Cancer Biol Med 2026. doi: 10.20892/j.issn.2095-3941.2026.0145

LETTER

Genetic susceptibility, environmental risk factors, and incident gastric cancer risk among individuals with different *Helicobacter pylori* infection status: a population-based study

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Gastric cancer (GC) remains a leading cause of cancer mortality worldwide[1]. *Helicobacter pylori (H. pylori)* infection is the dominant etiologic factor[2], yet GC also arises in individuals without infection or after eradication, suggesting alternative carcinogenic pathways[3]. Accordingly, increasing attention has been paid to potential differences between *H. pylori*-negative and -positive GC. Clinicopathologic differences by *H. pylori* infection status have been reported but most evidence derives from case-control studies in which infection status assessed at diagnosis is prone to misclassification due to prior eradication, spontaneous clearance, or tumor-related changes. As a result, prospective data defining the long-term clinical and biological imprint of baseline *H. pylori* status are limited.

While genetic susceptibility contributes to GC risk, genome-wide association studies (GWAS)[4-8] have rarely accounted for infection status, leaving it unclear whether reported loci reflect infection-dependent mechanisms or host-intrinsic pathways. Clarifying whether inherited risk differs between *H. pylori*-negative and -positive GC is increasingly important as *H. pylori* prevalence declines. Using a large population-based intervention trial with long-term follow-up, we evaluated the clinicopathologic features and genetic susceptibility of incident GC according to rigorously defined baseline *H. pylori* status, aiming to delineate etiologic heterogeneity between infection strata.

This study was designed as a case-cohort study within the framework of the Mass Intervention Trial in Linqu, Shandong Province (MITS)[9], a community-based randomized controlled trial to evaluate the GC prevention effect of anti-*H. pylori* treatment (no. ChiCTRTRC-10000979; **Figure 1A**). Primary analyses were stratified according to baseline *H. pylori* infection, which was defined by concordant results from ^{13}C-urea breath test (^{13}C-UBT) and recomLine *H. pylori* IgG immunoblot assays to improve specificity and better reflect sustained infection. Among participants receiving eradication therapy, *H. pylori* status was reassessed 45 d after treatment using ^{13}C-UBT to determine eradication success[9]. Incident GC cases were identified through local cancer registries, active follow-up by village health workers, and review of hospital medical or pathologic records. For convenience, we refer to GC cases developing in baseline *H. pylori*-negative and -positive individuals as "*H. pylori*-negative GC" and "*H. pylori*-positive GC." Genome-wide genotyping was performed, followed by standardized imputation and quality control[4]. Genetic susceptibility was evaluated using both variant-level analyses and the polygenic risk score (PRS) derived from large East Asian GWASs. An environmental risk score (ERS) was constructed based on multiple lifestyle and dietary factors with components defined *a priori* and weighted according to the associations with GC risk. Associations with GC risk were estimated using weighted Cox proportional hazards models within *H. pylori*-negative and -positive strata, and heterogeneity by infection status was tested. The detailed methods are provided in the **Supplementary Materials**.

Clinicopathologic features of GC by *H. pylori* status

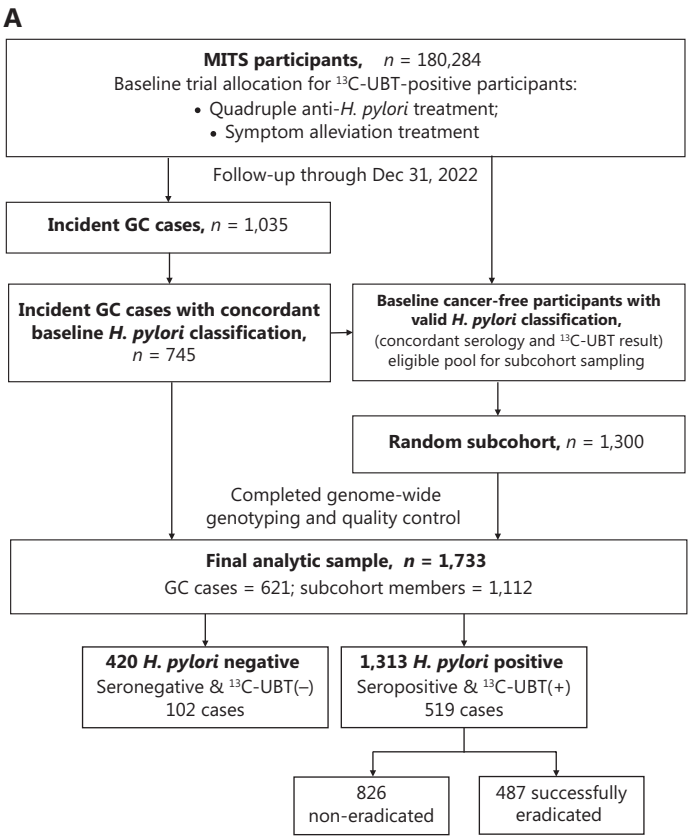
Among 1733 participants (mean age, 45.0 years; 39.7% women), 420 were *H. pylori*-negative and 1313 were *H.*

