Received: 9 February 2021 | Revised: 12 April 2021 | Accepted: 13 April 2021

DOI: 10.1002/ijc.33678

CANCER EPIDEMIOLOGY

IJC International Journal of Cancer

Exploring the interactions between Helicobacter pylori (Hp) infection and other risk factors of gastric cancer: A pooled analysis in the Stomach cancer Pooling (StoP) Project

Giulia Collatuzzo[1] | Claudio Pelucchi[2] | Eva Negri[3] | Lizbeth López-Carrillo[4] | Shoichiro Tsugane[5] | Akihisa Hidaka[5] | Gerson Shigueaki Hamada[6] | Raúl Ulises Hernández-Ramírez[7] | Malaquias López-Cervantes[8] | Reza Malekzadeh[9] | Farhad Pourfarzi[9,10] | Lina Mu[11] | Zuo-Feng Zhang[12] | Nuno Lunet[13,14] | Carlo La Vecchia[2] | Paolo Boffetta[1,15]

[1]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

[2]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

[3]Department of Biomedical and Clinical Sciences L. Sacco, University of Milan, Milan, Italy

[4]Mexico National Institute of Public Health, Morelos, Mexico

[5]Epidemiology and Prevention Group, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan

[6]Nikkei Disease Prevention Center, São Paulo, Brazil

[7]Department of Biostatistics, Yale School of Public Health, Yale School of Medicine, New Haven, Connecticut

[8]Facultad de Medicina, UNAM, Coyoacán, Mexico

[9]Digestive Oncology Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran

[10]Digestive Disease Research Center, Ardabil University of Medical Sciences, Ardabil, Iran

[11]Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, Buffalo, New York

[12]Department of Epidemiology, UCLA Fielding School of Public Health and Jonsson Comprehensive Cancer Center, Los Angeles, California

[13]Department of Epidemiology, EPIUnit-Instituto de Saúde Pública da Universidade do Porto, Porto, Portugal

[14]Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina da Universidade do Porto, Porto, Portugal

[15]Stony Brook Cancer Center, Stony Brook University, Stony Brook, New York

Correspondence
Paolo Boffetta, Stony Brook Cancer Center, Stony Brook University, Lauterbur Drive, Stony Brook, NY 11794.
Email: paolo.boffetta@stonybrookmedicine.edu

Funding information
Associazione Italiana per la Ricerca sul Cancro, Grant/Award Number: 21378; Italian League for the Fight Against Cancer (LILT)

Abstract

Helicobacter pylori (Hp) is crucial in gastric carcinogenesis, but infection alone is not a sufficient cause, and the interaction between Hp infection and other risk factors has not been adequately studied. We conducted a pooled analysis of seven case-control studies from the Stomach cancer Pooling (StoP) Project, comprising 1377 cases and 2470 controls, to explore the interaction among Hp infection and tobacco smoking, alcohol drinking, socioeconomic status (SES) and dietary salt intake on the risk of gastric cancer. We estimated summary odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) by multivariate unconditional logistic regression. The analysis showed no consistent interaction between Hp infection and cigarette smoking,

Abbreviations: Cag-A, cytotoxin-associated gene A; CI, confidence interval; GC, gastric cancer; Hp, *Helicobacter pylori*; OR, odds ratio; SES, socioeconomic status; StoP Project, Stomach cancer Pooling (StoP) Project.

while interaction was more than multiplicative for alcohol drinking (OR = 1.38, 95% CI: 1.07-1.77, *P*-interaction 0.02) and high intake of salt (OR = 2.62, 95% CI: 1.88-3.65, *P*-interaction = 0.04). The interaction with SES followed the multiplicative model ($P = 0.49$), resulting in a weakening among infected individuals of the protective effect of high SES among observed Hp-negative individuals. The interactions found were more pronounced in subjects with history of peptic ulcer. The interactions with Hp infection were stronger for cigarette smoking and dietary salt in the case of non-cardia cancer, and for alcohol and SES in the case of cardia cancer. No differences were found when stratifying for histologic type. This large-scale study aimed to quantify the interaction between Hp infection and other modifiable risk factors of gastric cancer revealed that the benefit of combined Hp eradication and lifestyle modification on gastric cancer prevention may be larger than commonly appreciated.

