

eGastroenterology Global and regional burden of colorectal cancer potentially related to *Helicobacter pylori* exposure: a risk attribution modelling study

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ABSTRACT

Background Emerging epidemiological and mechanistic studies suggest that *Helicobacter pylori* (*H. pylori*) exposure may be associated with colorectal cancer (CRC); however, the findings remain controversial. We aim to quantify the CRC burden potentially related to *H. pylori* exposure, with the overarching objective to inform prioritisation and future evaluation of *H. pylori* control as a candidate adjunct to existing CRC prevention efforts in settings with high prevalence and limited resources.

Methods We estimated global and regional *H. pylori* exposure and its epidemiological association with CRC using data from systematic reviews and meta-analyses, stratified by region, diagnostic method and eradication status, among others. We derived CRC estimates from the Global Cancer Observatory (GLOBOCAN). To evaluate the related CRC burden, we calculated the estimated related proportion (ERP) with 95% uncertainty intervals (UIs) and absolute and rate-based burdens using Monte Carlo simulations. We further examined correlations between country-level ERPs, *H. pylori* prevalence and CRC incidence. Lastly, we used a pseudo-cohort approach to explore birth cohort-related patterns based on GLOBOCAN 2022.

Results Exposure to *H. pylori* was associated with a 1.59-fold increased risk of CRC (95% CI 1.36 to 1.87), consistent across most subgroups. In limited observational studies, *H. pylori* eradication was associated with a reduced risk of CRC, but only after 10 years of follow-up. Globally, under the pooled risk-attribution model based on estimates from 43 studies, an estimated 22.0% (95% UI 14.7% to 29.4%) of CRC cases were potentially related to *H. pylori* exposure; corresponding estimates were lower when restricted to population-based and cohort studies (n=14). Higher *H. pylori*-related burdens were observed in settings with lower CRC incidence and increased with rising *H. pylori* prevalence. Exploratory pseudo-cohort patterns suggested higher ERPs in later birth cohorts, while absolute case counts remained relatively stable.

Conclusion *H. pylori* exposure may meaningfully contribute to global CRC burden, with the extent of preventable burden dependent on the causal nature and other modifying variables related to *H. pylori* exposure (eg, timing, duration). This underscores the importance of well-designed randomised clinical trials and other prospective investigations evaluating the impact of *H. pylori* and its

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ *Helicobacter pylori* (*H. pylori*) is categorised as a type I (definitive) carcinogen given its established causal association with gastric cancer; however, the related burden of other cancers, including colorectal cancer (CRC), is incompletely investigated.
- ⇒ The relationship between *H. pylori* and CRC remains controversial, despite a growing body of supportive epidemiological and mechanistic evidence.
- ⇒ The global and regional CRC burden potentially related to *H. pylori* exposure remains poorly quantified, and its associations with countries' *H. pylori* exposure and CRC incidence, or birth cohort patterns remain insufficiently characterised.

WHAT THIS STUDY ADDS

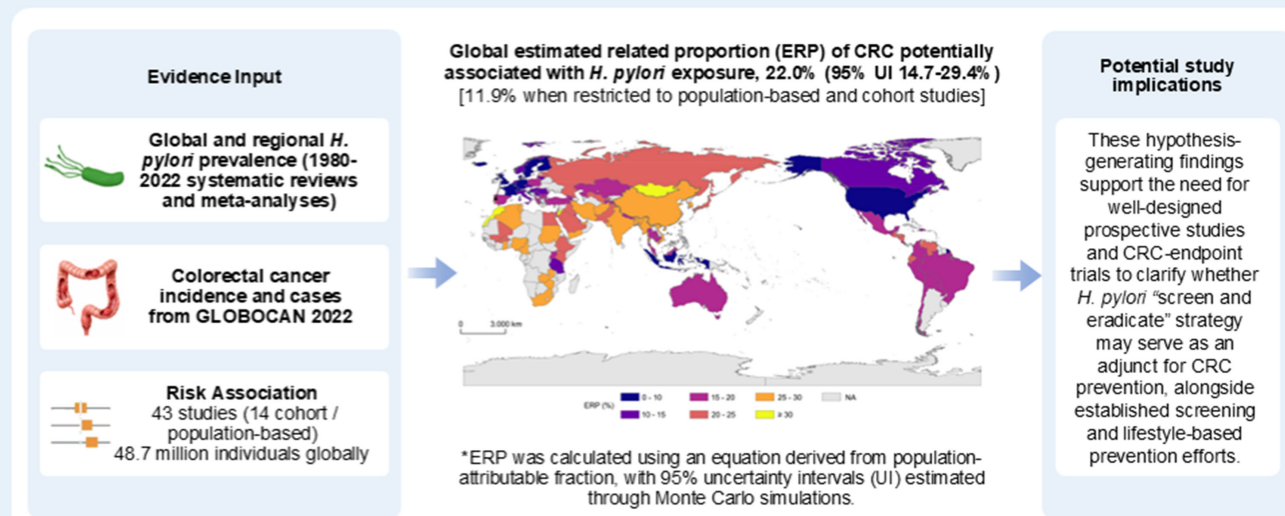
- ⇒ Globally, under the pooled risk-attribution model based on estimates from 43 studies, an estimated 22.0% (95% uncertainty interval (UI) 14.7–29.4%) of CRC cases were potentially related to *H. pylori* exposure.
- ⇒ Estimates were lower when analyses were restricted to population-based and cohort studies only (n=14 studies) (11.9%, 95% UI 0.7–22.8%), with the wider UI reflecting fewer studies with narrower evidence.
- ⇒ We also found regional variation, with the Western Pacific region carrying the highest burden. Across countries, higher *H. pylori*-related burdens were observed in settings with lower CRC incidence and burden increased non-linearly with rising *H. pylori* prevalence.
- ⇒ Exploratory pseudo-cohort patterns suggested a higher estimated related proportion among later-born cohorts, while absolute case counts remained relatively stable.

eradication on CRC risk, as well as potential modifying factors.

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related death

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Bacterial and intestinal images were created with Biorender.com.

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Visual abstract Bacterial and intestinal images were created with Biorender.com. The map is based on standard map no. GS (2016)1666 downloaded from the service website of standard maps, with no changes in the base map. The service website of standard maps: Map of the World (<http://bzdt.ch.mnr.gov.cn/>).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The findings of this study should be considered exploratory and motivational, as the true clinical implications hinge on future well-designed studies aiming to establish a causal association between *H. pylori* and CRC.
- ⇒ At a minimum, such studies should capture eradication status, have sufficient latency time (>10 years) and refine country-level estimates where data are sparse.
- ⇒ These findings are noteworthy in the context of the clear successes of population-level *H. pylori* screen-and-eradicate programmes for gastric cancer prevention and underscore the potential dual benefit of *H. pylori* eradication on CRC risk, particularly in high *H. pylori* prevalence and resource-constrained settings.

worldwide, representing a significant global health burden. In 2022, CRC affected approximately 1.9 million individuals and accounted for 903 859 deaths.¹ The aetiology of CRC is multifactorial and includes both non-modifiable (eg, genetics, age) and modifiable risk factors, such as those related to lifestyle and diet.^{2–4} According to the Global Burden of Disease study, in 2021, the population-attributable fractions (PAFs) of behavioural risks (eg, high alcohol use, obesity, low physical activity, smoking) and dietary risks (eg, diet high in red meat, processed meat) for CRC were estimated at 48.2% and 38.7%, respectively.⁵

Helicobacter pylori (*H. pylori*) is an established gastric carcinogen,⁶ with a reported PAF of 74.7–89.0%⁸ for gastric cancer. However, the causal relationship between *H. pylori* and CRC remains highly controversial. Accumulating evidence suggests that *H. pylori* exposure may be linked to colorectal carcinogenesis and aligns with several Bradford Hill considerations.^{9–11} Epidemiological consistency is demonstrated by multiple epidemiological studies from diverse global populations, which consistently report a 1.5–2-fold increased risk of CRC among infected individuals.^{12–15} The modest magnitude of the effect estimate does not exclude causality but increases susceptibility to residual confounding. A dose–response pattern is suggested in some studies, including higher CRC risk among carriers of virulence-factor–positive *H. pylori* strains (eg, cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA)) or those with premalignant lesions.^{13 16 17} From a biological plausibility and experimental perspective, Ralser *et al* demonstrated that *H. pylori* infection directly promotes CRC development by modulating intestinal and colonic immune responses in mice, resulting in significant alterations in the gut and colonic microbiota and epithelial homeostasis.¹⁸ Eradicating *H. pylori* infection prevented these tumour-promoting effects in mice, independent of antibiotic exposure alone. Third, treatment effect

is suggested by a recent nationwide cohort study among 812 736 US Veterans,¹⁹ where *H. pylori* eradication was associated with a reduced incidence of CRC and mortality compared with persistent infection.

