Supplementary Content

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Supplementary methods

Study population

This study was designed as a case-cohort study within the framework of the Mass Intervention Trial in Linqu, Shandong Province (MITS)[1,2]. The MITS is a community-based, cluster-randomized, controlled, superiority intervention trial (no. ChiCTRTRC-10000979) initiated in March 2011 to evaluate the gastric cancer (GC) prevention effect of anti-*Helicobacter pylori* (*H. pylori*) eradication. Details of the MITS design and implementation have been described previously[1,2]. A total of 180,284 eligible individuals in 980 villages were enrolled. Individuals who tested positive for *H. pylori* using a ^{13}C-urea breath test (^{13}C-UBT) randomly assigned to receiving either (1) a 10-day, quadruple anti-*H. pylori* eradication (comprising 20 mg of omeprazole, 750 mg of tetracycline, 400 mg of metronidazole and 300 mg of bismuth citrate) or (2) symptom alleviation treatment with a single daily dosage of omeprazole and bismuth citrate. *H. pylori*-negative individuals did not receive any treatment. Baseline data collection included standardized interviews on demographics and lifestyle, as well as blood sampling for serologic and genetic analyses. The study was approved by the Institutional Review Board of Peking University Cancer Hospital, and all participants provided written informed consent.

During follow-up through December 31, 2022, 1035 incident GC cases were recorded. For the present study, we established a case-cohort sub-study within the MITS. Among participants with available baseline biospecimens, *H. pylori* serologic profiles and ^{13}C-UBT results were first evaluated. Participants with missing results on either test or with discordant classifications were excluded, and all incident GC cases with concordant baseline *H. pylori* status (n = 745) were included. In parallel, a

random subcohort was selected from baseline cancer-free participants with concordant *H. pylori* classification across the two assays (n = 1300). Both groups underwent genome-wide genotyping and quality-control procedures. After excluding samples failing quality control, the final analytic set comprised 1733 participants, including 621 GC cases and 1112 subcohort participants (**Figure 1A**).

Examination of *H. pylori* infection status

Baseline *H. pylori* infection was assessed using a dual-testing approach. All participants underwent a ^{13}C-UBT test, and baseline serum samples were subsequently tested using the recomLine Helicobacter IgG 2.0 immunoblot assay (Mikrogen Diagnostik, Neuried, Germany) for *H. pylori*-specific IgG detection[3]. Concordant negative results on both tests defined *H. pylori*-negative status, while concordant positive results defined *H. pylori*-positive status. For analyses among *H. pylori*-positive individuals, post-intervention infection status was categorized based on the 45-day reassessment using the ^{13}C-UBT test, as successful eradication (participants with successful eradication confirmed by negative follow-up ^{13}C-UBT) and non-eradicated (participants assigned to placebo or remaining ^{13}C-UBT positive after eradication).

Outcome assessment

Incident GC cases were identified through multiple sources, including linkage with local cancer registries, active follow-up by village health workers, and review of hospital medical or pathological records. All suspected cases were verified by qualified clinicians. Cancer diagnoses were coded according to the International Classification of Diseases, 10th Revision (ICD-10). Tumor-node-metastasis (TNM) stages were classified following the Union for International Cancer Control (UICC)

and American Joint Committee on Cancer (AJCC) gastric cancer staging system, 8th edition.

Genotyping, imputation and quality control

Peripheral blood leucocyte DNA samples were genotyped using the Asian Screening Array beadchip for MITS participants, followed by the standard quality control and imputation procedures[4]. Variants with a call rate < 95%, Hardy-Weinberg equilibrium $P < 1.0\times10^{-6}$, minor allele frequency (MAF) ≤ 0.5%, or duplication were excluded. Samples were removed for variant missing rate > 5%, heterozygosity deviating by > ±3 standard deviation (SD) from the mean, sex inconsistency, or duplication. Genotypes were phased with SHAPEIT (v2) and imputed using IMPUTE2 (v2.3.1); imputed variants were excluded if INFO ≤ 0.3, MAF ≤ 0.5%, or missing rate > 10%.

Statistical analysis

All analyses were conducted within the case-cohort framework, accounting for the sampling design using weighted Cox proportional hazards models. Baseline characteristics were summarized by *H. pylori* infection status, and clinicopathologic features of GC cases were compared using Welch's *t*-tests for continuous variables and Pearson's χ^2 tests (or Fisher's exact tests when expected cell counts were < 5) for categorical variables. Analyses were restricted to participants with known information on relevant variables.

Genetic susceptibility and variant-level heterogeneity by H. pylori status

Summary statistics were obtained from three large-scale East Asian genome-wide association studies (GWAS), including the BioBank Japan (BBJ)[5], Korea Genome and Epidemiology Study (KoGES)[6], and China Kadoorie Biobank (CKB)[7], comprising a total of 315,446 individuals. In addition, we incorporated candidate variants from two

previously published GC-polygenic risk score (PRS) panels (112 reported by Jin et al[8]. and 12 reported by Xu et al[4].) with reported effect sizes. All variants from these five sources were aligned on strand and underwent standard quality control, retaining variants with INFO > 0.8, MAF > 1%, and missingness < 0.1. Meta-analysis was conducted using inverse-variance weighted fixed-effect models across the three GWAS datasets, jointly integrating the 124 candidate variants when available. Variants within MHC region (chr6:25-34 Mb, GRCh37) were excluded. The resulting association statistics were linkage disequilibrium (LD)-clumped ($r^2 < 0.1$ within 500 kb), yielding 103 independent single nucleotide variants (SNVs) above suggestive level ($P < 5\times10^{-5}$).

For each independent variant, hazard ratios (HRs) and 95% confidence intervals (CIs) for GC were estimated within *H. pylori*-negative and -positive strata using weighted Cox models. Heterogeneity by *H. pylori* status was assessed using Cochran's *Q* test. Variants with *P* for heterogeneity (*P*-het) < 0.10 and nominal significance ($P < 0.05$ in either stratum) were considered to show infection-dependent differences in genetic effects. To account for multiple testing across 103 independent variants, *P*-het were further adjusted using the false discovery rate (FDR) method of Benjamini-Hochberg.

Polygenic risk score construction and modelling of GC risk

To evaluate polygenic effects, PRS associations were examined at multiple SNV inclusion thresholds ($P < 5\times10^{-8}$, 5×10^{-7}, 5×10^{-6}, 5×10^{-5}, and 5×10^{-4}), with variants LD-clumped at $r^2 < 0.1$ within 500 kb. For each threshold, the PRS for each participant i was calculated as the weighted sum of risk-allele dosages: $PRS_i = \sum \beta_j G_{ij}$, where β_j denotes the log odds ratio from the meta-analysis, and was

standardized before analysis. For subsequent analyses, we selected the PRS derived from genome-wide significant loci ($P < 5\times10^{-8}$; 16 independent variants), which showed the strongest and most consistent associations with GC risk.