KEYWORDS

alcohol drinking, gastric cancer, helicobacter pylori, interaction, socioeconomic status, salt intake, tobacco smoking

1 | INTRODUCTION

Gastric cancer (GC) is causally associated with chronic infection with *Helicobacter pylori* (Hp),[1] but the bacterium alone is not sufficient to cause cancer in those who are infected. For this reason, investigation of other risk factors is needed. There are environmental risk factors other than Hp that are established carcinogens for the stomach, including tobacco smoking, high dietary salt intake, and low socioeconomic status (SES).[2] The interaction between Hp infection and these other environmental risk factors has not been adequately investigated.

In addition, the association between alcohol drinking and GC is weak and based on inconsistent results. In fact, the stomach is the only site of the gastrointestinal tract which is not an established target of alcohol carcinogenicity.[3] Starting from these observations, we hypothesized that gastric acidity and Hp infection, that modifies gastric pH,[4] may be implicated in alcohol-mediated effect. To date, the role of alcohol consumption has not yet been evaluated in large-scale epidemiology studies after stratification by Hp status neither has it been evaluated after controlling for potential confounding factors such as SES, smoking and dietary habits.

The primary aim of this analysis is to explore the interaction between Hp infection and other risk factors of GC, focusing in particular on tobacco smoking, alcohol drinking, low SES and salt consumption. Secondary aims include exploring these interactions after stratification by histology, subsite, Hp strain and history of peptic ulcer. To address these aims, we carried out a pooled analysis of data from studies included in the Stomach cancer Pooling (StoP) Project.

What's new?

Why do some *Helicobacter pylori* infections lead to gastric cancer, but not others? In this study, the authors investigated the interaction between *H. pylori* and other gastric cancer risk factors, including tobacco smoking, alcohol drinking, socioeconomic status (SES) and dietary salt. They combined seven case-control studies and performed pooled analysis to quantify the interaction between risk factors. They found that the associations with alcohol and salt were more than multiplicative. Smoking and SES, on the other hand, combined with *H. pylori* infection in a multiplicative fashion. Thus, lifestyle modifications could boost the benefit of eradicating *H. pylori*.

2 | METHODS

2.1 | Study population

StoP Project is a consortium of case-control and cohort studies collecting epidemiological data on GC.[5] Potentially relevant studies are identified through literature searches and principal investigators are invited to join the consortium and share original data, including demographic and clinical variables, as well as known and suspected risk factors for GC. For the purpose of data harmonization, the data were split into several sections (eg, sociodemographic characteristics, tobacco smoking, Hp infection, etc.) and a codebook was created for each topic. The data were then standardized for the variables included in each analysis of the consortium. Completeness and consistency of the variables were centrally checked. Implausible and inconsistent values as well as outliers were checked in collaboration with original investigators.

For the purpose of this analysis, we selected eight studies included in version 3.1 of the StoP database, with data on both Hp infection and the other risk factors of GC included in the analysis. We excluded one study because more than 10% of subjects had missing values for Hp infection. We therefore retained for this

TABLE 1 Selected characteristics of the studies included in the pooled analysis

Country	N ca/co	Prevalence of Hp infection ca/co (%)	Period of enrolment	Study population	Inclusion in secondary analyses[a]	Reference
China	206/415	35.3/31.2	2000	Population-based case-control study; Taixing City, Jiangsu Province, China; case group are newly diagnosed, controls are a random sample from the same local population; people living in Taixing for 10 years or more		6
Iran	217/394	80.7/71.2	2003-2005	Population-based case-control study; Ardabil, North-West of Iran; Ardabil residents for at least 5 years before diagnosis/interview; cases from Cancer Registry and active surveillance; controls randomly selected from Ardabil community	H, S	7
Mexico	248/478	71.9/76.0	2004-2005	Population-based case-control study, Mexico City, Mexico; cases from nine Mexico City hospitals; control group form a representative sample of residents of the same area	H, St	8
Mexico	234/468	80.6/80.8	1994-1996	Hospital-based case-control study performed in Mexico (Mexico City, Puebla and Yucatan regions); cases were identified from social security and government hospitals; hospital controls individually matched by age, sex and city of residence	H, U	9
Brazil	226/226	75.7/78.8	1991-1994	Hospital-based case-control study in São Paulo, Brazil; cases and controls were non-Japanese subjects from 13 collaborating hospitals except in one cancer hospital, whose controls from a neighboring public hospital	H, S, U	10
Brazil	93/186	63.4/68.3	1991-1994	Same design as Reference 9; cases and controls were of Japanese origin	H, S, U	11
Japan	153/303	82.4/55.0	1998-2002	Multicenter, hospital-based, case-control study; Nagano prefecture, Japan; cases and controls from four hospitals	S, St, U	12

