = 0.0249) were protective.

Conclusion: This MR study indicates that PDGF-BB may increase susceptibility to PUD, whereas MIP-1A and SDF-1A appear protective. These findings strengthen the evidence for cytokines as potential biomarkers and therapeutic targets in PUD.

INTRODUCTION

Peptic ulcer disease (PUD) is a major gastrointestinal condition characterized by mucosal erosion in the stomach or duodenum due to the damaging action of gastric acid and pepsin. Lanas A et al. (2017), Malfertheiner P et al. (2009) It remains a significant global health problem, with an estimated lifetime prevalence of 5–10% and a high risk of complications such as bleeding, perforation, and gastric outlet obstruction. Salagacka A et al. (2014), Dincă AL et al. (2022) Although the incidence has declined in high-income countries due to the recognition of Helicobacter pylori as a primary etiological agent and the widespread use of proton pump inhibitors, PUD continues to impose a substantial burden in low- and middle-income regions.

In Brazil and across Latin America, the prevalence of H. pylori infection remains elevated, ranging from 40% to 70% in different population-based studies. Sugimoto M et al. (2007), Sugimoto M et al. (2007) This high prevalence contributes significantly to the persistence of PUD in the region, especially in socioeconomically vulnerable groups with limited access to preventive healthcare. Jafarzadeh A et al. (2009), Polonikov AV et al. (2007) However, H. pylori infection and nonsteroidal anti-inflammatory drug (NSAID) use do not fully explain the pathogenesis of PUD, and additional biological pathways — particularly inflammatory and immune responses — are increasingly recognized as central to disease development and progression.

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Cytokines, small signaling proteins involved in immune regulation and inflammation, have been implicated in PUD. Tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-10 (IL-10), and C-reactive protein (CRP) are among the most studied. Jo Y et al. (2010) Yet, observational studies often suffer from confounding and reverse causation, making causal inference difficult.

Mendelian randomization (MR) offers a powerful method to strengthen causal inference by using genetic variants as proxies (instrumental variables) for modifiable exposures such as cytokine levels. Wootton RE et al. (2020) Because alleles are randomly allocated at conception, MR minimizes confounding and reverse causality, allowing for more reliable conclusions.

In this study, we applied a two-sample MR design to examine the causal role of 41 circulating cytokines in the risk of PUD. Burgess S et al. (2015) By using large-scale GWAS summary statistics, we aimed to clarify whether inflammatory pathways directly contribute to ulcer development. Hartwig FP et al. (2016) This approach not only advances global understanding of PUD pathogenesis but also provides insights relevant for Brazil and Latin America, where the disease burden remains considerable.

METHODS

Ethical Approval

This Mendelian randomization (MR) analysis was conducted using publicly available genome-wide association study (GWAS) summary statistics. All individual studies contributing to the GWAS datasets had obtained approval from their respective institutional review boards, and all participants had provided written informed consent. Therefore, no additional informed consent or ethical clearance was required for the present analysis.

MR Assumptions

The MR framework relies on three fundamental assumptions:

1. Relevance – the selected genetic variants are strongly associated with the exposure (risk factors).

2. Independence – these variants are not associated with confounders of the exposure–outcome relationship.

3. Exclusion restriction – the variants influence the outcome only through the exposure of interest and not through alternative pathways Emdin CA et al. (2017).

In this bidirectional two-sample MR study, GWAS summary data for 41 circulating inflammatory cytokines and peptic ulcer disease (PUD) were analyzed to explore causal relationships in both directions.

Instrumental Variable Selection

Single nucleotide polymorphisms (SNPs) associated with cytokines or peptic ulcer were initially selected at genome-wide significance ($P < 5 \times 10^{-8}$). When only a small number of SNPs were identified for certain cytokines, a relaxed threshold ($P < 5 \times 10^{-6}$) was applied. To ensure independence, SNPs were pruned for linkage disequilibrium (LD) using a 10,000 kb window and $R^2 < 0.001$. Palindromic SNPs were excluded to avoid ambiguity in allele orientation.

For each SNP, the proportion of variance explained (R^2) and F-statistic were calculated to confirm instrument strength, with $F > 10$ considered sufficient to minimize weak instrument bias Pierce BL et al. (2011), Palmer TM et al. (2012) When exposure SNPs were absent in the outcome dataset, proxies in high LD ($R^2 > 0.9$) were identified using LDlink Machiela MJ et al. (2015).

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Data Sources

All datasets were derived from large, publicly available GWAS meta-analyses.