Associations between the PRS and incident GC were estimated using weighted Cox proportional hazards models, adjusted for age, sex, and top 10 principal components (PCs) of ancestry to account for population structure. The proportional hazards assumption was not violated in the overall model or within *H. pylori*-negative and -positive strata (all $P > 0.05$ based on Schoenfeld residual tests). In addition, no significant interaction between PRS and follow-up time was observed in any analysis (all $P > 0.05$). Person-years were calculated from baseline to GC diagnosis, death, loss to follow-up, or December 31, 2022, whichever came first. PRS was analyzed per SD increase and in categories (low: bottom 20%, medium: 20-80%, high: top 20%), and all models were repeated within *H. pylori*-negative and positive strata.

Demographic and environmental factors, environmental risk score, and genetic risk with GC risk

We next assessed demographic and environmental factors in relation to GC risk using the same weighted Cox framework and covariate adjustment. Demographic variables included age (< 45 or ≥ 45 years), sex, education level (middle school or above *vs.* primary school or below), family history of GC (yes *vs.* no), and household size (≤ 3, 4, or ≥ 5 members). Lifestyle and environmental exposures encompassed smoking (≤ 20 pack-years, > 20 pack-years), alcohol consumption (≤ 30 g ethanol/day, > 30 g ethanol/day), and overweight status [body mass index (BMI) < 24 kg/m², ≥ 24 kg/m²] . Dietary exposures were assessed at baseline using a dietary questionnaire, from which average intake levels (g/day) were derived for each participant[2]. To

capture overall dietary patterns relevant to gastric carcinogenesis, key dietary variables were selected a priori based on existing epidemiological evidence. Because several dietary variables did not have universally accepted risk thresholds, they were categorized using a uniform data-driven approach based on the median value of each variable in the study population. This approach is consistent with widely used dietary scoring methods, including the original Mediterranean diet score, in which population-specific median cut-offs are used to define dietary components[9]. Specifically, lower vegetable intake (< 427.3 g/day), lower fruit intake (< 171.0 g/day), lower soybean intake (< 128.2 g/day), higher meat intake (> 170.9 g/day), higher fried food intake (> 171.0 g/day), higher pickled food intake (> 42.7 g/day), and high-salt food preference were defined as unfavorable dietary components.

An environmental risk score (ERS) was constructed by combining 10 lifestyle and dietary factors, including smoking, alcohol consumption, BMI, vegetables, fruits, soybean products, meat, fried foods, pickled foods, and high-salt foods. Each component was coded as 1 for the unfavorable category and 0 otherwise. To account for differences in effect sizes across components, weights were derived from regression coefficients estimated from a multivariable Cox proportional hazards model including all ERS components simultaneously, with adjustment for age and sex. The weighted ERS for each participant was calculated as: $ERS = \sum_{i=1}^{10} \beta_i X_i$, where X_i denotes the binary indicator for the i-th unfavorable component and β_i denotes the corresponding regression coefficient. The weighted ERS was subsequently categorized into low- and high-risk groups according to its distribution in the study population, with the highest 20% defined as the high-risk group. The association between the ERS and GC risk was evaluated by modeling the score both as a continuous variable (standardized to z-scores) and as a categorical variable (low

vs. high, defined by the highest 20% of the distribution). In sensitivity analyses, we additionally reconstructed the ERS by modeling the corresponding environmental variables as continuous measures rather than binary components. The overall pattern of association remained materially unchanged (data not shown).

Joint and stratified analyses were performed to assess the combined and interactive effects of PRS and ERS on GC risk. Interaction was tested using likelihood ratio tests. Associations of ERS with GC risk were further evaluated across PRS categories and *H. pylori* infection strata. Among *H. pylori*-positive individuals, post-intervention infection status (successful eradication *vs.* non-eradicated) was additionally considered. Follow-up time was calculated from the 45-day post-treatment assessment at which eradication status was determined, and person-years were accumulated accordingly. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

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Table S1. Clinicopathological characteristics of gastric cancer cases by *H. pylori* infection status

Categories[a]	Negative	Positive	*P*[b]
N	102	519	
Diagnosed age, year, mean±SD	58.16 ± 5.92	57.15 ± 6.57	0.13
Site, *n* (%)			
Cardia (C16.0)	13 (12.7)	41 (7.9)	0.10
Non-cardia	63 (61.8)	373 (71.9)	
Unspecified (C16.9)	26 (25.5)	105 (20.2)	
Histopathological types, *n* (%)			
Adenocarcinoma	88 (86.3)	479 (92.3)	0.10
Squamous	2 (2.0)	1 (0.2)	
Adenosquamous	0 (0.0)	1 (0.2)	
Carcinoid	3 (2.9)	10 (1.9)	
Unspecified	9 (8.8)	28 (5.4)	
Lauren classification, *n* (%)			
Diffuse-type	4 (3.9)	57 (11.0)	0.73
Intestinal-type	10 (9.8)	89 (17.1)	
Mixed-type	8 (7.8)	90 (17.3)	
Unknown	80 (78.5)	283 (54.6)	
Histological differentiation, *n* (%)			
Well/moderately differentiated	22 (21.6)	86 (16.6)	0.015
Poorly differentiated	15 (14.7)	148 (28.5)	
Unknown	65 (63.7)	285 (54.9)	
T-stage, *n* (%)			
Tx	0 (0.0)	6 (1.2)	0.029
T0	18 (17.6)	60 (11.6)	
Tis	1 (1.1)	0 (0.0)	
T1	10 (9.8)	50 (9.6)	
T2	4 (3.9)	19 (3.7)	
T3	8 (7.8)	48 (9.2)	
T4	9 (8.8)	103 (19.8)	
Unspecified	52 (51.0)	233 (44.9)	
N-stage, *n* (%)			
Nx	0 (0.0)	8 (1.5)	0.54
N0	7 (6.9)	43 (8.3)	
N1	6 (5.9)	57 (11.0)	
N2	6 (5.9)	36 (6.9)	
N3	4 (3.9)	58 (11.2)	
Unspecified	79 (77.4)	317 (61.1)	
M-stage, *n* (%)			
Mx	2 (2.0)	35 (6.7)	0.23
M0	12 (11.8)	97 (18.7)	
M1	3 (2.9)	72 (13.9)	