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Received February 13, 2026; accepted May 11, 2026;
published online July 14, 2026.
Available at www.cancerbiomed.org

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CHR:POS	RSID	Effect allele	HR (95% CI)	*P*-het	FDR
1:155143946	rs4971092	C	2.66 (1.62–4.35) 0.46 (0.06–3.29)	0.090	0.41
1:222074508	rs6657194	G	0.80 (0.71–0.90) 1.09 (0.82–1.46)	0.052	0.41
5:40790551	rs10074991	G	1.19 (1.05–1.34) 1.82 (1.37–2.41)	0.0062	0.13
5:41241333	rs117389282	G	0.84 (0.60–1.17) 0.42 (0.21–0.84)	0.082	0.41
7:122275322	rs138577550	C	1.20 (0.73–1.97) 0.22 (0.11–0.44)	9.74×10^{-5}	0.0050
9:85020619	rs150732720	G	0.75 (0.40–1.40) 4.35 (1.72–11.01)	0.0021	0.0054
9:108206091	rs148857870	G	1.83 (1.04–3.24) 12.75 (4.61–35.26)	0.0011	0.0038
9:136126636	rs7849280	G	1.35 (1.16–1.58) 0.88 (0.59–1.32)	0.048	0.41
10:37802532	rs2475206	G	0.91 (0.80–1.03) 0.70 (0.54–0.91)	0.083	0.41
11:86108212	rs56371957	G	0.98 (0.84–1.13) 2.14 (1.55–2.95)	1.36×10^{-5}	0.0014
15:86817415	rs117709414	G	1.14 (0.68–1.90) 3.62 (1.75–7.50)	0.011	0.19
16:69201758	rs1110549	T	18.57 (7.58–45.48) 2.96 (0.72–12.12)	0.030	0.39
17:13599004	rs141766945	C	1.11 (0.86–1.43) 0.57 (0.33–0.98)	0.029	0.39
22:39405511	rs5995654	G	0.91 (0.80–1.03) 0.64 (0.46–0.87)	0.041	0.41