To date, evidence for a clear exposure–response remains incomplete, and definitive evidence from randomised clinical trials (RCTs) with CRC as the primary endpoint is still lacking. Although limited in number, observational studies consistently suggest that the potential benefit of *H. pylori* eradication on CRC risk might require over 10 years of follow-up,^{19–21} which may be due to the long latency period of colorectal carcinogenesis. This latency hypothesis aligns with RCTs of *H. pylori* eradication and gastric cancer risk, where the protective benefits of *H. pylori* eradication become apparent after prolonged follow-up.^{22 23}

Our study aims to evaluate the putative burden of CRC that may be related to *H. pylori*, a modifiable and preventable risk factor. We applied a modified PAF risk modelling framework to estimate the global and regional burden of CRC potentially related to *H. pylori* exposure, fully acknowledging that causality is not definitively established. The overarching goal is to provide evidence to inform public health and research prioritisation, and to guide infection-targeted cancer prevention strategies at both global and regional levels that complement and extend beyond *H. pylori* eradication for gastric cancer prevention.

METHODS

The detailed flowchart of study inclusion is shown in figure 1.

H. pylori prevalence and CRC burden data

We collected and generated the baseline data for the model from the following sources. We obtained global, regional and national *H. pylori* prevalence data from our previously published systematic reviews and meta-analyses.²⁴ We further stratified *H. pylori* prevalence estimates by diagnostic methods, sex and WHO regions (Africa, the Americas, South-East Asia, Europe, Eastern Mediterranean and Western Pacific). Seropositivity may persist after spontaneous clearance or eradication and therefore can overestimate current or active infection in settings with rapidly declining prevalence or widespread eradication programmes. Accordingly, our prevalence inputs are interpreted as markers of *H. pylori* exposure, and we present diagnostic-modality-stratified estimates (serology vs non-serology) to provide complementary bounds for exposure-based versus active-infection-based interpretations. We obtained the latest data on global, regional and country-specific CRC estimates, including age-standardised incidence rates (ASIRs) and newly diagnosed CRC cases from Global Cancer Observatory (GLOBOCAN) 2022.¹

H. pylori exposure and CRC association

To assess the risk of CRC related to *H. pylori* exposure, we conducted an updated, comprehensive meta-analysis

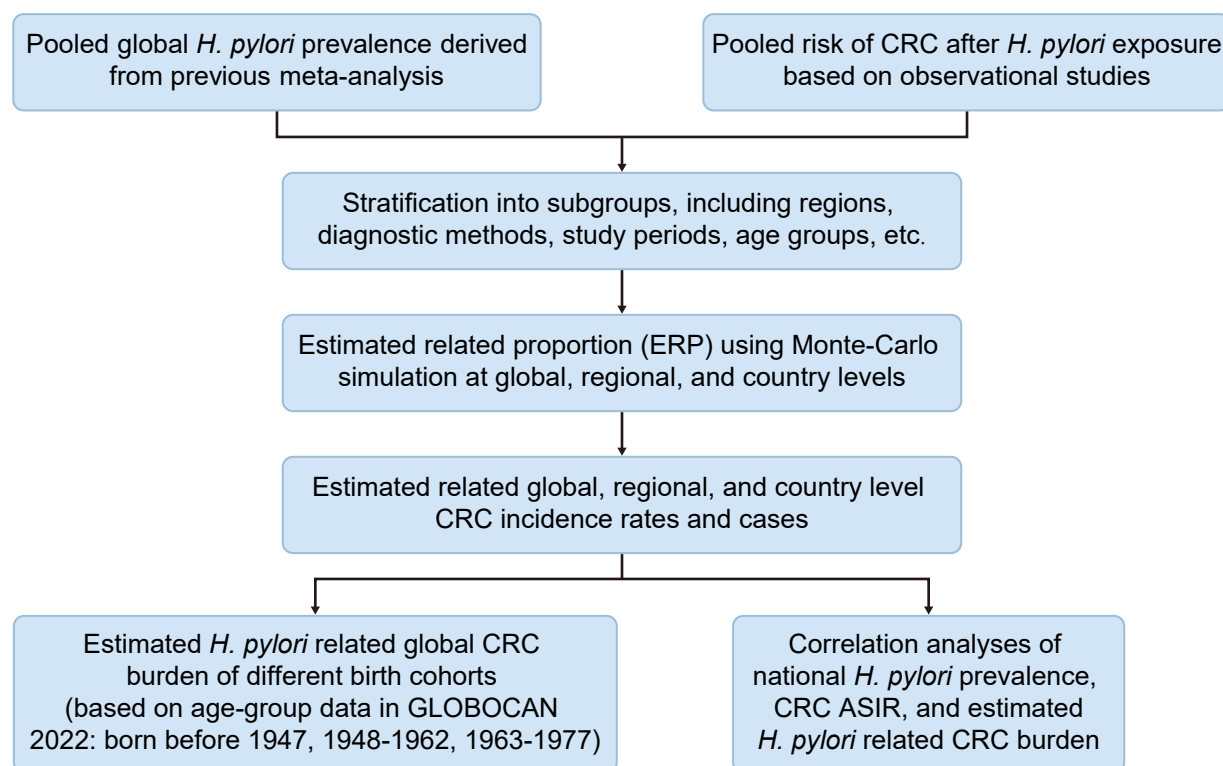


Figure 1 Workflow for burden estimation of *H. pylori* exposure-related CRC. ASIR, age-standardised incidence rate; CRC, colorectal cancer; GLOBOCAN, Global Cancer Observatory; *H. pylori*, *Helicobacter pylori*.

building on prior systematic reviews,^{25–29} with extension of the search to 31 July 2025. The detailed literature search strategy, inclusion and exclusion criteria, data extraction procedures and risk-of-bias assessment are presented in online supplemental table 1.

We conducted subgroup analyses to explore potential effect modifiers of the association between *H. pylori* exposure and CRC risk, given the heterogeneity across populations and study characteristics, and recognising that such factors have been rarely examined in previous studies of *H. pylori* and CRC risk. Subgroups were defined by: (1) study population setting (population-based or hospital-based); (2) age group stratification, with <60 vs ≥60 years as the predetermined cut-off since this was most commonly used in the included studies; (3) sex; (4) birth cohort (divided into participants born in 1930s and before, 1940s and 1950s, 1960s and 1970s, categorised based on available literature); (5) WHO regions; (6) diagnostic modality for *H. pylori* detection (non-serological modalities including urea breath test, stool antigen test, histology, rapid urease test and culture; serology; and mixed modalities when more than one diagnostic modality was used without stratified effect estimates by test type). We grouped ‘mixed’ with non-serology methods because these approaches typically include tests indicative of current or active infection; (7) risk of bias was assessed using the Newcastle-Ottawa Scale (NOS).³⁰ The original NOS was applied to cohort and case-control studies, while a modified version of the NOS was used for cross-sectional studies³¹; (8) study design (case-control study, cross-sectional study and cohort study); (9) tumour anatomical location (colon vs rectum); (10) presence of a nationwide CRC screening programme (yes vs no); (11) *H. pylori* eradication status (eradicated vs non-eradicated and subsequent follow-up time post eradication), where available; (12) presence of *H. pylori* virulence factors (primarily CagA, VacA and GroEL), where available. Effect measures were harmonised prior to pooling. Because the majority of included studies reported odds ratios (ORs), we used OR as the primary metric; when studies reported relative risks (RRs) or hazard ratios (HRs), we treated these as approximations of OR and pooled them on the log scale with ORs when necessary. We further assessed robustness by converting the pooled OR to RR using baseline risks (ASIR-based) for burden estimation.

Estimation of *H. pylori* exposure-related CRC burden

We used three measures to estimate the *H. pylori* exposure-associated CRC burden: (1) estimated related proportion (ERP); (2) corresponding CRC incidence rate; (3) estimated absolute case numbers. To calculate ERP, we used the standard Levin formula,³² modified from the PAF framework, as recommended in the GATHER (Guidelines for Accurate and Transparent Health Estimates Reporting) statement.^{33–34} We favoured using the term ERP rather than PAF, as ERP enables cautious, descriptive burden estimation rather than intervention-effect

prediction, while simultaneously retaining the PAF-based computational framework.

$$\text{ERP} = \frac{\text{Pooled } H. \text{pylori prevalence} \times (\text{Pooled Estimated OR} - 1)}{\text{Pooled } H. \text{pylori prevalence} \times (\text{Pooled Estimated OR} - 1) + 1}$$

$$\text{ERP}_i = \frac{p_i \times (\text{OR}_i - 1)}{p_i \times (\text{OR}_i - 1) + 1}$$

The *H. pylori* prevalence p_i was drawn from a Beta distribution. The parameters α and β were estimated using the method of moments³⁵ based on the reported mean and 95% CI of prevalence:

$$p_i \sim \text{Beta}(\alpha, \beta)$$

The log-transformed OR $\log(\text{OR}_i)$ was assumed to follow a normal distribution:

$$\log(\text{OR}_i) \sim N(\mu, \sigma^2)$$

We estimated ERPs using the Monte Carlo simulation with 10 000 iterations to balance computational efficiency and numerical stability. For each iteration, ERPs were calculated based on randomly sampled prevalence and OR values, and the 2.5th, 50th and 97.5th percentiles were used to determine point estimates and 95% uncertainty intervals (UIs).^{8,36,37} When available, country-specific ORs were used, provided that at least two eligible studies (including one population-based study with a sample size ≥500) were identified. In countries lacking sufficient data, regional ORs were used. If regional estimates were unavailable, global pooled ORs were applied.