Unspecified	85 (83.3)	315 (60.7)	
cTNM-stage, *n* (%)			
I	3 (2.9)	24 (4.6)	0.11
IIA	3 (2.9)	24 (4.6)	
IIB	3 (2.9)	11 (2.1)	
III	8 (7.8)	60 (11.6)	
IVA	1 (1.0)	36 (6.9)	
IVB	3 (2.9)	72 (13.9)	
Unspecified	81 (79.6)	292 (56.3)	
pTNM-stage, *n* (%)			
IA	3 (2.9)	21 (4.0)	0.025
IB	0 (0.0)	10 (1.9)	
IIA	6 (5.9)	15 (2.9)	
IIB	1 (1.0)	24 (4.6)	
IIIA	4 (3.9)	29 (5.6)	
IIIB	4 (3.9)	34 (6.6)	
IIIC	0 (0.0)	21 (4.0)	
IV	3 (2.9)	72 (13.9)	
Unspecified	81 (79.5)	293 (56.5)	

[a] TNM Stages were classified adhering to the Union for International Cancer Control (UICC) and American Joint committee on Cancer (AJCC) gastric cancer staging system (8th edition). Cases included those of the cardia, non-cardia, and unspecified sites.
[b] *P* values represent pairwise comparisons between *H. pylori* infection and never-infected groups. Welch's *t*-test for continuous variables and Pearson's χ^2 (or Fisher's exact if expected < 5) for categorical variables were applied. Statistical comparisons were performed using only cases with available data.

Table S2. Independent variants identified from meta-analysis of genome-wide association studies