Abbreviation: N ca/co, number of cases/controls.

[a]H, histologic type; S, subsite within the stomach; St, Hp strain; U, history of peptic ulcer.

analysis seven case-controls studies, including 1377 cases (885 men and 492 women) and 2470 controls (1570 men and 900 women). Specifically, we included data from one study from China,[6] one from Iran,[7] two from Mexico,[8,9] two from Brazil[10,11] and one from Japan.[12] Selected characteristics of each study are shown in Table 1. In addition to data on Hp status, we used information on age, sex, alcohol drinking, tobacco smoking, SES, salt consumption and history of peptic ulcer among cases and controls for each study involved. For GC cases, we also obtained data on site of the lesion within the stomach (cardia, noncardia excluding overlapping sites) and on histologic type (intestinal, diffuse). All Hp positive subjects were diagnosed through ELISA (enzyme-linked immunosorbent assay) and a subset of them were distinguished by strain (cytotoxin-associated gene A [Cag-A]+ or Cag-A−). The data had already been harmonized for previous analyses at the StoP Data Center at the University of Milan, Italy.[13-16] Detailed information about collection and harmonization of data in the StoP consortium is given elsewhere.[5]

2.2 | Statistical analysis

We generated four variables of interaction, combining Hp status (positive or negative) with each of the other risk factors considered: never/former/current tobacco smoking, never/ever alcohol drinking, low/intermediate/high socioeconomic status (based on study-specific adjusted indicators: income/school degree,[6] education,[7-11] occupation[12]); salt consumption was adjusted in the models using study-specific tertiles of intake for studies with continuous estimation of sodium intake, or as low/intermediate/high consumption for studies that collected ordinal information on salt use in the food frequency questionnaires.

Age was included in the regression models as categorical variable (<50, 50-59, 60-69 and >70 years old). We also applied multiple imputations for variables with up to 10% missing values, in order to increase the statistical power of the analysis (Hp infection status, tobacco smoking and alcohol drinking, salt intake).[17] We included in the regression models used for multiple imputation the same variables included in the logistic regression models used for the primary analysis (see below). In secondary analyses, we repeated the logistic regression models considering imputed values for both confounders and interaction terms.

The primary analysis included GC case/control status as outcome; secondary analyses were conducted according to site within the stomach, histologic types and presence of Cag-A protein. In addition, we considered the potential effect of peptic ulcer on the interaction between Hp infection and exposure to other risk factors. We therefore fitted regression models with GC as outcome and history of peptic ulcer as potential determinant, as well as models with peptic ulcer as outcome and Hp, cigarette smoking, alcohol drinking, SES and salt intake as determinants: the latter analysis was restricted to controls. We finally repeated the primary interaction analysis on GC risk after stratifying for history of peptic ulcer. We also repeated the analysis based on the design of the case-control studies, separating population-based studies[6-8] and hospital-based studies,[9-12] as well excluding three studies conducted in the 1990s.[9-11]

The main analytic strategy consisted of estimating overall odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) based on multivariate unconditional logistic regression (polytomous logistic regression for nonbinary outcomes such as tumor site and histology); models included terms for study, age, sex, as well as the variable for the interaction between Hp infection and each of the four risk factors, and the main effect variables for the other risk factors. To assess the departure of the joint effect of Hp infection and exposure the other risk factors from a multiplicative model of interaction,[18] we considered the statistical significance of a Wald global test for interaction.[19] In this test, we reversed the categories for SES to obtain positive OR.[20]