• Peptic ulcer disease (PUD): Derived from the Finnish database, comprising 130 cases and 189,695 controls of European ancestry. PUD diagnoses were based on ICD-10 criteria.

•Inflammatory cytokines: Based on the largest cytokine-related GWAS meta-analysis to date, which combined three Finnish cohorts—the Young Finns Study (YFS) and two FINRISK surveys (1997 and 2002)—involving 8,293 participants. Concentrations of 41 cytokines were normalized using a two-step inverse transformation. Associations between ~10.7 million SNPs and cytokine levels were estimated under additive genetic models, with adjustments for age, sex, body mass index (BMI), and the first 10 genetic principal components Ahola-Olli AV et al. (2017).

Importantly, there was no sample overlap between the cytokine GWAS and the PUD GWAS datasets.

Statistical Analysis

For cytokines instrumented by a single SNP, causal estimates were obtained using the Wald ratio method Perry BI et al. (2021). For exposures with two or more SNPs, inverse variance weighting (IVW) served as the primary analytic method Lawlor DA et al. (2008). Heterogeneity across SNP-specific estimates was assessed using Cochran's Q test. Although mild mild heterogeneity

was noted in some results, IVW estimates remained the primary causal inference method Burgess S et al. (2019)

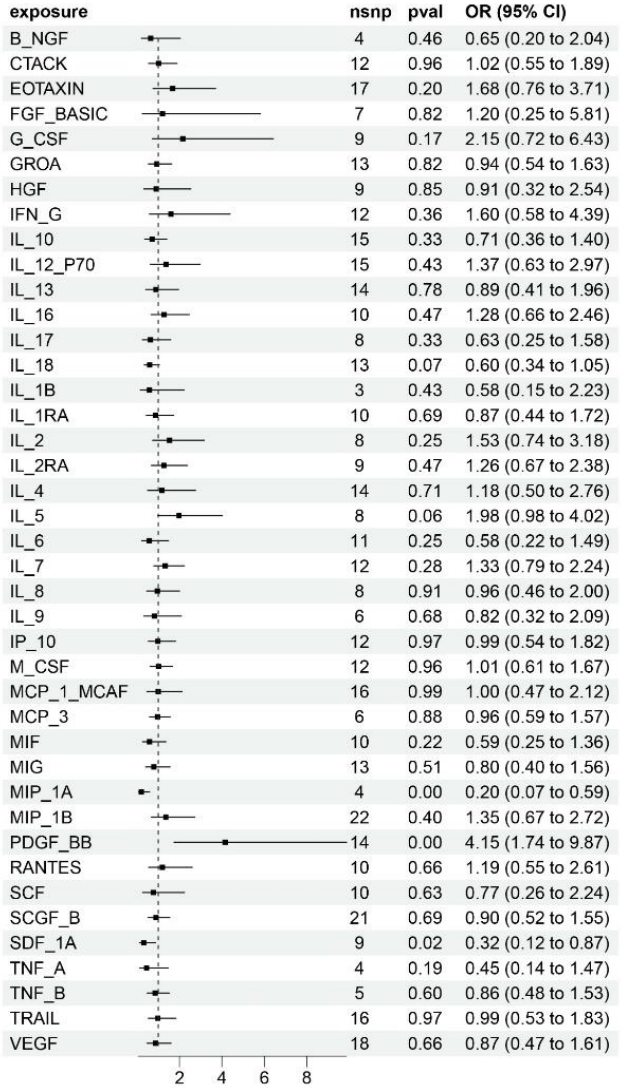
To assess potential pleiotropy and validate robustness, additional methods were applied:

• MR-Egger regression and MR-PRESSO for horizontal pleiotropy Cui Z et al. (2021)

• Leave-one-out analysis to test the influence of individual SNPs.

• PhenoScanner searches to exclude SNPs with pleiotropic associations.

Figure 1: Causal associations of 41 inflammatory cytokines with peptic ulcer risk.



Odds ratios (ORs) with 95% confidence intervals represent the change in peptic ulcer risk per one–standard deviation increases in cytokine levels. A Bonferroni-corrected significance threshold of $P < 0.0012$ (0.05/41) was applied. Results are derived from the inverse variance weighted method for all cytokines.