We estimated the burden at the global and regional levels, and stratified by sex and diagnostic modality. In addition to estimates based on all eligible studies, we performed sensitivity analyses restricted to high-quality population-based studies and cohort studies, which typically provide larger sample sizes, longer follow-up and more rigorous exposure and outcome ascertainment than case-control and cross-sectional studies. We conducted an exploratory pseudo-cohort analysis using repeated cross-sectional age-specific CRC incidence rates from GLOBOCAN 2022. Age groups were cross-sectionally aligned to approximate birth cohorts, and external estimates of *H. pylori* prevalence²⁴ and pooled RRs were applied to generate hypothesis-generating patterns of *H. pylori*-related CRC burden. Detailed methods and cohort definitions are provided in the online supplemental table 2.

Statistical analysis

We used random-effects models, employing the DerSimonian and Laird method with inverse-variance weighting, to perform a meta-analysis of *H. pylori* exposure and CRC risk. The Hartung-Knapp-Sidik-Jonkman adjustment was applied to improve variance estimation accuracy.³⁸ Between-study heterogeneity was assessed using the I^2 statistic, with $I^2 \geq 50\%$ indicating significant heterogeneity. To assess the robustness of the pooled estimates to unmeasured confounding, E-values were calculated for the pooled effect and its lower 95% confidence bound.³⁹

To explore sources of heterogeneity, random-effects meta-regression was performed using mixed-effects models implemented in the ‘metafor’ R package.

Candidate moderators included the midpoint year of the study period, diagnostic method, study design, screening programme status and study population setting. Model selection was guided by the Akaike information criterion (AIC).⁴⁰ Additionally, we conducted an ecological correlation between country-level ASIRs and ERPs using Spearman's rank correlation, and modelled the exposure–response relationship between *H. pylori* prevalence and ERP using a generalised additive model (GAM) with penalised splines ($k=5$, restricted maximum likelihood).

We applied funnel plots and Egger's regression test to assess potential publication bias. To evaluate the robustness of the pooled effect estimates and identify influential studies, we performed a leave-one-out analysis, in which each study was sequentially omitted and the pooled OR and its 95% CI were recalculated. Except for the estimate based on population-based and cohort studies only, we conducted additional sensitivity analyses to evaluate the robustness of global estimation by (1) increasing the Monte Carlo simulations to 20 000 to assess the robustness of results against potential simulation variability; (2) limiting the risk estimates to studies that reported multivariable-adjusted risk to minimise residual confounding; (3) we repeated the global, regional and sex-specified estimation after converting pooled ORs to RRs using stratum-specific baseline risks according to the formula⁴¹ $RR=OR/[(1-P_0)+P_0 \times OR]$, where P_0 denotes the baseline risk of CRC, approximated by the ASIR per 100 000 population as reported in GLOBOCAN 2022; (4) adopting the global summary estimate with the pooled OR derived exclusively from countries without established national CRC screening programmes.

RESULTS

Association between *H. pylori* exposure and CRC risk

Based on 43 included studies involving 48 694 403 individuals globally, *H. pylori* exposure was associated with a 1.59-fold higher risk of CRC (95% CI 1.36 to 1.87), with substantial heterogeneity (I^2 : 92.6%). The E-value for the pooled estimated risk was 2.56 (95% lower bound: 2.06). Details of the included studies are shown in online supplemental table 3. Significant differences by study setting (P for subgroup=0.009) and study risk of bias (P for subgroup=0.013) were noted. There was some regional variation in risk estimates, but most CIs overlapped or crossed 1 ($p=0.428$). No statistically significant subgroup differences were observed across sex, age group, diagnostic method or presence of a national CRC screening programme (all P for subgroup >0.05; table 1). Detailed subgroup analysis results are shown in table 1 and online supplemental figures 1–12.

Only four studies,^{19–21 42} including one study that set CRC as a secondary endpoint,⁴² reported data on the impact of *H. pylori* eradication on CRC risk. Two cohort studies^{19 20} conducted subgroup analyses over a follow-up period of more than 10 years and demonstrated that *H. pylori* eradication was associated with reduced risk of

CRC (RR: 0.90 (95% CI 0.84 to 0.96)). This benefit was not demonstrated in shorter-term follow-up (≤ 5 years: RR=1.01 (0.78–1.30); 5–10 years: RR=0.92 (0.81–1.05)). The best-fitting model (lowest AIC=64.2) retained four covariates from the prespecified set of potential study-level factors listed in the methods section above: study midpoint year, study population setting, study risk of bias and *H. pylori* diagnostic methods. These covariates were identified as the most informative predictors. The selected model reduced between-study variance (τ^2) to 0.2 and accounted for 6.8% of the observed heterogeneity. Results of the random-effects meta-regression are presented in online supplemental table 4.

Global and regional CRC burden related to *H. pylori* exposure

Overall, under the pooled risk-attribution model based on all 43 included studies, *H. pylori* exposure was potentially related to 22.0% (95% UI 14.7% to 29.4%) of global CRC burden (table 2). The corresponding ERP restricted solely to high-quality population-based and cohort studies ($n=14$ studies; median follow-up 14 years, IQR: 8.7 years) was lower (11.9%, 95% UI 0.7% to 22.8%); the wider UI is an expected statistical consequence of the modelling approach, as the Monte Carlo framework jointly propagates uncertainty from both prevalence and RR estimates. ERP varied according to the WHO region. The Western Pacific Region had the highest related burden (ERP: 25.1%, 95% UI 16.4% to 34.1%). Females had a higher ERP compared with males (24.8%, 95% UI 10.8% to 38.7% vs 19.9%, 95% UI 8.1% to 31.4%). When stratified by diagnostic method, individuals with confirmed active *H. pylori* infection based on non-serology or mixed methods had higher ERP versus individuals diagnosed based on serology only, but with overlapping UI (ERP 25.4%, 95% UI 14.9% to 35.8% vs ERP of 19.9%, 95% UI 8.9% to 30.5%). The latest (based on GLOBOCAN 2022 data) estimations of the global CRC burden related to *H. pylori* exposure across subgroups are shown in table 3.

Country-specific ERPs and *H. pylori*-related CRC burden are illustrated in figure 2 and online supplemental table 5. In 2022, Mongolia had the highest ERP (36.1%, 95% UI 23.3% to 47.5%). Regarding CRC ASIR, Japan (9.0 per 100 000), Portugal (8.4 per 100 000) and South Korea (7.8 per 100 000) showed the highest CRC ASIR potentially related to *H. pylori* exposure. From an absolute case-count perspective, China had the highest number of CRC cases potentially linked to *H. pylori* exposure (139 619; 95% UI 87 908 to 186 158). Figure 3A shows an inverse correlation between country-level CRC ASIR and the ERP of *H. pylori*-related CRC (Spearman $\rho = -0.57$, $p<0.001$). Countries such as Japan, China, Portugal, South Korea and Russia are clustered in the upper-right quadrant, indicating both high ERPs and high CRC incidence. In contrast, European countries, depicted in the lower-right quadrant, exhibit high CRC incidence but lower ERPs. The exposure–response relationship showed that the ERP increased steeply with rising *H. pylori* prevalence up to approximately 60.0%, beyond which the curve plateaued.

Table 1 Summary of global, regional and other subgroups of pooled effect estimates for the association between *H. pylori* exposure and colorectal cancer risk