Figure 1 Continued

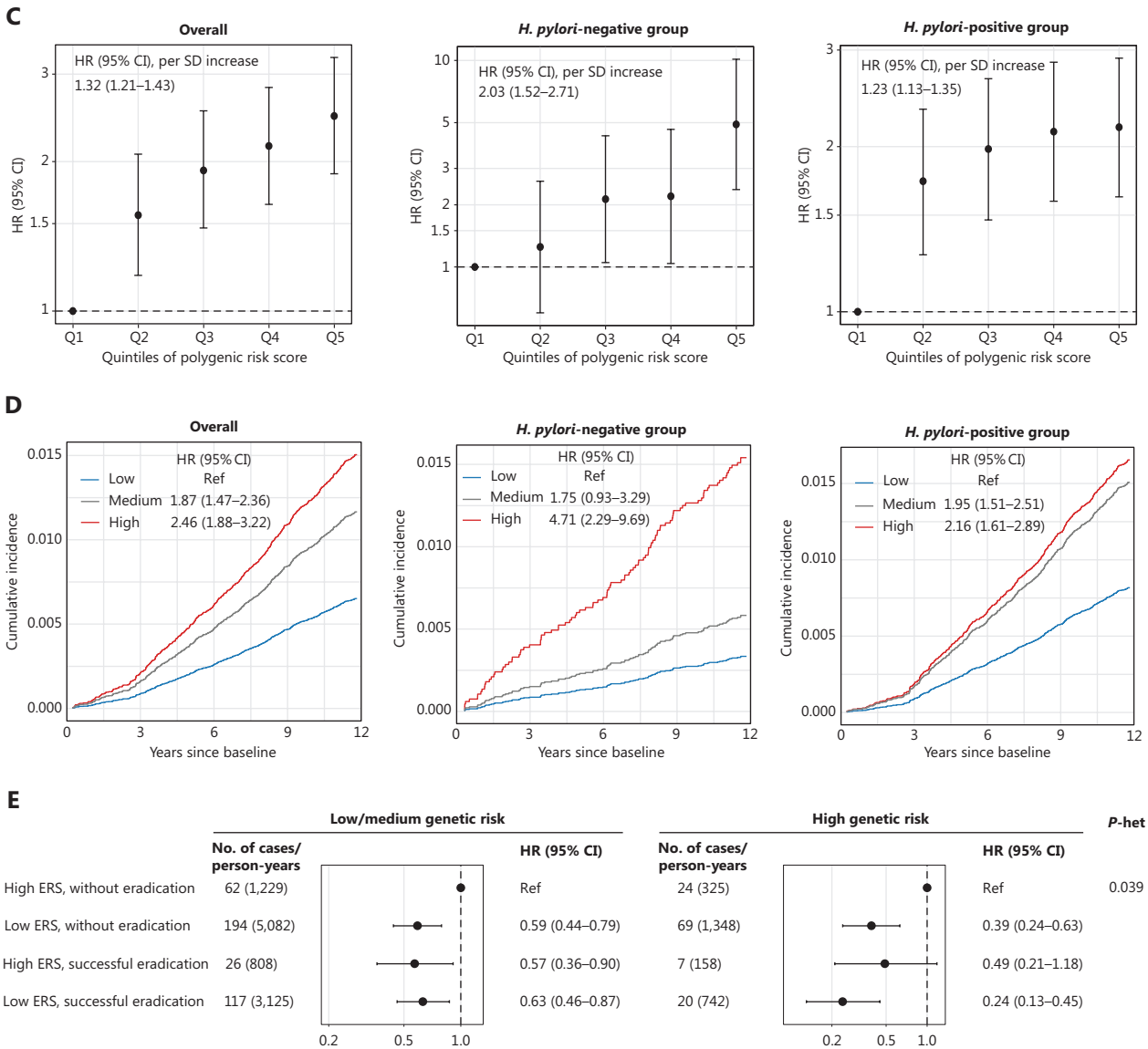


Figure 1 (A) Procedure of inclusion and exclusion of study populations. (B) *H. pylori*-stratified associations of 14 genetic variants showing nominal heterogeneity in gastric cancer risk. (C) Hazard ratios for gastric cancer across polygenic risk score quintiles by *H. pylori* infection status. (D) Cumulative incidence of gastric cancer across polygenic risk score groups by *H. pylori* status. (E) Associations of *H. pylori* eradication and environmental risk score with gastric cancer risk by genetic risk group. CI, confidence interval; ERS, environmental risk score; GC, gastric cancer; FDR, false discovery rate; *H. pylori*, *Helicobacter pylori*; HR, hazard ratio; UBT, urea breath test.

pylori-positive at baseline. During follow-up, 621 incident GC cases were identified, including 102 among *H. pylori*-negative and 519 among *H. pylori*-positive individuals. Despite broadly comparable clinicopathologic characteristics, *H. pylori*-negative GCs more often exhibited well-differentiated histology (21.6% *vs.* 16.6%, $P = 0.015$) and less advanced stages (**Table S1**).

Variant-level genetic risk for GC by *H. pylori* infection status

A meta-analysis involving three large East Asian GWAS (BioBank Japan, KoGES, and China Kadoorie Biobank[6-8]; total $n = 315{,}446$) was performed to characterize inherited susceptibility, together with candidate variants from two published

GC PRS panels[4,5] with minimal genomic inflation (λ = 1.02). After quality control and linkage disequilibrium clumping, 103 independent variants were identified, including 16 genome-wide significant loci ($P < 5 \times 10^{-8}$) and 87 suggestive loci ($P < 5 \times 10^{-5}$; **Table S2**). We then evaluated heterogeneity of these variants between *H. pylori*-negative and -positive GCs. Fourteen variants showed nominal evidence of heterogeneity in the associations with GC risk [*P*-heterogeneity (*P*-het) < 0.10; **Figure 1B**], although only a subset remained significant after false discovery rate (FDR) correction. Among these variants, rs138577550-C (*CADPS2*) was inversely associated with GC risk in *H. pylori*-negative individuals but not in *H. pylori*-positive individuals [negative: hazard ratio (HR) = 0.22, 95% confidence interval (CI): 0.11–0.44; positive: HR = 1.20, 95% CI: 0.73–1.97; *P*-het (FDR) = 0.0050; **Table S2**]. In addition, rs10074991-G within *PRKAA1*, a well-established GC susceptibility locus, showed nominal heterogeneity (*P*-het = 0.0062) with a stronger association in *H. pylori*-negative individuals (HR = 1.82, 95% CI: 1.37–2.41) than *H. pylori*-positive individuals (HR = 1.19, 95% CI: 1.05–1.34). Conversely, the *ABO* locus (rs7849280-G) was exclusively associated increased risk among *H. pylori*-positive cases (HR = 1.35, 95% CI: 1.16–1.58) with little evidence of association in *H. pylori*-negative cases (*P*-het = 0.048).