Basic information			Meta-analysis[b]				Stratified by *H. pylori* infection status[c]						
RSID	CHR:POS[a]	NEA/EA	EAF	beta	se	*P*	EAF	*H. pylori* positive		*H. pylori* negative		*P*-het	FDR
								HR (95% CI)	*P*	HR (95% CI)	*P*		
rs150206290	1:18755544	T/C	0.983	-0.27	0.07	4.25E-05	0.954	1.25 (0.66-2.33)	0.49	0.32 (0.08-1.30)	0.11	0.083	0.41
rs78078728	1:103580618	T/C	0.957	0.25	0.06	3.63E-06	0.959	1.90 (0.85-4.26)	0.12	2.57 (0.20-32.55)	0.47	0.82	0.94
rs12144914	1:151789647	T/G	0.51	-0.071	0.02	6.25E-06	0.47	0.79 (0.69-0.91)	0.0011	0.87 (0.64-1.17)	0.34	0.61	0.89
rs139822562	1:155102577	T/G	0.026	-0.31	0.06	3.29E-07	0.073	0.41 (0.20-0.85)	0.015	0.70 (0.10-5.03)	0.72	0.62	0.89
rs4971092	**1:155143946**	**T/C**	**0.018**	**0.34**	**0.06**	**3.44E-09**	0.013	**2.66 (1.62-4.35)**	**1.05×10^{-4}**	**0.46 (0.06-3.29)**	**0.44**	**0.090**	**0.41**
rs7366775	**1:155168930**	**A/G**	**0.19**	**-0.34**	**0.01**	**1.26E-262**	0.26	0.72 (0.61-0.86)	2.56×10^{-4}	0.60 (0.38-0.93)	0.023	0.43	0.85
rs35154152	1:155172725	T/C	0.017	-0.32	0.07	1.67E-06	0.022	0.80 (0.46-1.39)	0.43	1.62 (0.72-3.63)	0.25	0.16	0.53
rs145906888	1:155221353	C/G	0.008	-0.43	0.1	3.10E-05	0.018	1.17 (0.70-1.94)	0.56	1.93 (0.48-7.86)	0.36	0.51	0.85
rs80142782	**1:155485027**	**T/C**	**0.057**	**-0.36**	**0.04**	**2.85E-17**	0.13	0.63 (0.44-0.92)	0.017	0.35 (0.12-1.04)	0.059	0.31	0.75
rs74188952	**1:155797665**	**T/C**	**0.70**	**0.15**	**0.02**	**1.47E-17**	0.64	1.24 (1.07-1.45)	0.0051	1.18 (0.85-1.63)	0.33	0.76	0.92
rs138554234	**1:156089034**	**A/G**	**0.947**	**0.42**	**0.05**	**1.02E-17**	0.907	1.46 (0.95-2.24)	0.083	1.53 (0.56-4.16)	0.41	0.93	0.98
rs3021335	1:172625116	A/G	0.70	-0.34	0.08	2.42E-05	0.73	0.89 (0.77-1.02)	0.093	1.18 (0.85-1.65)	0.33	0.12	0.46
rs6657194	1:222074508	C/G	0.60	0.069	0.02	1.48E-05	0.66	**0.80 (0.71-0.90)**	**2.58×10^{-4}**	**1.09 (0.82-1.46)**	**0.56**	**0.052**	**0.41**
rs77658485	2:160722403	T/C	0.968	-0.20	0.04	4.46E-06	0.991	0.82 (0.45-1.49)	0.52	0.52 (0.19-1.41)	0.2	0.44	0.85
rs10203669	2:225626306	T/C	0.68	0.19	0.05	2.90E-05	0.64	0.77 (0.68-0.89)	2.09×10^{-4}	0.90 (0.68-1.19)	0.47	0.34	0.76
rs2177686	3:65510177	A/T	0.32	-0.071	0.02	2.53E-05	0.32	1.18 (1.04-1.35)	0.011	1.33 (1.00-1.77)	0.051	0.47	0.85
rs1046844	3:66428282	T/C	0.945	-0.15	0.04	3.60E-05	0.95	1.21 (0.91-1.61)	0.2	0.85 (0.42-1.73)	0.66	0.37	0.79
rs573149449	3:75091578	T/C	0.990	-1.48	0.35	2.09E-05	0.984	1.16 (0.43-3.11)	0.77	-	-	-	-
rs2581622	3:142631077	C/G	0.49	-0.066	0.02	2.63E-05	0.55	1.01 (0.89-1.15)	0.89	0.94 (0.71-1.25)	0.67	0.66	0.91
rs11927141	**3:169039385**	**A/G**	**0.16**	**0.098**	**0.02**	**3.20E-08**	0.15	1.05 (0.87-1.26)	0.59	0.69 (0.44-1.09)	0.11	0.092	0.41
rs9993352	4:25465249	T/C	0.967	-0.49	0.12	3.51E-05	0.98	1.70 (1.18-2.45)	0.0042	4.51 (1.15-17.78)	0.031	0.18	0.55
rs12510876	4:82147877	A/G	0.82	0.089	0.02	2.23E-05	0.80	0.90 (0.75-1.07)	0.23	1.48 (0.91-2.40)	0.11	0.058	0.41
rs28676641	4:113176270	T/C	0.60	-0.077	0.02	1.27E-06	0.60	0.69 (0.60-0.79)	6.62×10^{-8}	0.78 (0.57-1.06)	0.11	0.47	0.85
rs34439547	4:131589398	T/C	0.956	0.16	0.04	9.67E-06	0.961	1.48 (1.03-2.13)	0.034	1.03 (0.52-2.05)	0.93	0.36	0.79
rs9784515	4:189064582	A/G	0.978	0.28	0.06	2.34E-06	0.955	1.17 (0.79-1.73)	0.44	1.06 (0.49-2.28)	0.89	0.82	0.94
rs113881808	5:26404541	T/C	0.977	-0.24	0.06	4.74E-05	0.978	0.81 (0.48-1.36)	0.42	0.42 (0.13-1.34)	0.15	0.32	0.75
rs187992361	5:40362657	T/C	0.958	-0.18	0.04	5.04E-06	0.967	0.84 (0.57-1.24)	0.37	0.72 (0.31-1.65)	0.43	0.74	0.92
rs10512738	5:40428801	A/G	0.13	0.096	0.02	3.85E-05	0.16	0.77 (0.62-0.97)	0.025	0.72 (0.40-1.32)	0.29	0.85	0.95
rs10041894	5:40493234	A/G	0.63	0.074	0.02	5.87E-06	0.68	0.94 (0.82-1.08)	0.39	1.10 (0.83-1.47)	0.5	0.33	0.76
rs78311621	5:40620290	A/G	0.063	0.15	0.03	2.56E-06	0.089	0.86 (0.64-1.16)	0.33	0.76 (0.37-1.55)	0.45	0.75	0.92
rs13359359	5:40636764	T/C	0.90	-0.14	0.03	1.72E-07	0.929	0.75 (0.60-0.93)	0.0099	0.90 (0.57-1.44)	0.66	0.48	0.85
rs10074991	**5:40790551**	**A/G**	**0.45**	**0.23**	**0.01**	**1.10E-163**	0.55	**1.19 (1.05-1.34)**	**0.0056**	**1.82 (1.37-2.41)**	**3.09×10^{-4}**	**0.0062**	**0.13**
rs7725655	5:40857314	T/C	0.25	-0.072	0.02	4.28E-05	0.20	1.05 (0.90-1.24)	0.54	0.99 (0.65-1.49)	0.96	0.78	0.93
rs188932	5:40874422	T/C	0.30	0.090	0.02	1.65E-07	0.38	1.01 (0.88-1.15)	0.92	1.09 (0.79-1.50)	0.59	0.64	0.90
rs2675982	**5:40960278**	**T/C**	**0.908**	**-0.13**	**0.02**	**9.83E-10**	0.937	0.85 (0.69-1.06)	0.15	1.06 (0.63-1.79)	0.82	0.45	0.85
rs117389282	5:41241333	T/G	0.966	-0.20	0.04	9.28E-06	0.970	**0.84 (0.60-1.17)**	**0.3**	**0.42 (0.21-0.84)**	**0.014**	**0.082**	**0.41**
rs28533840	5:72907606	T/C	0.20	-0.085	0.02	6.62E-06	0.16	0.92 (0.76-1.11)	0.36	0.67 (0.43-1.04)	0.076	0.20	0.59
rs6871548	5:73076024	T/C	0.71	0.070	0.02	4.95E-05	0.68	1.13 (1.00-1.28)	0.056	1.15 (0.83-1.60)	0.39	0.91	0.97
rs145046470	5:155112367	T/C	0.987	-1.24	0.29	2.07E-05	0.980	1.07 (0.73-1.57)	0.73	0.79 (0.32-1.94)	0.6	0.54	0.87
rs6879467	5:169093410	A/G	0.56	-0.051	0.01	6.33E-08	0.52	1.04 (0.92-1.18)	0.53	0.80 (0.60-1.07)	0.14	0.11	0.45
rs76454322	6:4878776	A/G	0.057	0.39	0.1	4.76E-05	0.059	0.68 (0.51-0.92)	0.013	0.53 (0.22-1.27)	0.15	0.58	0.89
rs9358356	**6:20667382**	**T/C**	**0.43**	**-0.087**	**0.02**	**3.45E-08**	0.40	1.12 (0.99-1.27)	0.079	1.01 (0.77-1.34)	0.93	0.52	0.85
rs9381024	**6:40984262**	**T/G**	**0.75**	**-0.094**	**0.01**	**1.31E-10**	0.73	1.04 (0.90-1.20)	0.59	0.93 (0.67-1.27)	0.63	0.51	0.85
rs9321249	6:131030234	C/G	0.69	0.080	0.02	3.54E-06	0.65	1.05 (0.92-1.20)	0.46	0.89 (0.67-1.19)	0.43	0.31	0.75
rs117831482	7:31087602	T/C	0.949	0.17	0.04	4.05E-05	0.936	0.82 (0.64-1.06)	0.13	0.69 (0.38-1.23)	0.2	0.58	0.89
rs138577550	7:122275322	T/C	0.957	-0.16	0.04	2.54E-05	0.965	**1.20 (0.73-1.97)**	**0.48**	**0.22 (0.11-0.44)**	**1.73×10^{-5}**	**9.74×10^{-5}**	**0.0050**
rs10954104	7:125765022	A/G	0.28	-0.072	0.02	4.79E-05	0.26	1.04 (0.90-1.20)	0.62	1.11 (0.80-1.56)	0.52	0.70	0.92
rs11764822	7:138590630	T/C	0.076	-0.14	0.03	2.68E-05	0.098	1.18 (0.95-1.46)	0.13	1.10 (0.69-1.77)	0.69	0.80	0.94
rs73491224	7:153984326	A/G	0.034	0.49	0.12	4.88E-05	0.028	1.30 (0.89-1.88)	0.17	0.39 (0.12-1.23)	0.11	0.052	0.41
rs149933650	8:107812787	A/C	0.017	0.29	0.06	6.89E-06	0.013	0.19 (0.03-1.38)	0.1	-	-	-	-
rs78416774	8:143610455	A/G	0.950	-0.16	0.04	2.73E-05	0.956	0.80 (0.58-1.11)	0.18	0.76 (0.35-1.67)	0.5	0.91	0.97