Abbreviations: bNGF, beta nerve growth factor; CTACK, cutaneous T cell–attracting chemokine; FGFBasic, basic fibroblast growth factor; GCSF, granulocyte colony-stimulating factor; GROa, growth-regulated oncogene-a; HGF, hepatocyte growth factor; IFNg, interferon gamma; IL, interleukin; IP, interferon gamma-induced protein 10; MCP1, monocyte chemotactic protein 1; MCP3, monocyte-specific chemokine 3; MCSF, macrophage colony-stimulating factor; MIF, macrophage migration inhibitory factor; MIG, monokine induced by interferon gamma; MIP1a, macrophage inflammatory protein-1a; MIP1b, macrophage inflammatory protein-1b; PDGFbb, platelet-derived growth factor BB; RANTES, regulated upon activation normal T cell expressed and secreted factor; SCF, stem cell factor; SCGFb, stem cell growth factor beta; SDF1a, stromal cell–derived factor-1 alpha; SNPs, single nucleotide polymorphisms; TNFa, tumor necrosis factor alpha; TNFb, tumor necrosis factor beta; TRAIL, TNF-related apoptosis-inducing ligand; VEGF, vascular endothelial growth factor.

Multiple testing correction was performed using the Bonferroni method, setting a significance threshold at $P < 0.0012$ (0.05/41). Associations with P-values between 0.0012 and 0.05 were considered suggestive Georgakis MK et al. (2019) All analyses were conducted in R (v4.2.2) using the TwoSampleMR (v0.5.6) and MR-PRESSO packages Verbanck M et al. (2018).

Bidirectional MR Analysis

To assess reverse causality, a bidirectional MR framework was applied. SNP effect sizes, standard errors, alleles, allele frequencies, and P-values were harmonized between exposure and outcome datasets. Palindromic SNPs were excluded due to strand ambiguity. Causal estimates were calculated using the Wald ratio for each SNP and summarized using IVW with multiplicative random effects to account for heterogeneity.

Effects of cytokines on PUD risk were reported as odds ratios (ORs) with 95% confidence intervals (CIs) per 1 SD increase in genetically predicted cytokine concentration. Conversely, the effect of PUD on cytokine levels was expressed as β coefficients with 95% CIs.

RESULTS

Instrument strength and validity

Using the relaxed genome-wide significance threshold ($P < 5 \times 10^{-6}$), we were able to construct genetic instruments for all 41 cytokines. The calculated F-statistics ranged from 20.79 to 345.00, all well above the

conventional threshold of 10, indicating that weak instrument bias was unlikely to substantially affect the results. SNP harmonization ensured consistency in effect allele alignment, and no palindromic SNPs were retained.

Causal effects of cytokines on peptic ulcer risk

Three cytokines demonstrated evidence of causal associations with peptic ulcer disease (PUD) (Figure 1, Table 1).

Platelet-derived growth factor-BB (PDGF-BB)

Genetically elevated PDGF-BB was significantly associated with increased risk of PUD (IVW OR = 4.15; 95% CI: 1.74–9.87; P = 0.0013). Sensitivity analyses supported this association: the weighted median method produced a consistent estimate (OR = 4.04; 95% CI: 1.16–14.09; P = 0.028), and MR-Egger regression also showed a positive effect (OR = 18.32; 95% CI: 2.59–129.66; P = 0.013). Although the magnitude of effect varied, the direction remained concordant across methods, reinforcing the robustness of this finding.

Macrophage inflammatory protein-1α (MIP-1α)

Higher genetically predicted MIP-1α concentrations were inversely associated with PUD risk (IVW OR = 0.20; 95% CI: 0.07–0.59; P = 0.0037). The weighted median method confirmed the protective effect (OR = 0.19; 95% CI: 0.05–0.71; P = 0.0139). While MR-Egger regression produced a nonsignificant estimate (OR = 0.06; P = 0.236), the effect direction was consistent with the IVW results.

Stromal cell-derived factor-1α (SDF-1α)

Genetically elevated SDF-1α was also inversely associated with PUD (IVW OR = 0.31; 95% CI: 0.12–0.87; P = 0.025). Sensitivity methods showed the same protective direction, although statistical significance was not reached in the weighted median (P = 0.086) or MR-Egger (P = 0.702) analyses.

For these three cytokines, diagnostic analyses did not reveal substantial heterogeneity or pleiotropy. Cochrane's Q test suggested no notable heterogeneity across SNP-specific estimates ($p > 0.05$). The MR-Egger intercept was nonsignificant, and MR-PRESSO did not detect any outlier SNPs. Visual inspection of scatter plots, funnel plots, leave-one-out analyses, and forest plots further supported the stability of the findings.