	No. of studies	Total participants	Pooled estimated risk (95% CI)*†	I ² (%)	P value (heterogeneity)	P value (subgroup difference)
Global	43	48 694 403	1.59 (1.36 to 1.87)	92.6	<0.001	
WHO regions						0.429
Eastern Mediterranean region	4	329	2.31 (0.46 to 11.54)	57.8	0.069	
European region	17	71 765	1.38 (1.06 to 1.79)	64.8	<0.001	
Region of the Americas	6	48 537 802	1.36 (0.76 to 2.42)	98.8	<0.001	
South-East Asian region	1	90	1.73 (0.72 to 3.93)	NA		
Western Pacific region	15	84 417	1.73 (1.40 to 2.14)	71.7	<0.001	
Anatomical location						0.681
Colon cancer	10	21 957	1.35 (1.00 to 1.80)	64.0	0.003	
Rectal cancer	8	11 879	1.23 (0.84 to 1.81)	75.8	<0.001	
Detection methods						0.392
Serology	26	47 749 364	1.48 (1.19 to 1.85)	94.2	<0.001	
Non-serology/mixed	17	945 039	1.79 (1.41 to 2.29)	84.0	<0.001	
Histology	4	13 596	2.08 (0.81 to 5.36)	23.2	0.272	
RUT	2	40 575	1.54 (0.13 to 17.74)	62.8	0.101	
UBT	4	22 275	2.35 (1.13 to 4.88)	45.8	0.136	
Mixed	7	868 593	1.59 (0.99 to 2.55)	90.4	<0.001	
Study design						0.240
Case-control study	26	29 101	1.41 (1.18 to 1.69)	75.1	<0.001	
Cohort study	5	48 607 243	1.63 (0.82 to 3.23)	99.0	<0.001	
Cross-sectional study	12	58 059	1.92 (1.35 to 2.73)	61.2	0.003	
National screening programmes‡						0.147
Yes	27	48 630 852	1.47 (1.19 to 1.80)	94.9	<0.001	
No	16	63 551	1.84 (1.42 to 2.38)	71.9	<0.001	
Age groups						0.966
<60 years	4	889	1.46 (0.89 to 2.38)	45.3	0.140	
≥60 years	4	2153	1.45 (1.16 to 1.81)	0	0.495	
Sex						0.364
Male	4	1303	1.52 (1.19 to 1.94)	0	0.619	
Female	4	735	1.70 (1.25 to 2.30)	0	0.448	
Risk after eradication	4	1 039 993	1.02 (0.84 to 1.23)			0.667
Follow-up ≤5 years	3		1.01 (0.78 to 1.30)	93.7	<0.001	
Follow-up 5–10 years	3		0.92 (0.81 to 1.05)	64.6	0.037	
Follow-up ≥10 years	2		0.90 (0.84 to 0.96)	NA	0.416	
Study setting						0.009
Hospital-based	29	67 305	1.84 (1.51 to 2.25)	65.7	<0.001	
Population-based	14	48 627 098	1.27 (1.01 to 1.59)	97.2	<0.001	
Study risk of bias						0.012
Low	14	48 627 098	1.27 (1.01 to 1.59)	97.2	<0.001	
Moderate	20	62 295	1.86 (1.43 to 2.44)	74.5	<0.001	
High	9	4928	2.04 (1.42 to 2.92)	8.1	0.368	
<i>H. pylori</i> virulence factors positive						0.765
CagA ⁺	16	29 854	1.26 (1.08 to 1.47)	67.5	<0.001	

Continued

Table 1 Continued

	No. of studies	Total participants	Pooled estimated risk (95% CI)*†	I ² (%)	P value (heterogeneity)	P value (subgroup difference)
VacA [‡]	5	13 844	1.15 (0.92 to 1.43)	75.2	0.003	
GroEL [‡]	6	15 010	1.15 (1.07 to 1.26)	0	0.744	
Study periods§						0.331
<2000	7	2687	1.24 (0.83 to 1.85)	38.4	0.140	
2001–2010	14	48 565 160	1.57 (1.12 to 2.21)	97.2	<0.001	
After 2011	18	117 847	1.68 (1.30 to 2.17)	79.1	<0.001	
Birth cohort¶						0.861
1930s and before	4	5052	1.17 (0.98 to 1.40)	0	0.690	
1940s and 1950s	3	23 912	1.22 (0.98 to 1.52)	6.1	0.370	
1960s and 1970s	2	20 531	1.44 (0.15 to 13.90)	59.7	0.084	

*Random-effects meta-analysis was conducted using the DerSimonian and Laird estimator with HartungKnapp–Sidik–Jonkman adjustment.

†Pooled estimates are based on log-transformed ORs or relative risks and back-transformed for presentation.

‡Countries (or territories) involved that have established national colorectal cancer screening programmes include the USA, Israel, the UK, Poland, Finland, Ireland, Germany, Spain, Turkey, Japan, South Korea and Taiwan (Province of China). The US programme is not organised at a national level; however, it has established national initiatives and guidelines to encourage screening. The US Preventive Services Task Force recommends screening for adults aged 45–75. The National Colorectal Cancer Roundtable aims to achieve an 80% screening rate among adults aged 45–75.

§Determined by the midpoint year for the participants' enrolled periods.

¶Determined by the studies' reported age-group risk and the participants' enrolled period.

CagA, cytotoxin-associated gene A; GroEL, heat shock protein 60; *H. pylori*, *Helicobacter pylori*; NA, not available; ORs, odds ratios; RUT, rapid urease test; UBT, urea breath test; VacA, vacuolating cytotoxin A.

Table 2 ERP of colorectal cancer related to *H. pylori* exposure, overall and by subgroups

	<i>H. pylori</i> prevalence (%) (95% CI)*	ERP estimate (%) (mean, 95% UI)†	ΔERP (%) (95% UI)†
Global (based on all eligible studies)	48.0 (45.7 to 50.3)	22.0 (14.7 to 29.4)	
Global (based on population-based studies and cohort studies only)	50.3 (47.3 to 53.3)	11.9 (0.7 to 22.8)	
Sex (overall)			−4.9 (−22.6 to 13.3)
Male	48.3 (43.7 to 52.9)	19.9 (8.1 to 31.4)	
Female	47.9 (43.8 to 52.0)	24.8 (10.8 to 38.7)	
Diagnostic methods (overall)			−5.4 (−20.6 to 9.9)
Serology test	52.2 (48.5 to 55.9)	19.9 (8.9 to 30.5)	
Non-serology and mixed test	43.3 (40.4 to 46.2)	25.4 (14.9 to 35.8)	
WHO regions (overall)			
Western Pacific region	46.3 (43.1 to 49.4)	25.1 (16.4 to 34.1)	Ref
African region	57.1 (46.6 to 67.6)	24.1 (15.5 to 33.8)	−1.0 (−14.8 to 12.7)
Region of the Americas	44.6 (41.3 to 47.8)	13.7 (0 to 38.6)	−11.5 (−38.4 to 15.0)
Eastern Mediterranean region	49.1 (42.0 to 56.2)	22.4 (14.5 to 30.2)	−2.8 (−15.0 to 9.5)
South-East Asia region	40.0 (27.4 to 52.8)	19.0 (11.2 to 27.6)	−6.2 (−18.6 to 6.7)
European region	45.7 (40.9 to 50.5)	14.8 (2.6 to 26.9)	−10.6 (−26.1 to 4.6)

*Estimates of *H. pylori* prevalence are derived from previously published meta-analysis, involving studies with sample collection midpoint years ranging from 1990 to 2022.

†Calculated using Monte Carlo simulations based on uncertainty distributions with 10 000 iterations.

ERP, estimated related proportion; *H. pylori*, *Helicobacter pylori*; UI, uncertainty interval.

Table 3 Estimated global and regional CRC burden related to *H. pylori* exposure in 2022

Estimation of burden in 2022	<i>H. pylori</i> prevalence (%) (95% CI)*	CRC ASIR in 2022 (per 100 000)†	New CRC cases in 2022 (n)†	ERP estimate (%) (mean, 95% UI)‡	Related CRC cases (mean, 95% UI)‡	Related CRC ASIR (per 100 000; mean, 95% UI)‡
Global	42.6 (37.2 to 48.3)	18.4	1 926 425	22.3 (11.1 to 33.6)	429 593 (214 755 to 647 872)	4.1 (2.1 to 6.1)
Sex*						
Male	44.2 (26.9 to 58.5)	21.9	1 069 446	18.7 (7.4 to 29.7)	199 986 (79 130 to 347 655)	4.1 (1.6 to 6.5)
Female	44.1 (21.9 to 59.5)	15.2	856 979	23.5 (9.9 to 36.6)	201 390 (84 055 to 313 004)	3.6 (1.5 to 5.6)
Diagnostic methods						
Serology test	54.6 (47.0 to 62.2)	–	–	20.7 (9.3 to 31.8)	398 770 (179 158 to 612 603)	3.8 (1.7 to 5.9)
Non-serology/mixed test	38.0 (33.7 to 42.4)	–	–	23.0 (12.9 to 32.8)	443 078 (248 509 to 631 867)	4.2 (2.4 to 6.0)
WHO regions						
Western Pacific region	46.4 (44.5 to 48.3)	22.1	766 180	25.2 (15.4 to 34.7)	193 077 (117 992 to 265 864)	5.6 (3.4 to 7.7)
African region	53.3 (42.4 to 64.2)	8.2	53 786	23.8 (15.2 to 32.5)	12 801 (8175 to 17 480)	2.0 (1.2 to 2.7)
Region of the Americas	32.8 (19.3 to 46.4)	21.0	328 680	10.9 (8.4 to 33.1)	35 826 (27 609 to 108 793)	2.3 (1.8 to 7.0)
Eastern Mediterranean region	56.1 (37.3 to 74.9)	8.9	53 941	24.8 (14.9 to 35.0)	13 377 (8037 to 18 879)	2.2 (1.3 to 3.1)
South-East Asia region	39.2 (24.3 to 54.2)	6.9	148 288	18.7 (10.7 to 27.8)	27 730 (15 867 to 41 224)	1.3 (0.7 to 1.9)
European region	44.2 (29.5 to 58.9)	28.8	574 953	14.2 (2.8 to 27.0)	81 643 (16 099 to 155 237)	4.1 (0.8 to 7.8)

*Estimates of *H. pylori* prevalence are derived from previously published meta-analysis, involving studies with sample collection midpoint years ranging from 2011 to 2022.

†From GLOBOCAN 2022.