rs28728212	**8:143703571**	**T/C**	**0.76**	**-0.14**	**0.02**	**1.46E-13**	0.82	0.93 (0.78-1.11)	0.41	0.72 (0.52-1.00)	0.047	0.17	0.55
rs4736361	**8:143741375**	**A/G**	**0.74**	**0.15**	**0.02**	**1.94E-15**	0.64	1.03 (0.90-1.18)	0.69	1.12 (0.83-1.52)	0.46	0.61	0.89
rs2976397	**8:143764613**	**T/G**	**0.61**	**-0.24**	**0.02**	**2.91E-51**	0.77	1.03 (0.87-1.21)	0.75	0.72 (0.51-1.02)	0.066	0.072	0.41
rs75030135	8:143835206	C/G	0.040	0.16	0.04	1.05E-05	0.018	1.71 (0.81-3.63)	0.16	0.37 (0.05-2.66)	0.32	0.15	0.52
rs3808491	8:143869071	T/C	0.76	-0.091	0.02	5.51E-07	0.79	0.83 (0.70-0.98)	0.03	0.81 (0.57-1.15)	0.23	0.91	0.97
rs7841267	**8:143881683**	**A/C**	**0.84**	**0.13**	**0.02**	**1.77E-08**	0.84	0.88 (0.75-1.03)	0.11	1.26 (0.86-1.84)	0.23	0.085	0.41
rs150732720	9:85020619	T/G	0.031	0.83	0.19	1.64E-05	0.037	**0.75 (0.40-1.40)**	**0.37**	**4.35 (1.72-11.01)**	**0.002 0**	**0.002 1**	**0.054**
rs148857870	9:108206091	T/G	0.033	0.63	0.14	8.85E-06	0.043	**1.83 (1.04-3.24)**	**0.038**	**12.75 (4.61-35.26)**	**9.35×10^{-7}**	**0.001 1**	**0.038**
rs7849280	**9:136126636**	**A/G**	**0.23**	**0.11**	**0.02**	**3.54E-09**	0.18	1.35 (1.16-1.58)	9.35×10^{-5}	0.88 (0.59-1.32)	0.55	0.048	0.41
rs8176747	9:136131315	C/G	0.19	-0.10	0.02	5.33E-07	0.19	0.84 (0.73-0.97)	0.019	1.03 (0.75-1.40)	0.87	0.25	0.68
rs11592999	10:10833307	A/G	0.015	1.05	0.22	2.10E-06	0.009	0.83 (0.34-2.01)	0.68	-	-	-	-
rs2475206	10:37802532	A/G	0.53	0.052	0.01	3.65E-05	0.54	0.91 (0.80-1.03)	0.12	0.70 (0.54-0.91)	0.008 0	0.083	0.41
rs140259923	10:55305380	A/G	0.024	1.01	0.24	2.74E-05	0.034	1.02 (0.66-1.56)	0.94	0.85 (0.12-6.27)	0.88	0.87	0.95
rs10509670	**10:96067947**	**A/G**	**0.24**	**0.20**	**0.01**	**6.70E-116**	0.24	1.20 (1.04-1.38)	0.014	1.53 (1.10-2.12)	0.011	0.18	0.55
rs11591693	10:96141697	A/G	0.30	-0.11	0.02	4.11E-07	0.32	1.01 (0.88-1.16)	0.91	1.09 (0.79-1.50)	0.60	0.67	0.91
rs2915186	11:34851183	T/C	0.21	0.085	0.02	4.89E-06	0.18	1.05 (0.88-1.24)	0.6	0.72 (0.51-1.02)	0.067	0.061	0.41
rs2074223	11:60774578	C/G	0.73	0.075	0.02	3.70E-05	0.75	0.92 (0.80-1.05)	0.23	1.02 (0.76-1.37)	0.88	0.52	0.85
rs56371957	11:86108212	A/G	0.21	0.080	0.02	4.44E-05	0.26	**0.98 (0.84-1.13)**	**0.75**	**2.14 (1.55-2.95)**	**3.46×10^{-6}**	**1.36×10^{-5}**	**0.001 4**
rs2125363	11:86167202	C/G	0.76	0.059	0.01	5.25E-08	0.76	1.01 (0.87-1.18)	0.85	1.36 (0.96-1.94)	0.084	0.13	0.48
rs11540721	11:111753191	A/C	0.071	0.13	0.03	3.46E-05	0.092	1.24 (0.98-1.56)	0.075	0.91 (0.51-1.59)	0.73	0.32	0.75
rs143193174	11:113510777	A/G	0.938	-0.64	0.16	4.77E-05	0.976	1.15 (0.89-1.49)	0.29	0.91 (0.48-1.72)	0.77	0.5	0.85
rs2156850	11:118030186	A/G	0.23	-0.21	0.05	4.18E-05	0.26	0.94 (0.81-1.08)	0.38	1.00 (0.69-1.45)	0.99	0.76	0.92
rs77514135	12:27123470	A/G	0.966	0.21	0.05	1.42E-05	0.972	1.27 (0.90-1.79)	0.17	1.62 (0.68-3.86)	0.28	0.61	0.89
rs12228580	12:61625410	A/T	0.048	-0.19	0.04	1.95E-06	0.049	1.56 (1.23-1.99)	2.65×10^{-4}	0.93 (0.53-1.65)	0.81	0.1	0.43
rs12422798	12:80739019	A/T	0.19	0.24	0.05	1.09E-05	0.20	0.93 (0.79-1.11)	0.43	0.75 (0.51-1.11)	0.15	0.32	0.75
rs111463574	12:95399358	T/C	0.80	-0.081	0.02	1.88E-05	0.85	0.85 (0.72-0.99)	0.042	0.83 (0.58-1.19)	0.32	0.94	0.98
rs12580792	12:130630603	A/G	0.80	-0.079	0.02	4.24E-05	0.80	1.06 (0.89-1.26)	0.51	1.13 (0.75-1.70)	0.57	0.79	0.94
rs28520330	12:132890880	A/G	0.096	0.30	0.07	3.62E-05	0.10	1.04 (0.83-1.29)	0.75	1.25 (0.78-2.00)	0.35	0.47	0.85
rs9533962	13:45334194	T/C	0.42	-0.067	0.02	2.91E-05	0.46	1.10 (0.97-1.24)	0.15	1.16 (0.89-1.50)	0.27	0.72	0.92
rs80108660	14:20674678	A/C	0.978	-0.22	0.05	4.88E-05	0.985	0.86 (0.56-1.32)	0.49	0.97 (0.26-3.66)	0.97	0.86	0.95
rs2277484	14:24629744	A/G	0.84	0.089	0.02	2.28E-05	0.86	0.91 (0.77-1.08)	0.29	0.83 (0.60-1.16)	0.29	0.65	0.90
rs142456862	14:36119514	T/C	0.970	-0.54	0.13	4.97E-05	0.946	0.77 (0.47-1.25)	0.29	3.83 (0.53-27.50)	0.18	0.12	0.46
rs10147214	14:72872021	A/T	0.017	-0.35	0.08	3.45E-06	0.022	0.59 (0.19-1.84)	0.36	0.71 (0.18-2.89)	0.63	0.84	0.95
rs10139287	14:91896534	A/C	0.38	0.073	0.02	4.40E-06	0.42	0.95 (0.83-1.09)	0.47	0.72 (0.52-1.01)	0.056	0.14	0.50
rs11639039	15:61770523	T/C	0.76	0.087	0.02	4.84E-06	0.73	1.16 (1.00-1.33)	0.049	1.27 (0.91-1.77)	0.16	0.62	0.89
rs311915	15:69361169	A/G	0.035	-0.15	0.04	4.92E-05	0.027	0.94 (0.65-1.36)	0.75	1.18 (0.52-2.71)	0.69	0.62	0.89
rs117709414	15:86817415	A/G	0.019	-0.25	0.06	3.37E-05	0.023	**1.14 (0.68-1.90)**	**0.62**	**3.62 (1.75-7.50)**	**5.16×10^{-4}**	**0.011**	**0.19**
rs16977781	15:87081216	A/G	0.84	0.090	0.02	3.86E-05	0.84	0.80 (0.68-0.95)	0.0093	0.75 (0.51-1.09)	0.13	0.72	0.92
rs1110549	16:69201758	A/T	0.015	-0.36	0.07	7.51E-07	0.012	**18.57 (7.58-45.48)**	**1.63×10^{-10}**	**2.96 (0.72-12.12)**	**0.13**	**0.030**	**0.39**
rs141766945	17:13599004	T/C	0.917	0.12	0.03	4.90E-05	0.912	**1.11 (0.86-1.43)**	**0.44**	**0.57 (0.33-0.98)**	**0.040**	**0.029**	**0.39**
rs17138478	17:36073320	A/C	0.77	0.10	0.02	1.16E-07	0.75	1.02 (0.88-1.18)	0.79	0.95 (0.68-1.33)	0.77	0.71	0.92
rs61194361	18:59250128	A/G	0.032	0.19	0.04	2.37E-05	0.041	1.15 (0.79-1.67)	0.47	0.44 (0.15-1.26)	0.13	0.092	0.41
rs5025392	18:70944258	A/C	0.957	-0.48	0.11	1.46E-05	0.962	1.15 (0.80-1.66)	0.45	2.01 (0.91-4.46)	0.086	0.21	0.60
rs11670654	19:20494900	A/C	0.53	0.067	0.02	3.01E-05	0.56	0.97 (0.86-1.10)	0.64	1.09 (0.83-1.43)	0.53	0.45	0.85
rs75471356	19:32770962	A/G	0.74	0.079	0.02	8.25E-06	0.76	0.87 (0.74-1.01)	0.07	1.09 (0.74-1.60)	0.67	0.29	0.75
rs71333760	20:29644222	A/C	0.25	0.085	0.02	4.71E-05	0.28	0.94 (0.82-1.09)	0.42	0.85 (0.63-1.14)	0.28	0.52	0.85
rs6088161	20:30007548	A/G	0.28	0.077	0.02	8.92E-06	0.25	0.90 (0.78-1.04)	0.16	0.89 (0.64-1.24)	0.49	0.95	0.98
rs6101739	20:38492803	A/G	0.41	-0.065	0.02	3.77E-05	0.35	0.86 (0.76-0.97)	0.012	1.04 (0.76-1.41)	0.82	0.25	0.68
rs6066825	20:47340117	A/G	0.30	-0.073	0.02	1.48E-05	0.29	0.91 (0.80-1.05)	0.2	0.87 (0.63-1.19)	0.37	0.76	0.92
rs146808747	22:38226158	T/C	0.032	0.52	0.13	3.84E-05	0.026	1.00 (0.47-2.12)	0.99	2.08 (0.29-14.98)	0.47	0.5	0.85
rs5995654	22:39405511	A/G	0.61	0.045	0.01	3.26E-06	0.67	0.91 (0.80-1.03)	0.13	0.64 (0.46-0.87)	0.005	0.041	0.41
rs7284152	22:49532171	T/C	0.982	-0.30	0.07	4.62E-05	0.968	**1.35 (0.93-1.96)**	**0.11**	**0.62 (0.31-1.23)**	**0.17**	**0.051**	**0.41**