Reverse causality analysis

To explore whether peptic ulcer disease exerts causal effects on systemic inflammatory regulator levels, we extracted five genome-wide significant SNPs ($P < 5 \times 10^{-6}$) associated with PUD. After harmonization and proxy substitution, causal estimates were calculated for each cytokine No significant associations were detected

Table 1:

outcome	exposure	method	SNPs	Beta	Se	p-value	low_ci	up_ci	or	or_lci95	or_uci95
Peptic ulcer	MIP_1A	MR Egger	4	-2.88061	1.720813	0.236112	-6.2534	0.492185	0.056101	0.001924	1.635886
Peptic ulcer	MIP_1A	Weighted median	4	-1.65171	0.686379	0.01611	-2.99701	-0.30641	0.191722	0.049936	0.736087
Peptic ulcer	MIP_1A	Inverse variance weighted	4	-1.61029	0.555209	0.003728	-2.6985	-0.52208	0.199829	0.067306	0.593283
Peptic ulcer	MIP_1A	Simple mode	4	-2.00498	0.913787	0.115804	-3.796	-0.21396	0.134663	0.02246	0.80738
Peptic ulcer	MIP_1A	Weighted mode	4	-2.01195	0.88452	0.107467	-3.74561	-0.27829	0.133728	0.023621	0.757081
Peptic ulcer	PDGF_BB	MR Egger	14	2.908243	0.998314	0.013005	0.951547	4.864938	18.32457	2.589714	129.6629
Peptic ulcer	PDGF_BB	Weighted median	14	1.396396	0.640957	0.02936	0.140121	2.652671	4.040611	1.150413	14.19189
Peptic ulcer	PDGF_BB	Inverse variance weighted	14	1.422644	0.442448	0.001303	0.555446	2.289842	4.148073	1.742717	9.873381
Peptic ulcer	PDGF_BB	Simple mode	14	1.1975	1.150604	0.316958	-1.05768	3.452683	3.311828	0.347259	31.58503
Peptic ulcer	PDGF_BB	Weighted mode	14	0.956386	1.124033	0.41025	-1.24672	3.159492	2.602276	0.287446	23.55862
Peptic ulcer	SDF_1A	MR Egger	7	-0.24987	1.033548	0.818566	-2.27563	1.775881	0.778899	0.102732	5.90548
Peptic ulcer	SDF_1A	Weighted median	7	-1.15989	0.698681	0.096892	-2.5293	0.209528	0.313521	0.079715	1.233095
Peptic ulcer	SDF_1A	Inverse variance weighted	7	-1.2561	0.57711	0.029515	-2.38724	-0.12497	0.284762	0.091883	0.882526
Peptic ulcer	SDF_1A	Simple mode	7	-1.10142	1.067677	0.342035	-3.19407	0.991225	0.332398	0.041005	2.694534
Peptic ulcer	SDF_1A	Weighted mode	7	-0.80749	1.042197	0.467886	-2.8502	1.235218	0.445976	0.057833	3.439127

between genetically predicted PUD and cytokine levels across any of the 41 inflammatory factors using the IVW method. Multiple sensitivity approaches, including MR-Egger and MR-PRESSO, confirmed the absence of reverse causality (Supplementary Table S4). Together, these results indicate that the causal pathway likely runs from cytokines to ulcer development, but not vice versa.

DISCUSSION

Main findings

In this large-scale, bidirectional MR analysis, we identified three cytokines with causal effects on peptic ulcer disease. Elevated PDGF-BB increased PUD risk, whereas MIP-1α and SDF-1α exerted protective effects. Notably, no evidence of reverse causality was observed, suggesting that alterations in cytokine levels are not merely a downstream consequence of ulcer disease but play a potential upstream role in pathogenesis.

Biological plausibility of PDGF-BB in ulcerogenesis

Our finding that PDGF-BB increases ulcer risk aligns with the known pro-inflammatory and proliferative functions of this growth factor. PDGF-BB promotes the recruitment of inflammatory cells to gastric mucosa and stimulates the release of inflammatory mediators Savikko J et al. (2001), Smyth LCD et al. (2022) These processes exacerbate mucosal injury, Yi ES et al. (1996), Tamura M et al. (2013), Yu J et al. (2003), Ge X et al. (2016) delay ulcer healing, and create a persistent pro-inflammatory environment.

Mechanistically, PDGF-BB activates key signaling cascades, including Ras/MAPK and PI3K/Akt, leading to excessive epithelial proliferation and impaired apoptosis Chang F et al. (2003), Song G et al. (2005), Zhao N et al. (2020), Li H et al. (2022) This imbalance between proliferation and programmed cell death disrupts mucosal repair and may enlarge ulcer craters. Furthermore, PDGF-BB promotes angiogenesis, which, while typically beneficial for tissue repair, may in this context increase vascular permeability, mucosal edema, and leukocyte infiltration Lee E et al. (2014), Cantanhede IG et al. (2017), Ariyanti AD et al. (2017), Wang H et al. (2012), van Roeyen CRC et al. (2006) The combined effects of enhanced inflammation, abnormal epithelial remodeling, and pathological angiogenesis provide a strong mechanistic explanation for the observed causal role of PDGF-BB in PUD.