‡Calculated using Monte Carlo simulations based on uncertainty distributions with 10 000 iterations.

ASIR, age-standardised incidence rate; CRC, colorectal cancer; ERP, estimated related proportion; GLOBOCAN, Global Cancer Observatory; *H. pylori*, *Helicobacter pylori*; UI, uncertainty interval.

The GAM confirmed a significant non-linear association between *H. pylori* prevalence and ERP (edf=2.79, $p<0.001$) (figure 3B).

Birth cohort trends in CRC burden related to *H. pylori* exposure

Based on the limited pseudo-cohort data derived from GLOBOCAN 2022, *H. pylori* prevalence showed a declining gradient across successive pseudo-cohorts, from the earliest (<1947) to the most recent (1963–1977) group (figure 4A). In contrast, the exploratory ERP appeared higher in later-born pseudo-cohorts, rising from 9.5% in those born before 1947 to 10.2% in 1948–1962 and 15.0% in 1963–1977. Across later pseudo-cohorts, the overall CRC ASIR showed a more pronounced decline, whereas the *H. pylori*-related CRC ASIR declined more modestly.

In contrast, absolute CRC case counts remained relatively stable, with a modestly higher burden observed in the 1948–1962 group (figure 4B).

Publication bias and sensitivity analysis

Studies assessing the association between *H. pylori* exposure and CRC risk showed no apparent asymmetry on the funnel plot, indicating low concern for publication bias (online supplemental figure 13). Egger's regression test yielded a non-significant result ($p=0.230$), with a bias coefficient of 0.3. The leave-one-out analysis indicated that no single study had a disproportionate impact on the overall pooled estimate. Sequential omission of individual studies yielded pooled ORs ranging from 1.52 to 1.73, with all

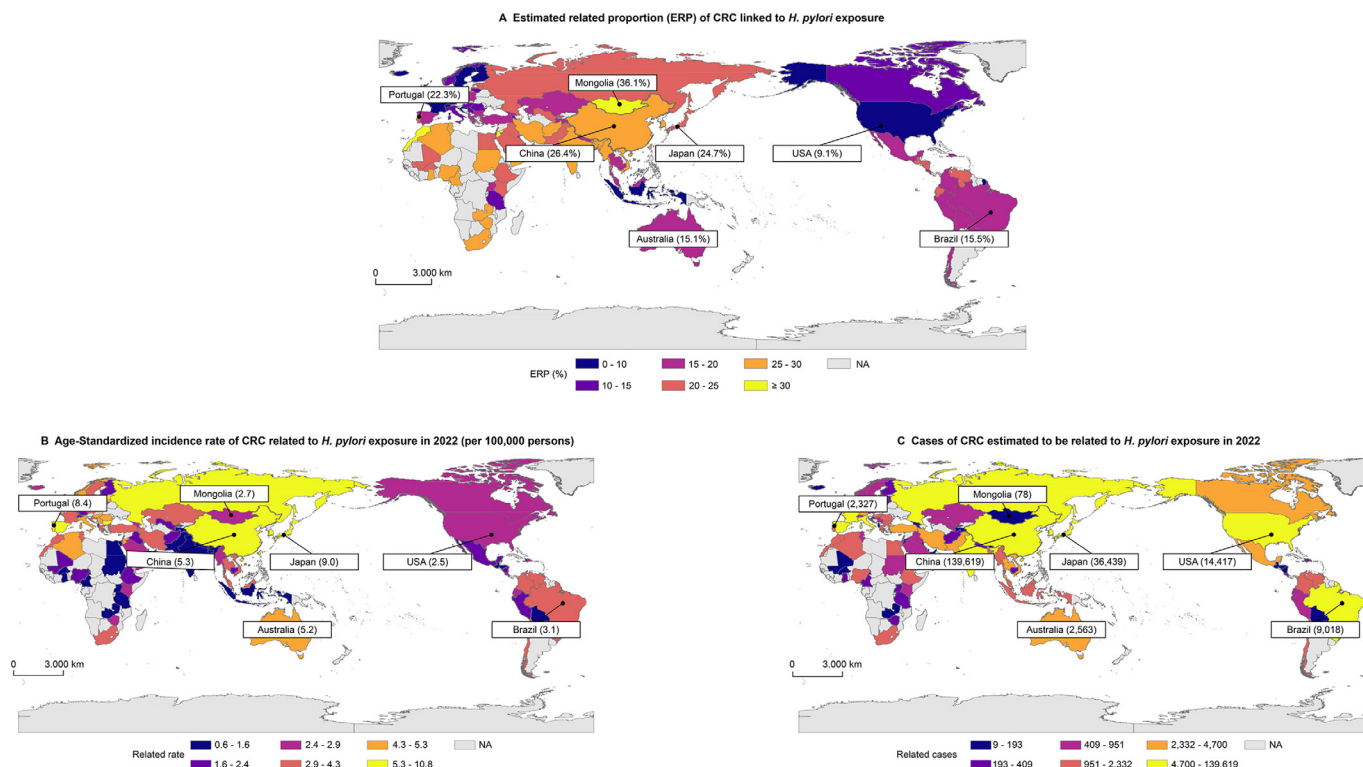


Figure 2 Global burden of CRC related to *H. pylori* exposure. (A) Global distribution of ERP of CRC related to *H. pylori* exposure; (B) Age-standardised incidence rate (per 100 000 population) of *H. pylori*-related CRC. (C) Estimated number of CRC cases related to *H. pylori* exposure in 2022. Data of Taiwan (Province of China) was not documented in GLOBOCAN 2022 and was therefore derived from the Taiwan Health Promotion Administration. Given the differences in estimation methodology compared with GLOBOCAN, these data were not included in the primary analysis but were used for supplementary estimation and reference purposes only (2022 *H. pylori*-related ASIR: 10.8; *H. pylori*-related CRC cases: 2526). The map is based on standard map no. GS (2016)1666 downloaded from the service website of standard maps. Source: The service website of standard maps: Map of the World (<http://bzdt.ch.mnr.gov.cn/>). The map was used only for data visualisation, and no geographical boundaries or territorial designations imply any expression of opinion by the author. ASIR, age-standardised incidence rate; CRC, colorectal cancer; ERP, estimated related proportion; GLOBOCAN, Global Cancer Observatory; *H. pylori*, *Helicobacter pylori*; NA, not assessed.

estimates remaining statistically significant ($p < 0.001$) and in the same direction as the primary analysis. Altering the number of iterations to 20 000 in the Monte Carlo simulation yielded an ERP of 22.7% (95% UI 11.6% to 33.6%), with comparable global estimates for *H. pylori*-related CRC ASIR (4.2 per 100 000 (95% UI 2.1 to 6.2)). Applying a multivariable-adjusted pooled OR of 1.53 (95% CI 1.30 to 1.87) produced a slightly lower ERP of 18.3% (95% UI 11.4% to 25.2%), corresponding to a global *H. pylori*-related ASIR of 3.4 per 100 000 (95% UI 2.1 to 4.6). Similarly, re-estimating ERPs after converting pooled ORs to RRs using stratum-specific baseline risks showed minimal changes (<1 percentage point difference) across global, sex and regional strata. Using the OR derived from countries without national CRC screening programmes (OR: 1.82; 95% CI 1.40 to 2.41) resulted in an ERP of 26.5% (95% UI 15.6% to 37.8%) and an ASIR of 4.9 per 100 000 (95% UI 2.9 to 6.9). These estimates, however, are primarily based on hospital-based studies with limited sample sizes and should be interpreted with caution.

DISCUSSION

In this risk-attribution modelling study, we estimated that *H. pylori* exposure may have contributed to approximately 22.0% of global CRC cases, which is lower than attribution from other common modifiable factors. This proportion decreased to 11.9% when risk estimates were derived from population-based and cohort studies. We noted regional variations, including a higher burden in the Western Pacific. Across countries, potential *H. pylori*-related CRC burden was higher in settings with lower overall CRC incidence and increased non-linearly with rising *H. pylori* prevalence. We also observed country-level heterogeneity and an inverse correlation between overall CRC ASIR and ERP. Across pseudo-cohorts, the corresponding CRC burden related to *H. pylori* exposure was higher in later-born groups. Taken together, our findings provide an integrated view of the magnitude, regional heterogeneity and birth cohort dynamics of CRC burden potentially related to *H. pylori* exposure.