[a] Genomic coordinates (CHR:POS) correspond to the NCBI human reference genome build 37 (GRCh37). The table summarizes the 103 linkage-disequilibrium-independent lead variants ($r^2 < 0.1$ within 500kb) that achieved suggestive

significance ($P < 5\times10^{-5}$) in the overall meta-analysis.
[b] Meta-analytic effect sizes (beta), standard errors (se), and *P* values were derived from fixed-effects inverse-variance-weighted meta-analysis using METAL. with effect allele frequencies computed from the combined analysis dataset. EAFs were calculated as weighted averages across contributing cohorts. Variants used for polygenic risk score construction ($P < 5\times10^{-8}$) were bolded.
[c] Stratified estimates were obtained from weighted Cox proportional hazards models fitted separately in the *H. pylori*-positive and *H. pylori*-negative subgroups, adjusting for age, sex, and the top 10 principal components. EAFs in MITS are also reported. Heterogeneity *P*-values (*P*-het) evaluate differences in effect estimates between infection strata. Variants showing nominal evidence of heterogeneity (*P*-het < 0.10 and $P < 0.05$ in either stratum) are highlighted in bold. *P* values for heterogeneity were further adjusted for multiple testing across 103 variants using the Benjamini-Hochberg FDR method.
Abbreviations: CHR, chromosome; CI, confidence interval; EA, effect allele; EAF, effect allele frequency; FDR, false discovery rate; HR, hazard ratio; NEA, non-effect allele; POS, physical position.

Table S3. Associations of polygenic risk scores with gastric cancer across SNV inclusion thresholds

Threshold of P[a]	Number of SNVs[b]			Association of PRS with gastric cancer [c]						
				Overall		*H. pylori* negative group		*H. pylori* positive group		
	Meta-analysis	Shared SNVs for MITS after QC	Independent SNVs	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	*P*-het[d]
5×10^{-4}	8587	6782	637	1.10 (1.02-1.19)	0.015	1.20 (0.99-1.46)	0.064	1.06 (0.97-1.15)	0.22	0.25
5×10^{-5}	3159	2456	103	1.11 (1.03-1.19)	0.0082	1.26 (1.03-1.56)	0.029	1.08 (0.99-1.17)	0.072	0.18
5×10^{-6}	1675	1240	40	1.30 (1.20-1.41)	7.54×10^{-11}	1.51 (1.20-1.89)	3.39×10^{-4}	1.26 (1.15-1.37)	1.96×10^{-7}	0.14
5×10^{-7}	1225	1003	23	1.33 (1.22-1.44)	1.59×10^{-11}	1.84 (1.43-2.39)	3.20×10^{-6}	1.26 (1.15-1.37)	3.06×10^{-7}	0.0062
5×10^{-8}	1016	885	16	1.32 (1.21-1.43)	6.49×10^{-11}	2.03 (1.52-2.71)	1.51×10^{-6}	1.23 (1.13-1.35)	1.76×10^{-6}	0.0012

[a] Polygenic risk scores (PRS) were constructed using SNVs selected at varying *P* value thresholds from GWAS meta-analysis.