In addition, we used a two-stage modeling approach.[21] In the first stage, we assessed the association between GC and the interaction variables within each study by estimating the ORs and the corresponding 95% CIs, using multivariable unconditional logistic regression. The models included the same terms listed above, except center. In the second stage, summary (pooled) effect estimates were computed using a random-effects model, as a weighted average of the study-specific log(ORs) obtained in the first stage, using as weights the inverse of the sum of the study-specific log(OR) variances, as applicable, and the corresponding between-study variance components.[22] Heterogeneity between studies was quantified using the Q statistic.[23] Visual inspection of funnel plots and Egger's regression asymmetry test were used for assessment of publication bias.[24]

Besides the case-control analysis, we also conducted a case-only analysis in order to overcome the possible misclassification of Hp infection status. In fact, data on Hp status are characterized by low sensitivity and high specificity in cases, while misclassification may be lower in controls. This is an example of "reverse causation,"[25] in which the prevalence of a risk factor is modified by the presence of the outcome: in this case, the presence of GC may cause a decrease in the prevalence of Hp infection because of progressive mucosal damage leading to an inhospitable environment for Hp colonization.[26] The net result is an underestimate of the prevalence of infection among cancer cases and of the ORs due to Hp infection.

To further quantify this possible misclassification, we estimated the sensitivity of the study-specific measure of Hp infection among cases (assuming 100% specificity) by calculating the expected prevalence of Hp positivity among cases, while keeping the observed prevalence among controls, needed to obtain a crude OR for Hp equal to 2.4, as reported in meta-analysis of cohort studies.[27,28] We did this simulation for all the studies except the one from Japan,[12] in which the observed OR for Hp was higher than 2.4 suggesting that no misclassification of Hp infection was operating in that study.

The statistical analyses were performed with STATA MP/16[29]; specifically we used the commands *mpi* for multiple imputation, *logistic* and *mlogit* for logistic regression, *metan* for meta-analysis, *metabias* for publication bias and *testparm* for global test for interaction.

3 | RESULTS

Table 2 shows the distribution of cases and controls by study, sex, age and selected covariates in the study population. The number of cases and controls for whom data were imputed are shown in Supplementary Table 1. Overall, excluding those with missing data for Hp (174 subjects, 4.5%), 919 cases (70.2%) and 1565 controls (66.2%) were Hp positive. Among infected subjects with available data, 84.7% of cases (n = 420) and 79.4% of controls (n = 764) were colonized by a Cag-A positive strain. With respect to cancer site and histology, 79.0% of cases were noncardia GC and 51.1% belonged to the diffuse type.

3.1 | Primary analysis

Results of the primary analysis are reported in Table 3. The interaction between Hp and cigarette smoking was not consistent: the OR of GC in those with Hp infection and current smoking was 1.31 (95% CI: 1.00-1.73), while the corresponding OR was 1.87 (95% CI: 1.42-2.46) in former smokers. The global test for interaction was not statistically significant.

In the analysis of the interaction between Hp infection and alcohol drinking, the OR was significantly increased only among alcohol drinkers who were positive for Hp (OR = 1.38; 95% CI: 1.07-1.77); the *P*-value of the test for interaction was 0.02, which however was increased to 0.13 after applying multiple imputation.

The interaction between infection and SES showed an inverse trend with the latter variable: the lowest OR was found among those of high SES who were Hp negative (OR = 0.62; 95% CI: 0.43-0.88); the protective effect of high SES was partly offset by Hp

TABLE 2 Distribution of cases of GC and controls according to study center, sex, age and selected covariates[a]