In a nationwide cohort study in the US through 15-year follow-up, *H. pylori* eradication was associated with an absolute risk reduction of 0.23–0.35%, which is on par

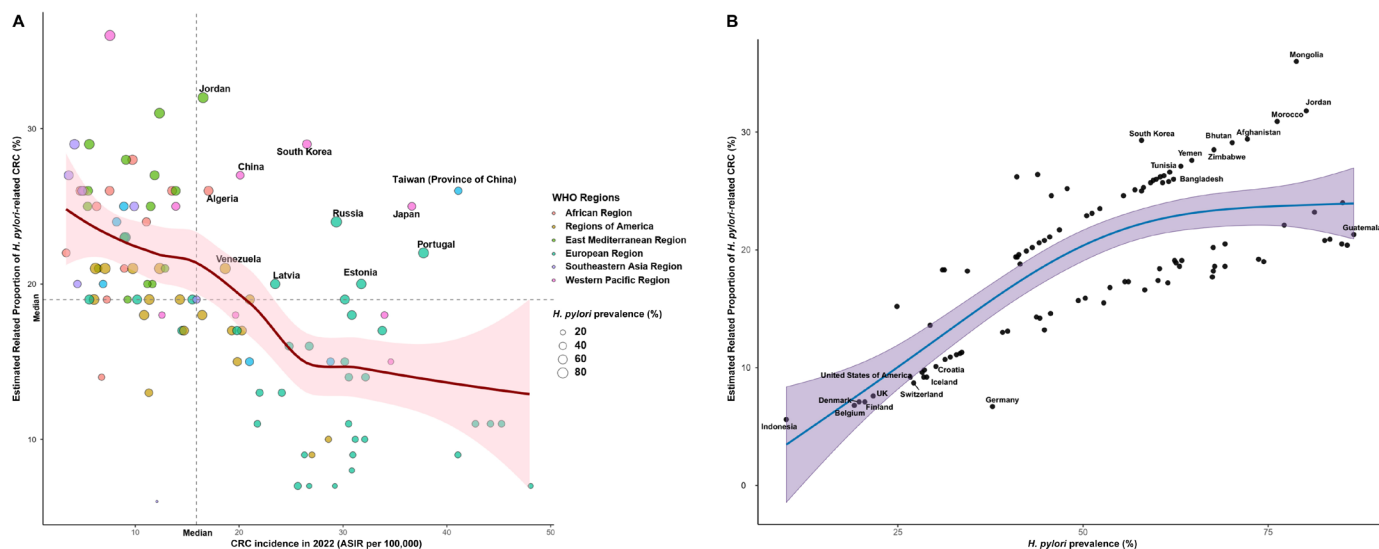


Figure 3 Country-level association and exposure–response relationship between CRC incidence, *H. pylori* prevalence and ERP. (A) Country-level relationship between overall CRC incidence and ERP of CRC associated with *H. pylori* exposure. Each bubble represents a country; the bubble size indicates the national pooled *H. pylori* prevalence, and the colour corresponds to the respective WHO region. Dashed lines denote the global medians of CRC incidence (ASIR) and ERP. A non-linear LOESS curve (with 95% CI) illustrates the association between ASIR and ERP. (B) Exposure–response relationship between *H. pylori* prevalence and ERP of CRC. The solid blue line denotes the fitted curve from a GAM and the shaded area indicates the 95% CI. ASIR, age-standardised incidence rate; CRC, colorectal cancer; ERP, estimated related proportion; GAM, generalised additive model; *H. pylori*, *Helicobacter pylori*; LOESS, locally estimated scatterplot smoothing.

with the 0.15–0.30% absolute risk reduction in fatal CRC afforded by colonoscopy (colonoscopy yields 0.84–1.22% absolute reduction in incident CRC).¹⁹ A recent pragmatic RCT in Changhua County, Taiwan (Province of China), demonstrated that co-screening for gastric cancer and CRC with *H. pylori* stool antigen and faecal immunochemical testing (FIT) versus FIT alone also

suggested potential added reduction in CRC incidence. However, follow-up was short, and treatment uptake varied, limiting causal inference.⁴³ Several factors can bias the observable benefit after eradication. A recent cluster-RCT⁴² conducted in Linqu County, China, implemented community-based *H. pylori* screen-and-treat primarily to prevent gastric cancer, enrolling adults aged

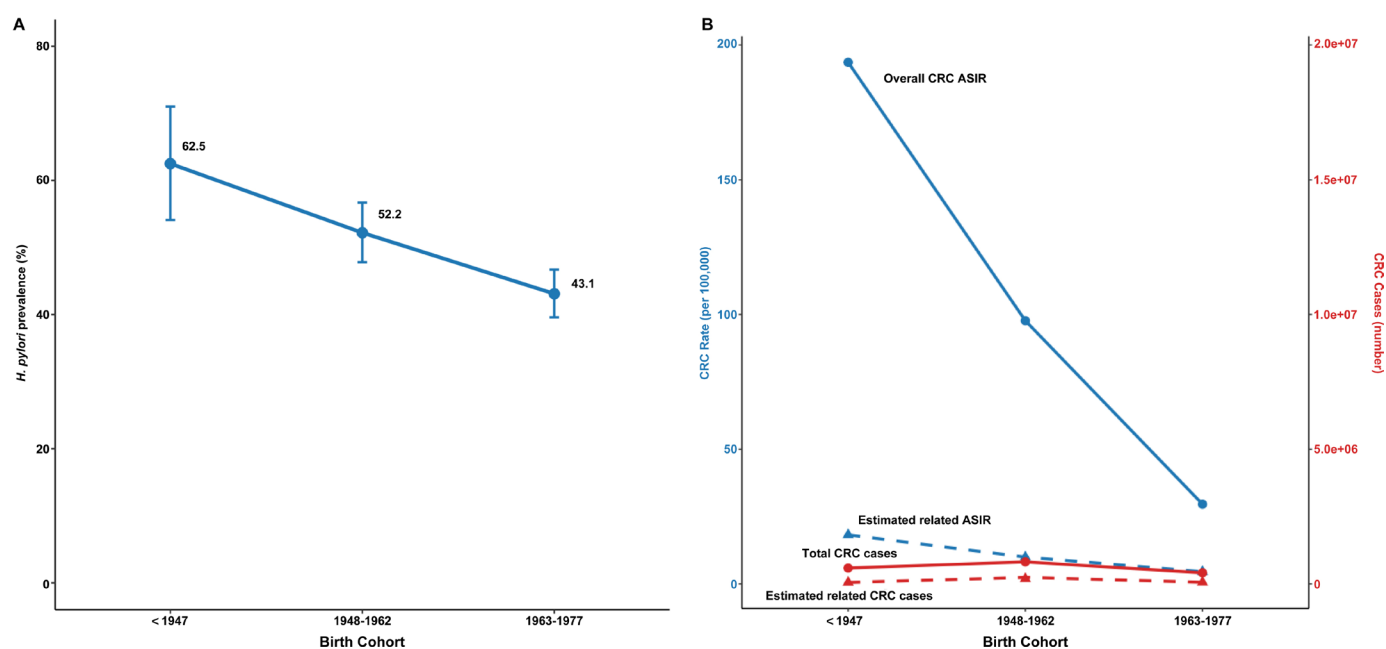


Figure 4 Birth cohort trends in *H. pylori* prevalence and *H. pylori*-related CRC burden. (A) *H. pylori* prevalence by birth cohort (<1947, 1948–1962, 1963–1977), acquired from previously published meta-analysis; (B) Overall CRC ASIR and total CRC cases, together with estimated CRC ASIR and case numbers of CRC related to *H. pylori* exposure by birth cohort. ASIR, age-standardised incidence rate; CRC, colorectal cancer; *H. pylori*, *Helicobacter pylori*.

25–54 years and using gastric neoplasia endpoints as the primary outcomes. CRC was not the primary endpoint, and the estimated effect on CRC incidence was not significant (HR: 1.02, 95% CI 0.78 to 1.34). This finding should be interpreted cautiously, as trials designed and powered for gastric cancer prevention may be underpowered to detect CRC effects, which may require longer follow-up given the prolonged adenoma–carcinoma sequence, as well as require concurrent colonoscopy to detect asymptomatic early-stage CRC; this particular trial also enrolled a relatively young population. Differences in the timing of intervention and prevention windows between gastric cancer and CRC should therefore be considered.^{44 45} Moreover, it is plausible that in many real-world settings, patients undergoing *H. pylori* testing or eradication might have upper gastrointestinal endoscopy and colonoscopy performed at the same encounter, enabling same-day detection and removal of colorectal polyps.⁴⁶ Such procedural overlap may contribute to a positive association between *H. pylori* exposure and CRC.

The Western Pacific region demonstrated the highest estimated *H. pylori*-related CRC burden. This finding may reflect multiple factors, including high background prevalence of *H. pylori* infection (such as China, Mongolia and Vietnam),^{24 47} limited population-wide eradication programmes,⁴⁸ as well as rising CRC incidence due to rapid urbanisation,⁴⁹ dietary shifts⁵⁰ and ageing demographics. By contrast, despite similarly high *H. pylori* prevalence levels in the African, South-East Asian and Eastern Mediterranean regions, the related CRC burden was comparatively lower. Indeed, there is a well-documented epidemiological observation known as the ‘African enigma’⁵¹ and the ‘Indian enigma’,⁵² which describes the paradoxical phenomenon where populations exhibit high *H. pylori* prevalence but low rates of *H. pylori*-related gastric cancer. Understanding the complex interactions among host genetics, *H. pylori* genetics and environmental factors that may plausibly contribute to the observed trend is beyond the scope of this work, but should motivate future research. Notably, we did not observe differences in the *H. pylori*–CRC association by national CRC screening programme status, suggesting that screening intensity alone might not account for the regional profile. The relative contribution of *H. pylori* in these regions may be diluted by competing behavioural risks (eg, diet, sedentary lifestyle, obesity, alcohol), which are more prominent risk factors for CRC in Western countries.^{2 53}

The rise in CRC incidence is partly driven by ‘contemporary’ risk factors, such as dietary changes (eg, high-fat, low-fibre diets), increasing rates of unhealthy living habits and enhanced screening efforts that improve detection, which may dilute the relative impact of *H. pylori*. Indeed, across successive pseudo-birth cohorts, *H. pylori* prevalence declined markedly, yet the ERP for CRC increased, rising from 9.5% to 15.0%. This discordance might reflect a latency effect, whereby the carcinogenic consequences of early-life infection manifest decades

later, combined with reduced competing mortality and improved longevity that allow individuals to reach ages at which CRC typically develops.⁵⁴ This latency effect is also consistently observed for gastric cancer.