[b] "Shared SNVs for MITS after QC" denotes variants present in the discovery cohort after quality control, and "Independent SNVs" were defined using PLINK clumping procedure.

[c] Associations of PRSs (per SD increase) and gastric cancer risk were evaluated overall and stratified by *H. pylori* infection status using weighted Cox proportional hazards models adjusted for age, sex, and 10 principal components.

[d] *P*-for-heterogeneity (*P*-het) values of HRs across strata were calculated using the Cochran's *Q* statistics.

Abbreviations: CI, confidence interval; *H. pylori*, *Helicobacter pylori*; HR, hazard ratio; PRS, polygenic risk score; SNV, single nucleotide variant.

Table S4 Joint associations of genetic and environmental risk with gastric cancer by *H. pylori* infection status

	***H. pylori* negative group**			***H. pylori* positive group**			*P*-het[d]
	No. of cases (person-years)	HR (95% CI)[b]	*P*	No. of cases (person-years)	HR (95% CI)[b]	*P*	
Low genetic risk							
Low ERS	9 (757)	Ref		65 (2175)	Ref		
High ERS	3 (190)	1.19 (0.17-8.11)	0.86	12 (481)	0.71 (0.31-1.63)	0.42	0.15
Medium genetic risk							
Low ERS	51 (1977)	1.98 (0.78-5.02)	0.15	246 (6135)	1.65 (1.10-2.47)	0.015	
High ERS	14 (624)	1.35 (0.41-4.42)	0.62	76 (1582)	2.82 (1.65-4.81)	1.40×10^{-4}	
High genetic risk							
Low ERS	22 (678)	4.76 (1.56-14.52)	0.0060	89 (2117)	1.71 (1.05-2.80)	0.031	
High ERS	3 (123)	6.09 (0.90-41.05)	0.064	31 (489)	4.12 (1.86-9.12)	4.73×10^{-4}	
P-int[c]	0.99			0.060			

[a] The environmental risk score (ERS) was constructed based on 10 lifestyle and dietary factors. Individuals in the top 20% of the distribution were classified as having high ERS, while the remainder were defined as low ERS.

[b] HRs were estimated using Cox proportional hazards models adjusted for age, sex, and 10 principal components.

[c] *P*-interaction values (*P*-int) between genetic risk group and ERS were calculated using likelihood ratio tests within each *H. pylori* stratum.

[d] *P*-heterogeneity values (*P*-het) comparing HRs between *H. pylori*-negative and -positive groups were calculated using Cochran's *Q* statistics.

Abbreviations: CI, confidence interval; ERS, environmental risk score; GC, gastric cancer; HR, hazard ratio; PRS, polygenic risk score.

Table S5. Associations of lifestyle and *H. pylori* eradication with GC risk across *H. pylori* infection strata and genetic risk groups

Categories	*H. pylori* negative group			*H. pylori* positive group			*P*-het[b]
	No. of cases (person-years)	HR (95% CI)[a]	*P*	No. of cases (person-years)	HR (95% CI)[a]	*P*	
Low/Medium genetic risk							
By ERS							
High	17 (813)	Ref		88 (2064)	Ref		
Low	60 (2735)	1.20 (0.68-2.11)	0.52	311 (8310)	0.74 (0.58-0.95)	0.016	0.12
By *H. pylori* eradication status							
Not eradicated	-	-	-	256 (6311)	Ref		
Successful eradication	-	-	-	143 (3934)	0.95 (0.77-1.17)	0.65	
High genetic risk							
By ERS							
High	3 (123)	Ref		31 (489)	Ref		
Low	22 (678)	0.50 (0.08-2.94)	0.44	89 (2117)	0.42 (0.28-0.65)	7.30×10^{-5}	0.86
By *H. pylori* eradication status							
Not eradicated	-	-	-	93 (1673)	Ref		-
Successful eradication	-	-	-	27 (900)	0.61 (0.39-0.95)	0.030	

[a] HRs were estimated using Cox proportional hazards models adjusted for age, sex and 10 principal components.
[b] *P*-heterogeneity values (*P*-het) of HRs across strata were calculated using the Cochran's *Q* statistics.
Abbreviations: CI, confidence interval; *H. pylori*, *Helicobacter pylori*; HR, hazard ratio; ERS, environmental risk score.