	Cases, N (%)	Controls, N (%)
Total	1377 (100.0)	2470 (100.0)
Sex		
Male	885 (64.3)	1570 (63.6)
Female	492 (35.7)	900 (36.4)
Age (years)		
<50	247 (17.9)	484 (19.6)
50-59	342 (24.8)	646 (26.1)
60-69	499 (36.2)	795 (32.2)
>70	289 (21.0)	545 (22.1)
Helicobacter pylori (Hp)		
Negative	390 (29.8)	799 (33.8)
Positive	919 (70.2)	1565 (66.2)
Hp strain		
CagA −	76 (15.3)	198 (20.6)
CagA +	420 (84.7)	764 (79.4)
Cigarette smoking		
Never	688 (51.1)	1340 (55.1)
Former	391 (29.0)	517 (21.3)
Current	268 (19.9)	574 (23.6)
Alcohol drinking		
Never	868 (63.3)	1552 (62.9)
Ever	504 (36.7)	915 (37.1)
Socioeconomic status		
Low	606 (44.2)	942 (38.2)
Intermediate	498 (36.3)	971 (39.4)
High	267 (19.5)	551 (22.4)
Salt consumption		
Low	722 (59.7)	1464 (68.2)
Intermediate	327 (27.0)	522 (24.3)
High	171 (17.3)	162 (7.5)
History of peptic ulcer		
No	193 (28.1)	812 (69.3)
Yes, since at least 1 year	493 (71.9)	360 (30.7)
Gastric cancer site		
Cardia	161 (21.0)	NA
Noncardia	606 (79.0)	
Histological type		
Intestinal	445 (48.9)	NA
Diffuse	464 (51.1)	

Abbreviation: NA, not applicable.
[a]Numbers might not add to the totals because of missing values.

seropositivity (OR = 0.89; 95% CI: 0.66-1.21). The test for interaction, however, did not show a departure from the multiplicative model ($P = 0.49$).

The presence of Hp infection enhanced the risk of GC due to salt consumption, reaching an OR of 2.62 (95% CI: 1.88-3.65) among those with high intake and Hp seropositivity. The *P*-value of the global test for interaction was 0.04.

Table 3 also shows the results obtained after applying multiple imputations for each of the variables considered in the interaction terms and each confounder: they confirmed those obtained without the imputation.

The analysis of the role of Cag-A strain was limited by the small number of Hp positive cases and controls with available data. For this reason, while there was a clear association between Cag-A-positive strain and risk of GC (OR = 1.68, 95% CI: 1.25-2.25), the analysis of the interaction between Cag-A-positive Hp infection and the other risk factors did not provide useful information (not shown in detail).

3.2 | Stratified analyses

History of peptic ulcer was a strong risk factor for GC (OR = 38.6, 95% CI: 25.6-58.3). In an analysis among controls, risk of peptic ulcer was not associated with any of the covariates. Table 4 shows the results of the analysis of the interaction between Hp and the other risk factors in determining GC risk after stratifying study subject by history of peptic ulcer. The interactions detected in the main analysis were more pronounced in subjects with history of ulcer. For example, among those with peptic ulcer, the OR for former smoking and Hp positivity was 5.51 (95% CI: 2.79-10.9), and that for current smoking and Hp positivity was 6.97 (95% CI: 3.40-14.3). Similarly, the OR for high salt intake and Hp positivity was 6.00 (95% CI: 2.52-14.3). A seemingly conflicting result among drinkers negative for Hp infection with negative and positive history of peptic ulcer may be explained by chance. Other results among those without history of peptic ulcer were unremarkable.

The results of the analysis based on stomach subsites are reported in Supplementary Table 2. In general, they suggested a stronger interaction between Hp infection and cigarette smoking on noncardia than cardia neoplasm: in particular, the ORs of cardia GC for Hp infection were increased in all categories of smoking, while an increase in OR of noncardia GC was present in former smokers (OR = 1.78, 95% CI: 1.25-2.54) and current smokers (OR = 1.25, 95% CI: 0.86-1.82) but not in never smokers. With respect to the interaction between Hp infection and alcohol drinking, both agents appeared to have an association—but no interaction—with cardia GC, while for noncardia GC an increased OR was shown only when both agents were present. Both the effect of low SES among Hp negative subjects and that of Hp positivity in all SES categories were stronger for noncardia than for cardia GC. The increased risk for increasing salt intake and its interaction with Hp positivity was clear for noncardia cancer, while results for cardia cancer were unremarkable.

Results of the interaction analysis according to histologic type of GC are shown in Supplementary Table 3. There were weak associations for both intestinal and diffuse types. The effect of salt is the only noticeable, with more evidence on intestinal type than on diffuse type.