In our subgroup analyses, ERP point estimates were slightly higher when *H. pylori* exposure was defined using non-serology or mixed modalities compared with serology-only definitions, but UIs overlapped. Non-serology tests capture current or active infection, which may indicate a longer duration of infection, whereas serology also includes individuals with prior but not current infection (eg, eradicated). Non-concordance between seroprevalence and active infection might be amplified in settings undergoing rapid epidemiological transition (eg, countries with rapid socio-economic development), in countries with organised endoscopic screening for gastric cancer (eg, Japan, Korea) and/or with population-level ‘screen-and-treat’ strategies, as recommended by the International Agency for Research on Cancer (IARC)/WHO, with concurrent high *H. pylori* eradication treatment uptake. Accordingly, serology-based prevalence may overestimate the prevalence of current infection. Diagnostic modality may also be a proxy for healthcare setting and study context, and contribute to residual confounding or selection bias that influence observed effect sizes. It is also relevant to acknowledge that studies of the PAF of gastric cancer related to *H. pylori* include both serological and non-serological diagnostic modalities, given that prior exposure is still associated with increased cancer risk. All points considered, we did not observe statistically significant differences in our estimates based on detailed analysis according to diagnostic modality (non-serology or mixed vs serology; invasive vs non-invasive).^{55 56}

This study has several strengths. First, it is comprehensive synthesis to date quantifying the global and regional burden of CRC potentially related to *H. pylori* exposure, incorporating data from studies globally and the latest GLOBOCAN data. The inclusion of diverse study designs, populations and detection methods enhances the generalisability of our findings. Second, we applied robust statistical methods, such as Monte Carlo simulation, to jointly account for uncertainty in both exposure prevalence and RR estimates, thereby generating more reliable estimates of attributable fractions; it is acknowledged, though, that this also has the consequence of inflating uncertainty when study numbers are limited, as in some of our sensitivity analyses. A recent policy-focused analysis by Mulder *et al* suggested that approximately 18% of CRC burden might be related to *H. pylori* exposure when considering outcomes beyond gastric cancer alone.⁵⁷ While broadly consistent in magnitude, that estimate was derived from a single previously published pooled association and did not incorporate stratification by region, sex or diagnostic modality, and did not consider study quality as we did here to further assess the robustness of the estimates and reasons for heterogeneity. Third, we conducted multiple subgroup

and sensitivity analyses to assess the robustness of our estimates.

Nevertheless, the limitations need to be acknowledged. First, the ERP estimates are structurally sensitive to the assumed prevalence and pooled RR, which may lead to overestimation or underestimation of the *H. pylori*-related burden; however, this limitation is not unique to *H. pylori* and applies to other CRC risk factors as well. Data gaps exist for specific areas in the relationship between *H. pylori* and CRC risk. For instance, in the African and Southeast Asia regions, we used average values derived from broader WHO regions or global estimates, which may introduce bias and reduce the specificity of country-level estimates.

Second, our comprehensive subgroup analyses and meta-regressions were able to explain only a modest proportion of the observed heterogeneity (6.8%).^{58–60} The potential sources of residual heterogeneity might originate from exposure assessment variability, CRC ascertainment, study population risk and follow-up duration across the individual studies, which we cannot fully address in this meta-analysis. In addition, overall heterogeneity and pooled risk estimates were largely influenced by the Region of the Americas, which contributed the majority of participants despite a limited number of studies, and by the predominant use of serological assays for *H. pylori* diagnosis. Moreover, the evidence base underlying the pooled risk estimates is dominated by case-control and cross-sectional studies (n=38), with comparatively fewer prospective cohorts (n=5). Hospital-based designs may be more susceptible to selection bias and differential healthcare-seeking and testing patterns than population-based samples, which could partly contribute to the stronger associations observed in some settings and to residual confounding. Accordingly, we also conducted sensitivity analyses restricted to high-quality population-based and cohort studies (n=14) and observed a lower ERP, which provides a conservative lower bound. It should be emphasised, though, that interpretation of the UI is limited for this sensitivity analysis, since the wide interval is a primary statistical consequence of the modelling approach propagating uncertainty based on the lesser number of studies versus the primary analysis. Our birth-cohort-related findings, derived from cross-sectional age-specific data in GLOBOCAN 2022, should therefore be interpreted as pseudo-cohort patterns rather than evidence from longitudinal follow-up. This pragmatic approach was adopted because harmonised, age-specific CRC incidence series using comparable methods with coverage across multiple historical years are not consistently available at the global scale. Accordingly, the 2022 estimates provide a standardised snapshot of age patterns rather than the full life-course burden across birth cohorts. These results may be affected by survivor bias, period-specific screening intensity and other unmeasured confounders and should therefore be viewed distinctly as exploratory and hypothesis-generating.

Third, evidence directly evaluating *H. pylori* eradication and subsequent CRC risk remains sparse and largely observational. Existing eradication studies are often limited by short follow-up durations and potential confounding factors, such as variations in endoscopy indications, antibiotic exposure, concomitant colonoscopy with upper endoscopy and disparities in healthcare access, all of which may influence the apparent association between *H. pylori* exposure and CRC. Therefore, our findings should be interpreted as hypothesis-generating, and further prospective and interventional studies are needed.

Regarding the public health implications, population-level *H. pylori* control may help prevent gastric cancer and, if the link with CRC is causal, could reduce CRC burden in high-prevalence areas. However, success depends on local epidemiology, healthcare capacity and integration with existing CRC screening. As with primary gastric cancer prevention, large-scale *H. pylori* eradication raises concerns about antibiotic stewardship and resistance, treatment side effects and population versus individual CRC risk modulation, which also considers the latency effect of *H. pylori* eradication on cancer. Therefore, *H. pylori* control should be implemented based on local context, prioritising high-prevalence, resource-limited settings. Prospective studies and trials with predefined CRC outcomes are needed to confirm benefits and guide integration into current cancer prevention programmes.

CONCLUSION

H. pylori exposure may be related to an estimated 22.0% of global CRC cases under a causal assumption, with regional, sex and birth cohort variability. These findings may inform primary CRC prevention strategies, particularly in regions with high *H. pylori* prevalence and limited resources. However, high-quality, prospective studies with long-term follow-up are warranted to clarify whether *H. pylori* eradication causally reduces CRC risk.