Protective roles of MIP-1α and SDF-1α

In contrast, MIP-1α and SDF-1α appear to confer protection against ulcer development.

MIP-1α is a chemokine that mobilizes neutrophils, macrophages, and monocytes to sites of tissue injury Hasegawa M et al. (1999), Ridiandries A et al. (2018) Neutrophils play a central role in bacterial clearance, particularly against Helicobacter pylori, a major cause of ulcer disease. By facilitating effective immune surveillance and reducing bacterial burden, MIP-1α may help preserve mucosal integrity and promote ulcer healing. SDF-1α (CXCL12) supports gastrointestinal mucosal defense by enhancing epithelial cell migration, proliferation, and survival. It also stabilizes epithelial barrier function and reduces apoptosis-induced mucosal injury. Additionally, SDF-1α modulates inflammatory responses by attenuating leukocyte infiltration and cytokine release in ischemic or inflamed tissues. Its angiogenic potential may further accelerate mucosal repair by improving blood supply to the ulcerated region (49–51). Collectively, these mechanisms are consistent with our finding of a protective association between SDF-1α and PUD risk.

Strengths of the study

This study offers several methodological strengths:

Causal inference using MR

By leveraging genetic instruments, our analysis minimizes confounding and reverse causality that often complicate traditional observational studies.

Bidirectional design

Examining both cytokines → ulcer and ulcer → cytokines directions strengthen causal interpretation and demonstrates that cytokines act upstream of disease.

Robust sensitivity analyses

Use of multiple MR approaches (IVW, MR-Egger, weighted median, MR-PRESSO) provided convergent evidence, and diagnostic tests confirmed the absence of substantial pleiotropy or weak instrument bias.

Comprehensive coverage of inflammatory factors

By assessing 41 cytokines, this study provides one of the most extensive genetic evaluations of inflammatory regulators in ulcer pathogenesis.

LIMITATIONS

Despite its strengths, some limitations must be acknowledged.

Population restriction

The GWAS datasets were based exclusively on European ancestry cohorts, which may limit

generalizability to other populations with different genetic and environmental backgrounds.

Relaxed instrument threshold

The use of a less stringent SNP selection cutoff ($P < 5 \times 10^{-6}$) improved instrument availability but may increase susceptibility to false positives. However, the strong F-statistics mitigate this concern.

Lack of clinical heterogeneity analysis

Peptic ulcer disease encompasses diverse clinical phenotypes, including bleeding, perforation, and refractory ulcers. Our summary-level MR design did not permit stratified analyses of these subtypes.

Uncaptured environmental influences

MR reflects lifelong genetic predisposition. Short-term or environmentally driven cytokine fluctuations—such as those induced by infection, NSAID use, or smoking—cannot be accounted for in this design.

Clinical and research implications

These findings underscore the importance of inflammatory regulators in ulcer pathogenesis and suggest that cytokine pathways could serve as therapeutic targets.

- PDGF-BB inhibition may represent a novel strategy to limit excessive mucosal inflammation and abnormal epithelial remodeling in ulcer patients.
- Conversely, enhancement of MIP-1α and SDF-1α signaling could be explored as protective or reparative interventions to support mucosal defense and healing.

Further translational studies are warranted to validate these cytokines as biomarkers of ulcer risk and to test whether pharmacological modulation of their pathways can alter disease outcomes.

CONCLUSION

In summary, this bidirectional MR study provides strong evidence that PDGF-BB contributes causally to peptic ulcer development, whereas MIP-1α and SDF-1α reduce disease risk. These results highlight the dual role of inflammatory regulators in gastrointestinal health—some as harmful drivers of ulcerogenesis and others as protective mediators of mucosal defense. Targeting these pathways could open new avenues for precision prevention and treatment of peptic ulcer disease.

DECLARATIONS

Ethics approval and consent to participate

In addition, ethical approval was not applicable for this study as publicly available data were used for the analysis.

Consent for publication

Not applicable.

Competing interests

The authors have stated that they have no conflict of interest.

Funding

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available from the open gwas (https://gwas.mrcieu.ac.uk) ID: finn-b-K11_PULC.

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