TABLE 3 Interaction between Hp and selected risk factors, without and with imputation of missing data

		No imputation		With imputation	
Variable of interaction		**Hp negative**	**Hp positive**	**Hp negative**	**Hp positive**
Never smokers	ca/co	204/428	438/852		
	OR	1.00	1.11	1.00	1.09
	95% CI	Ref.	0.88-1.39	Ref.	0.88-1.35
Former smokers	ca/co	100/158	278/341		
	OR	1.40	1.87	1.36	1.69
	95% CI	1.00-1.97	1.42-2.46	0.98-1.88	1.30-2.19
Current smokers	ca/co	73/203	186/346		
	OR	0.80	1.31	0.75	1.13
	95% CI	0.56-1.13	1.00-1.73	0.54-1.05	0.87-1.48
P-interaction			0.14		0.25
Never drinkers	ca/co	252/487	567/1004		
	OR	1.00	1.10	1.00	1.06
	95% CI	Ref.	0.90-1.35	Ref.	0.87-1.29
Ever drinkers	ca/co	133/310	352/560		
	OR	0.84	1.38	0.90	1.35
	95% CI	0.62-1.13	1.07-1.77	0.67-1.19	1.07-1.71
P-interaction			0.02		0.13
Low SES	ca/co	172/279	391/615		
	OR	1.00	1.13	1.00	1.05
	95% CI	Ref.	0.88-1.46	Ref.	0.82-1.33
Intermediate SES	ca/co	142/319	346/612		
	OR	0.71	0.95	0.70	0.88
	95% CI	0.53-0.96	0.73-1.24	0.53-0.94	0.69-1.14
High SES	ca/co	75/198	177/335		
	OR	0.62	0.89	0.61	0.88
	95% CI	0.43-0.88	0.66-1.21	0.43-0.86	0.66-1.17
P-interaction			0.49		0.24
Low salt intake	ca/co	190/425	499/1001		
	OR	1.00	1.07	1.00	1.00
	95% CI	Ref.	0.86-1.32	Ref.	0.82-1.23
Intermediate salt intake	ca/co	133/262	186/215		
	OR	1.36	2.27	1.26	2.04
	95% CI	0.99-1.87	1.71-3.00	0.93-1.70	1.57-2.64
High salt intake	ca/co	35/52	115/106		
	OR	1.62	2.62	1.58	2.54
	95% CI	1.01-2.62	1.88-3.65	0.99-2.52	1.84-3.50
P-interaction			0.04		0.01

Abbreviations: ca/co, number of cases/controls; CI, confidence interval; OR, odds ratio adjusted for study, sex, age (four categories), and the variables in the table (categorical); *P*-interaction, *P*-value of global test for interaction.

3.3 | Secondary analyses

The results of the interaction analysis based on the two-step meta-analytic approach are reported in Supplementary Table 4. Significant heterogeneity was detected in several meta-analyses. Overall, they were similar to those shown in Table 3, providing support to the data pooling approach. A modest difference involved the interaction between Hp infection and salt intake, which showed a stronger effect of salt intake among both Hp negative and Hp positive subjects. In particular, the meta-OR for high salt intake among Hp positive subjects was 2.98 (95% CI: 1.13-7.88).

TABLE 4 Interaction between Hp and selected risk factors, by history of peptic ulcer