Polygenic risk for GC by *H. pylori* infection status

To summarize inherited susceptibility, PRSs were constructed based on independent variants selected at multiple *P*-value thresholds from the meta-analysis. Across these thresholds, the genome-wide significant set ($P < 5 \times 10^{-8}$; 16 independent variants) had the strongest and most consistent association with GC overall and by *H. pylori* status, and was used for primary analyses (**Table S3**). In the overall population, GC risk increased with higher PRS [per standard deviation (SD): HR = 1.32, 95% CI: 1.21–1.43; **Figure 1C**] with a monotonic gradient across quintiles. Stratified analyses demonstrated heterogeneity by *H. pylori* infection status (*P*-het = 0.0012) with stronger association observed among *H. pylori*-negative individuals (per SD: HR = 2.03, 95% CI: 1.52–2.71) than among *H. pylori*-positive individuals (per SD: HR = 1.23, 95% CI: 1.13–1.35; **Figure 1C**). The highest PRS quintile was associated with a 4.71-fold higher GC risk in the *H. pylori*-negative stratum compared to the lowest quintile. These relative-risk gradients were reflected in cumulative incidence curves stratified by PRS categories, defined as the bottom 20% (low), middle 60% (medium), and top 20% (high) of the PRS distribution, which showed clear and widening separation of PRS strata over follow-up (**Figure 1D**).

PRS associations were generally consistent across subgroups (**Figure S1).** Association between genetic and GC risk was stronger among individuals with a family history of GC [HR = 3.00, 95% CI: 1.74–5.16 *vs.* HR = 1.24, 95% CI: 1.15–1.35 with no family history; *P*-for-interaction (*P*-int) = 0.011], a pattern that was consistently noted in both *H. pylori*-negative and positive groups. Additional heterogeneity by selected environmental factors existed, differing by *H. pylori* status.

An ERS was constructed based on 10 dietary and lifestyle factors to quantify the cumulative effect of environmental exposures. The ERS was significantly associated with GC risk when modeled as both a continuous variable (per SD increase: HR = 1.13, 95% CI: 1.04–1.22) and a categorical variable (top 20%, high *vs.* low: HR = 1.29, 95% CI: 1.06–1.55; **Table 1**). GC risk increased across joint PRS-ERS strata with elevated risk among individuals with medium PRS and high ERS (HR = 2.20, 95% CI: 1.60–3.01) and the highest risk among those with high PRS and high ERS (HR = 4.63, 95% CI: 3.07–6.98). A statistically significant interaction between PRS and ERS was noted (*P*-int = 0.041). Similar gradients existed in analyses stratified by *H. pylori* status with increased GC risk among individuals with combined high PRS and ERS in both strata (**Table S4**).

Lifestyle factors and *H. pylori* eradication in relation to GC risk across genetic risk groups

Further stratified analyses showed differences in the association between genetic risk and GC across lifestyle and *H. pylori* eradication groups. Among *H. pylori*-positive individuals, adopting a healthy lifestyle was associated with a lower risk of GC (HR = 0.42, 95% CI: 0.28–0.65), whereas no significant difference was noted in the *H. pylori*-negative group (**Table S5**). Successful *H. pylori* eradication also significantly reduced risk among individuals with a high genetic risk (HR = 0.61, 95% CI: 0.39–0.95; **Table S5**) but not among those with a low or medium PRS. The inverse association was more pronounced for high-genetic risk individuals who achieved both successful eradication and a healthy lifestyle (HR = 0.24, 95% CI: 0.13–0.45) with significant heterogeneity when compared with those at low or medium genetic risk (*P*-het = 0.039; **Figure 1E**).