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REFERENCES

- Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024;74:229–63.
- Roshandel G, Ghasemi-Kebria F, Malekzadeh R. Colorectal Cancer: Epidemiology, Risk Factors, and Prevention. *Cancers (Basel)* 2024;16:1530.
- Sawicki T, Ruskowska M, Danielewicz A, et al. A Review of Colorectal Cancer in Terms of Epidemiology, Risk Factors, Development, Symptoms and Diagnosis. *Cancers (Basel)* 2021;13:2025.
- Singh S, Singh PP, Murad MH, et al. Prevalence, Risk Factors, and Outcomes of Interval Colorectal Cancers: A Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2014;109:1375–89.
- Institute for Health Metrics and Evaluation. Global burden of disease 2021. 2021. Available: <https://vizhub.healthdata.org/gbd-results/>
- Moss SF. The Clinical Evidence Linking Helicobacter pylori to Gastric Cancer. *Cell Mol Gastroenterol Hepatol* 2017;3:183–91.
- de Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol* 2012;13:607–15.
- Plummer M, Franceschi S, Vignat J, et al. Global burden of gastric cancer attributable to Helicobacter pylori. *Int J Cancer* 2015;136:487–90.
- Frias-Ordoñez JS, Riquelme A, Marulanda-Fernandez H, et al. Helicobacter pylori and Colorectal Cancer: Meeting Sir Austin Bradford Hill's Causality Criteria. *Helicobacter* 2025;30:e70024.
- Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med* 1965;58:295–300.
- Evans AS. Causation and disease: the Henle-Koch postulates revisited. *Yale J Biol Med* 1976;49:175–95.
- Boustany A, Onwuzo S, Almomani A. Epidemiology and risk of colorectal cancer in patients with a history of Helicobacter pylori infection: a population-based study. *aog* 2023;36:203–7.
- Butt J, Jenab M, Pawlita M, et al. Antibody Responses to Helicobacter pylori and Risk of Developing Colorectal Cancer in a European Cohort. *Cancer Epidemiol Biomarkers Prev* 2020;29:1475–81.
- Nam KW, Baeg MK, Kwon JH, et al. Helicobacter pylori seropositivity is positively associated with colorectal neoplasms. *Korean J Gastroenterol* 2013;61:259–64.
- Liu I-L, Tsai C-H, Hsu C-H, et al. Helicobacter pylori infection and the risk of colorectal cancer: a nationwide population-based cohort study. *QJM* 2019;112:787–92.
- Butt J, Varga MG, Blot WJ, et al. Serologic Response to Helicobacter pylori Proteins Associated With Risk of Colorectal Cancer Among Diverse Populations in the United States. *Gastroenterology* 2019;156:S0016-5085(18)35088-1:175–186.
- Wang M, Kong W-J, Zhang J-Z, et al. Association of Helicobacter pylori infection with colorectal polyps and malignancy in China. *World J Gastrointest Oncol* 2020;12:582–91.
- Ralser A, Dietl A, Jarosch S, et al. Helicobacter pylori promotes colorectal carcinogenesis by deregulating intestinal immunity and inducing a mucus-degrading microbiota signature. *Gut* 2023;72:1258–70.
- Shah SC, Camargo MC, Lamm M, et al. Impact of Helicobacter pylori Infection and Treatment on Colorectal Cancer in a Large, Nationwide Cohort. *J Clin Oncol* 2024;42:1881–9.
- Guo C-G, Zhang F, Jiang F, et al. Long-term effect of Helicobacter pylori eradication on colorectal cancer incidences. *Therap Adv Gastroenterol* 2023;16:17562848231170943.
- Liu Q, Sadr-Azodi O, Engstrand L, et al. Helicobacter pylori Eradication Therapy and the Risk of Colorectal Cancer: A Population-Based Nationwide Cohort Study in Sweden. *Helicobacter* 2024;29:e70001.
- Li W-Q, Ma J-L, Zhang L, et al. Effects of Helicobacter pylori treatment on gastric cancer incidence and mortality in subgroups. *J Natl Cancer Inst* 2014;106:dju116.
- Mera R, Fonham ETH, Bravo LE, et al. Long term follow up of patients treated for Helicobacter pylori infection. *Gut* 2005;54:1536–40.
- Li Y, Choi H, Leung K, et al. Global prevalence of Helicobacter pylori infection between 1980 and 2022: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2023;8:553–64.
- Zuo Y, Jing Z, Bie M, et al. Association between Helicobacter pylori infection and the risk of colorectal cancer: A systematic review and meta-analysis. *Medicine (Baltimore)* 2020;99:e21832.
- Li X, Tao H-Q, Zhao J-E, et al. Helicobacter pylori infection, anti-Helicobacter pylori treatment and risk of colorectal cancer and adenoma: an observational study and a meta-analysis. *EClinicalMedicine* 2025;84:103299.
- Wang X, Wang G, Zhang L. Relationship between Helicobacter pylori infection and colorectal cancer: a meta-analysis of observational studies. *Int J Clin Exp Med* 2017;10:11402–8.
- Ma L, Guo W, Zeng Z, et al. Colorectal cancer risk in East Asian patients with Helicobacter pylori infection: A systematic review and meta-analysis. *Medicine (Baltimore)* 2023;102:e33177.
- Zumkeller N, Brenner H, Zwahlen M, et al. Helicobacter pylori infection and colorectal cancer risk: a meta-analysis. *Helicobacter* 2006;11:75–80.
- Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;7:iii–x.
- Herzog R, Álvarez-Pasquín MJ, Díaz C, et al. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? a systematic review. *BMC Public Health* 2013;13:154.
- LEVIN ML. The occurrence of lung cancer in man. *Acta Unio Int Contra Cancrum* 1953;9:531–41.
- Miettinen OS. Proportion of disease caused or prevented by a given exposure, trait or intervention. *Am J Epidemiol* 1974;99:325–32.
- Stevens GA, Alkema L, Black RE, et al. Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement. *Lancet* 2016;388:e19–23.
- Wooldridge JM. Applications of Generalized Method of Moments Estimation. *J Econ Perspect* 2001;15:87–100.
- Harrison RL, Granja C, Leroy C. Introduction to monte carlo simulation. *AIP Conf Proc* 2010;1204:17–21.
- Velikova T, Mileva N, Naseva E. Method "Monte Carlo" in healthcare. *World J Methodol* 2024;14:93930.
- Int'Hout J, Ioannidis JPA, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol* 2014;14:25.
- VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med* 2017;167:268–74.

- 40 Symonds MRE, Moussalli A. A brief guide to model selection, multimodel inference and model averaging in behavioural ecology using Akaike's information criterion. *Behav Ecol Sociobiol* 2011;65:13–21.
- 41 Prasad K, Jaeschke R, Wyer P, *et al.* Tips for teachers of evidence-based medicine: understanding odds ratios and their relationship to risk ratios. *J Gen Intern Med* 2008;23:635–40.
- 42 Pan K-F, Li W-Q, Zhang L, *et al.* Gastric cancer prevention by community eradication of *Helicobacter pylori*: a cluster-randomized controlled trial. *Nat Med* 2024;30:3250–60.
- 43 Lee Y-C, Chiang T-H, Chiu H-M, *et al.* Screening for *Helicobacter pylori* to Prevent Gastric Cancer: A Pragmatic Randomized Clinical Trial. *JAMA* 2024;332:1642–51.
- 44 Lee Y-C. Single-biopsy epigenetic profiling reveals persistent DNA methylation and gastric cancer risk after *Helicobacter pylori* eradication. *Gut* 2026;75:2–4.
- 45 Shin CM. Can Epigenetic and Gastric Microbiome Markers Predict the Risk of *Helicobacter pylori*-Negative Gastric Cancer? *Gut Liver* 2024;18:553–5.
- 46 Hammami MB, Reddy KM, Pandit P, *et al.* Sequence of same-day upper and lower gastrointestinal endoscopy does not affect total procedure' time or medication use: A randomized trial. *JGH Open* 2019;3:488–93.
- 47 Chen Y-C, Malfertheiner P, Yu H-T, *et al.* Global Prevalence of *Helicobacter pylori* Infection and Incidence of Gastric Cancer Between 1980 and 2022. *Gastroenterology* 2024;166:605–19.
- 48 Park JY. Population-based *helicobacter pylori* screen-and-treat strategies for gastric cancer prevention: guidance on implementation. 2025.
- 49 Wen D, Zou W, Wen X, *et al.* Urban-rural disparity in colorectal cancer incidence and increasing trend in relation to socioeconomic development and urbanization in China. *J Int Med Res* 2018;46:4181–96.
- 50 Sun X, Yon DK, Nguyen TT, *et al.* Dietary and other lifestyle factors and their influence on non-communicable diseases in the Western Pacific region. *Lancet Reg Health West Pac* 2024;43:100842.
- 51 Campbell DI, Warren BF, Thomas JE, *et al.* The African enigma: low prevalence of gastric atrophy, high prevalence of chronic inflammation in West African adults and children. *Helicobacter* 2001;6:263–7.
- 52 Misra V, Pandey R, Misra SP, *et al.* *Helicobacter pylori* and gastric cancer: Indian enigma. *World J Gastroenterol* 2014;20:1503–9.
- 53 Ghazanfar H, Javed N, Reina R, *et al.* Advances in Diagnostic Modalities for *Helicobacter pylori* Infection. *Life (Basel)* 2024;14:1170.
- 54 Chiang T-H, Chang W-J, Chen S-S, *et al.* Mass eradication of *Helicobacter pylori* to reduce gastric cancer incidence and mortality: a long-term cohort study on Matsu Islands. *Gut* 2021;70:243–50.
- 55 Charach L, Perets TT, Gingold-Belfer R, *et al.* Comparison of Four Tests for the Diagnosis of *Helicobacter pylori* Infection. *Healthcare (Basel)* 2024;12:1479.
- 56 Costa L, das Graças Carvalho M, La Guárdia Custódio Pereira AC, *et al.* Diagnostic Methods for *Helicobacter pylori*. *Med Princ Pract* 2024;33:173–84.
- 57 Müller DT, O'Mahony JF, Kapteijn N, *et al.* The Disease Burden of *Helicobacter pylori* Beyond Gastric Cancer: Quantifying the Forgotten Potential Benefits of Mass Eradication. *Gastroenterology* 2026;170:S0016-5085(25)05900-1:344–52.
- 58 Cooper H, Hedges LV, Valentine JC. The Handbook of Research Synthesis and Meta-Analysis. Russell Sage Foundation, 2019.
- 59 Geissbühler M, Hincapié CA, Aghlmandi S, *et al.* Most published meta-regression analyses based on aggregate data suffer from methodological pitfalls: a meta-epidemiological study. *BMC Med Res Methodol* 2021;21:123.
- 60 Rhodes KM, Turner RM, Savović J, *et al.* Between-trial heterogeneity in meta-analyses may be partially explained by reported design characteristics. *J Clin Epidemiol* 2018;95:45–54.