		Negative history		Positive history	
Variable of interaction		**Hp negative**	**Hp positive**	**Hp negative**	**Hp positive**
Never smokers	ca/co	17/107	84/331	66/71	146/104
	OR	1.00	1.03	1.00	2.06
	95% CI	Ref.	0.47-2.24	Ref.	1.19-3.56
Former smokers	ca/co	15/45	38/161	30/34	132/55
	OR	1.77	1.06	1.59	5.51
	95% CI	0.58-5.36	0.43-2.59	0.69-3.67	2.79-10.9
Current smokers	ca/co	2/27	16/105	20/38	79/48
	OR	0.67	0.86	1.81	6.97
	95% CI	0.12-3.60	0.30-2.47	0.76-4.30	3.40-14.3
Never drinkers	ca/co	20/127	73/379	87/52	211/77
	OR	1.00	1.00	1.00	1.68
	95% CI	Ref.	0.48-2.05	Ref.	0.97-2.93
Ever drinkers	ca/co	15/54	68/227	29/93	156/134
	OR	1.62	1.18	0.42	1.87
	95% CI	0.52-4.99	0.51-2.75	0.20-0.85	1.01-3.44
Low SES	ca/co	11/46	37/184	58/36	142/82
	OR	1.00	0.83	1.00	1.47
	95% CI	Ref.	0.28-2.46	Ref.	0.78-2.76
Intermediate SES	ca/co	18/94	67/295	42/73	163/88
	OR	1.00	0.75	0.33	1.38
	95% CI	0.30-3.30	0.26-2.20	0.16-0.70	0.72-2.64
High SES	ca/co	5/39	34/125	16/35	60/40
	OR	0.62	0.99	0.32	1.15
	95% CI	0.13-3.07	0.30-3.21	0.12-0.81	0.53-2.47
Low salt intake	ca/co	17/119	60/367	81/90	248/133
	OR	1.00	0.95	1.00	2.33
	95% CI	Ref.	0.52-1.75	Ref.	1.44-3.77
Intermediate salt intake	ca/co	1/4	3/17	16/38	57/43
	OR	1.55	0.97	1.28	4.41
	95% CI	0.13-18.2	0.21-4.45	0.58-2.83	2.37-8.22
High salt intake	ca/co	1/4	2/15	9/16	29/13
	OR	3.45	1.18	1.33	6.00
	95% CI	0.32-37.6	0.23-6.14	0.46-3.85	2.52-14.3

Abbreviations: ca/co, number of cases/controls; CI, confidence interval; OR, odds ratio adjusted for study, sex, age (four categories), and the variables in the table (categorical).

In the analysis stratified by study design, the interactions between Hp infection and alcohol drinking and salt intake were more evident in population-based than in hospital-based studies. Similar patterns of interactions were obtained after excluding studies conducted in the 1990s (not shown in detail).

The results of the case-only analysis, both without and with multiple imputations, were compatible with the multiplicative model of interaction (Supplementary Table 5).

The results of the simulation we conducted on the magnitude of misclassification of Hp infection status among cases resulted in estimates of sensitivity of the measure of Hp status equal to 64% for the study from China,[6] 94% for the study from Iran,[7] 90% for the combined studies from Mexico[8] and 83% for the combined studies from Brazil.[9,10]

4 | DISCUSSION

This large pooled analysis offers a unique opportunity to investigate the interaction between different risk factors of GC, with emphasis on

Hp infection. Alcohol is not a major stomach carcinogen.[2,14] We wondered whether other concomitant factors, and in particular Hp infection, could limit an effect of alcohol on the gastric mucosa, or modify its mechanism of damage. We therefore devised a multivariate analysis on the interaction between these two agents, and expanded it to other known risk factors of GC, tobacco smoking, SES and salt intake. Our main result is an interaction, beyond the multiplicative model, between Hp infection and both alcohol drinking and high salt intake. Results on tobacco smoking and SES suggested no departure from a multiplicative model of interaction, although the interpretation of the former requires caution, as the resulting pattern of risk was not linear across smoking categories. The results were stronger in individuals with history of peptic ulcer, even if the pattern of risk was unchanged. In addition, the strong association with ulcer may be due in part to reverse causation, that is, ulcer acting as an early manifestation of GC. The analysis stratified by cancer subsite within the stomach suggested only slight differences between cardia and noncardia cancer. This was mainly due to the limited number of cardia cancer cases. Still, an interaction between Hp infection and both tobacco smoking and alcohol drinking emerged for noncardia GC. No remarkable interaction was derived from the stratification by histologic type. The internal validity of the results was supported by several sensitivity analyses: imputation of missing values, two-stage meta-analysis of results of individual studies and case-only approach.

With the exception of one analysis of the interaction between genetic variants and Hp infection and alcohol drinking,[30] these results are based on small numbers and are not able to distinguish between the different interaction models. Moreover, the approach to estimate interaction is different between studies, hampering an effective comparison. Our analysis represents therefore the first attempt to study the interaction between Hp infection and other risk factors of GC with a large sample, and according to well-defined interaction models. We selected the multiplicative model of interaction because in our opinion it is the most appropriate to characterize the contribution of multiple risk factors to the process of carcinogenesis. However, in a secondary analysis based on the additive model, the results showed an interaction greater than additive (Supplementary Table 6).