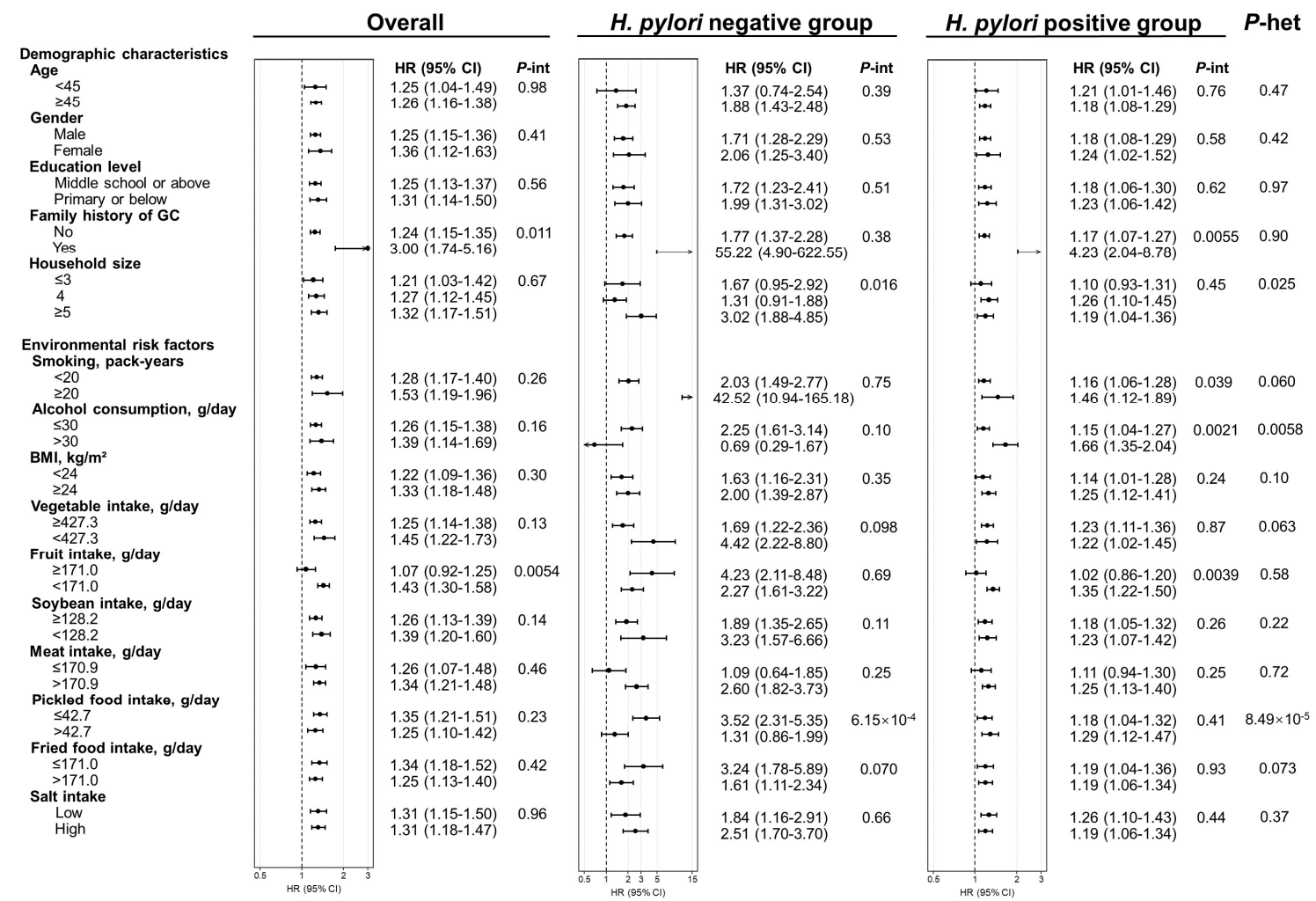
Overall
H. pylori negative group
H. pylori positive group
P-het
Demographic characteristics
Age
<45 1.25 (1.04-1.49) 0.98 1.37 (0.74-2.54) 0.39 1.21 (1.01-1.46) 0.76 0.47
≥45 1.26 (1.16-1.38) 1.88 (1.43-2.48) 1.18 (1.08-1.29)
Gender
Male 1.25 (1.15-1.36) 0.41 1.71 (1.28-2.29) 0.53 1.18 (1.08-1.29) 0.58 0.42
Female 1.36 (1.12-1.63) 2.06 (1.25-3.40) 1.24 (1.02-1.52)
Education level
Middle school or above 1.25 (1.13-1.37) 0.56 1.72 (1.23-2.41) 0.51 1.18 (1.06-1.30) 0.62 0.97
Primary or below 1.31 (1.14-1.50) 1.99 (1.31-3.02) 1.23 (1.06-1.42)
Family history of GC
No 1.24 (1.15-1.35) 0.011 1.77 (1.37-2.28) 0.38 1.17 (1.07-1.27) 0.0055 0.90
Yes 3.00 (1.74-5.16) 55.22 (4.90-622.55) 4.23 (2.04-8.78)
Household size
≤3 1.21 (1.03-1.42) 0.67 1.67 (0.95-2.92) 0.016 1.10 (0.93-1.31) 0.45 0.025
4 1.27 (1.12-1.45) 1.31 (0.91-1.88) 1.26 (1.10-1.45)
≥5 1.32 (1.17-1.51) 3.02 (1.88-4.85) 1.19 (1.04-1.36)
Environmental risk factors
Smoking, pack-years
<20 1.28 (1.17-1.40) 0.26 2.03 (1.49-2.77) 0.75 1.16 (1.06-1.28) 0.039 0.060
≥20 1.53 (1.19-1.96) 42.52 (10.94-165.18) 1.46 (1.12-1.89)
Alcohol consumption, g/day
≤30 1.26 (1.15-1.38) 0.16 2.25 (1.61-3.14) 0.10 1.15 (1.04-1.27) 0.0021 0.0058
>30 1.39 (1.14-1.69) 0.69 (0.29-1.67) 1.66 (1.35-2.04)
BMI, kg/m²
<24 1.22 (1.09-1.36) 0.30 1.63 (1.16-2.31) 0.35 1.14 (1.01-1.28) 0.24 0.10
≥24 1.33 (1.18-1.48) 2.00 (1.39-2.87) 1.25 (1.12-1.41)
Vegetable intake, g/day
≥427.3 1.25 (1.14-1.38) 0.13 1.69 (1.22-2.36) 0.098 1.23 (1.11-1.36) 0.87 0.063
<427.3 1.45 (1.22-1.73) 4.42 (2.22-8.80) 1.22 (1.02-1.45)
Fruit intake, g/day
≥171.0 1.07 (0.92-1.25) 0.0054 4.23 (2.11-8.48) 0.69 1.02 (0.86-1.20) 0.0039 0.58
<171.0 1.43 (1.30-1.58) 2.27 (1.61-3.22) 1.35 (1.22-1.50)
Soybean intake, g/day
≥128.2 1.26 (1.13-1.39) 0.14 1.89 (1.35-2.65) 0.11 1.18 (1.05-1.32) 0.26 0.22
<128.2 1.39 (1.20-1.60) 3.23 (1.57-6.66) 1.23 (1.07-1.42)
Meat intake, g/day
≤170.9 1.26 (1.07-1.48) 0.46 1.09 (0.64-1.85) 0.25 1.11 (0.94-1.30) 0.25 0.72
>170.9 1.34 (1.21-1.48) 2.60 (1.82-3.73) 1.25 (1.13-1.40)
Pickled food intake, g/day
≤42.7 1.35 (1.21-1.51) 0.23 3.52 (2.31-5.35) 6.15×10-4 1.18 (1.04-1.32) 0.41 8.49×10-5
>42.7 1.25 (1.10-1.42) 1.31 (0.86-1.99) 1.29 (1.12-1.47)
Fried food intake, g/day
≤171.0 1.34 (1.18-1.52) 0.42 3.24 (1.78-5.89) 0.070 1.19 (1.04-1.36) 0.93 0.073
>171.0 1.25 (1.13-1.40) 1.61 (1.11-2.34) 1.19 (1.06-1.34)
Salt intake
Low 1.31 (1.15-1.50) 0.96 1.84 (1.16-2.91) 0.66 1.26 (1.10-1.43) 0.44 0.37
High 1.31 (1.18-1.47) 2.51 (1.70-3.70) 1.19 (1.06-1.34)
0.5 1 2 3
HR (95% CI)
0.5 1 2 3 5 15
HR (95% CI)
0.5 1 2 3
HR (95% CI)

Figure S1. Polygenic risk score associations with gastric cancer across levels of demographic and environmental factors, stratified by *H. pylori* infection status. HRs per SD increase for association between polygenic risk score and gastric cancer risk were estimated using weighted Cox proportional hazards models with stratification by *H. pylori* infection status. *P* values for interaction between genetic risk and demographic or environmental risk factors were obtained using likelihood ratio tests comparing models. *P*-heterogeneity values of HRs across strata were calculated using the Cochran's *Q* statistics.
Abbreviations: BMI, body mass index; CI, confidence interval; GC, gastric cancer; *H. pylori*, *Helicobacter pylori*; HR, hazard ratio.