Several limitations should be acknowledged. First, because primary analyses were based on baseline *H. pylori* status, post-baseline changes in infection status may have introduced some misclassification. Second, although we noted stronger genetic associations among baseline *H. pylori*-negative individuals, the limited sample size in this stratum precluded the construction of *H. pylori*-specific PRSs. Larger studies are warranted to identify infection-specific loci and further improve risk stratification for *H. pylori*-negative individuals. Third, clinicopathologic data were incomplete for a proportion of cases, which limited further examinations of potential differences in genetic and environmental risk profiles across tumor subtypes and disease stages.

In conclusion, our findings highlight heterogeneity in genetic susceptibility according to *H. pylori* infection. Among

Table 1 Associations of environmental risk score and its joint effects with genetic risk on gastric cancer

	No. of cases (person-years)	HR (95% CI)[a]	*P*
Environmental risk score[b]			
Per SD increase	621 (17,329)	1.13 (1.04–1.22)	0.0023
Low ERS	482 (13,840)	Ref	
High ERS	139 (3,489)	1.29 (1.06–1.55)	0.0092
Grouped by genetic risk			
Low genetic risk			
Low ERS	74 (2,932)	Ref	
High ERS	15 (671)	0.79 (0.45–1.38)	0.41
Medium genetic risk			
Low ERS	297 (8,113)	1.68 (1.30–2.18)	8.39×10^{-5}
High ERS	90 (2,206)	2.20 (1.60–3.01)	8.86×10^{-7}
High genetic risk			
Low ERS	111 (2,795)	2.04 (1.51–2.76)	3.37×10^{-6}
High ERS	34 (612)	4.63 (3.07–6.98)	2.90×10^{-13}
P-int[c]	0.042		

[a]HRs were estimated using Cox proportional hazards models adjusted for age and gender, and 10 principal components (for joint analyses only).
[b]The environmental risk score (ERS) was constructed based on 10 environmental lifestyle and dietary risk factors. Individuals in the top 20% of the distribution were classified as having high ERS, while the remainder were defined as low ERS.
[c]*P*-interaction value (*P*-int) of genetic risk group and ERS was calculated using the likelihood ratio tests comparing models with and without the interaction term.
CI, confidence interval; HR, hazard ratio.

individuals at high genetic risk, *H. pylori* eradication and a healthy lifestyle were associated with lower GC risk. Integrating genetic risk assessment with infection control and behavioral interventions may help inform prevention strategies in high-risk populations.

Acknowledgements

We sincerely thank all the members of the Mass Intervention Trial in Linqu, Shandong Province.

Grant support

This study was funded by Beijing Hospitals Authority Clinical Medicine Development of Special Funding Support (No. ZLRK202325), the Noncommunicable Chronic Diseases-National Science and Technology Major Project (Nos. 2023ZD0501400, 2025ZD0545200), Capital's Funds for Health Improvement and Research (No. 2026-1Q-1091), National Natural Science Foundation of China (Nos. 82172555, 82273704, and 82504482), Beijing Hospitals Authority's Ascent Plan (DFL20241102), China Postdoctoral Science Foundation (2024M760152), Postdoctoral Fellowship Program of CPSF (GZB20250192), Peking University Medicine Fund for World's Leading Discipline or Discipline Cluster Development (No. BMU2022XKQ004), and Science Foundation of Peking University Cancer Hospital (Nos. BJCH2024BJ02, XKFZ2410, and BJCH2025CZ04).

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Hengmin Xu, Hui Ma, Wenqing Li, Kaifeng Pan.
Collected the data: Hengmin Xu, Hui Ma, Yuxin Wang, Xinling Wang, Xuan Han, Wenjing Zhao.

Contributed data or analysis tools: Yang Zhang, Tong Zhou, Jingying Zhang, Weicheng You.
Performed the analysis: Hengmin Xu, Hui Ma.
Wrote the paper: Hengmin Xu, Hui Ma, Wenqing Li, Kaifeng Pan.

Data availability statement

The data generated in this study are available upon request from the corresponding author.

Ethics statement

This study was approved by the Institutional Review Board of Peking University Cancer Hospital (Approval No. 2023KT138). All participants of the MITS provided written informed consent.

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Cite this article as: Xu H, Ma H, Wang Y, Wang X, Han X, Zhao W, et al. Genetic susceptibility, environmental risk factors, and incident gastric cancer risk among individuals with different *Helicobacter pylori* infection status: a population-based study. Cancer Biol Med. 2026; 23: 1038-1043. doi: 10.20892/j.issn.2095-3941.2026.0145