Mechanisms underlying the interaction between Hp and lifestyle risk factors are not fully explained, although there is some evidence that behavioral and environmental risk factors could become indirectly involved in gastric carcinogenesis by influencing gut microbiota composition through the alteration of mucus layer.[31] In particular, there might be a causal and bidirectional relationship between impaired gastric acid secretion and dysbiosis: gastric atrophy is characterized by lower acidity that causes dysbiosis, which in turn predisposes to preneoplastic lesions development, through higher production of N-nitroso compounds.[31]

Hp colonization is supposed to start in early childhood,[32] leading, if left untreated, to chronic gastritis. The pathogenic action of Hp is carried out through different pathways, involving enzymes and toxins secretion. In particular the bacterium releases the enzyme urease, which hydrolyses urea with the release of ammonia, compromising gastric defenses through pH neutralization and the damage of the mucus and the epithelial cells. Hp is also characterized by some virulence factors, as blood-antigen binding protein A, outer inflammatory protein A, Cag-A and vacuolating cytotoxin.[33] The one most strongly related to GC is Cag-A, positioned in the *H pylori cag* pathogenicity island encoding a Type IV secretion system that mediate the translocation of bacterial agents into cells. This toxin leads to the direct damage of gastric mucosa through the disruption of tight junction, the loss of cell and the destabilization of the E-cadherin-β-catenin complex. Moreover, it induces the activation of NF-κB. Hp appears also to be able to induce genes mutation and aberrant DNA methylation.[34] Other pathogenetic mechanisms are expressed through alteration of physiological gastric secretion, resulting in high levels of gastrin and pepsinogen and low levels of somatostatin, induction of autoantibodies production, inflammatory cascade activation (NF-κB upregulation leading to increased synthesis of IL-18, IL-8 and chemokines) and release of proinflammatory cytokines (TNF-α, IL-1 and INF-γ) resulting in neutrophils and monocytes infiltration of gastric wall, and altered proliferative-apoptotic balance.[35] An alteration of the immune response may also be involved, since the bacterium induces cell-mediated immunity, and a correlation between Th17 and IFN-γ expression have been associated to ulcer occurrence.[33]

A relationship between tobacco smoking and GC is established. In particular, there is a strong association with cardia cancer and a higher risk among men and for intestinal type.[36] This has been confirmed by the StoP Project.[15] Smoking can inhibit gastric cell renewal and ulcer healing by reducing EGF synthesis and alters stomach equilibrium by increasing acid secretion and reducing bicarbonate concentration.[37] In addition, its proinflammatory effect and the production of DNA adducts play a role on GC development. The concomitant presence of Hp and tobacco smoking can amplify and maintain these processes.

An increased risk of GC has been identified for high intake of alcohol.[38] Relying on self-reported information on alcohol drinking and lack of stratification by Hp status may result in underestimate of the association.[39] The StoP consortium detected an association between alcohol intake and GC regardless of Hp infection (OR = 1.52, 95% CI: 1.16-2.00 among infected; OR = 1.69, 95% CI: 0.95-3.01 among noninfected).[14] Several mechanisms have been proposed to explain the carcinogenicity of alcohol,[40] but a possible carcinogenic role on stomach mucosa is probably due to acetaldehyde, the primary metabolite of ethanol, that can damage DNA. Our study extended the results of the previous analysis in the StoP consortium[14] and detected a positive interaction between Hp infection and alcohol drinking, that is, the presence of one factor potentiated the effect of the other. Although *P* values for interaction were not formally significant in the analysis after multiple imputation, the pattern of these results were consistent with those of the main analysis that were significant and, in any case, deserve more weight. A possible explanation is that the damage to the gastric mucosa caused by the bacterium facilitates the genotoxic effect of acetaldehyde.

With regard to SES, a strong relationship between low education or occupation categories and GC risk has been found in systematic-reviews and meta-analyses,[41,42] as well as in a previous analysis of

data in the StoP consortium.[43] This inverse relation with SES is explained by concomitant factors, such as poor dietary habits, cigarette smoking, heavy alcohol drinking, less knowledge of health and cancer risk factors and less access to public sanitation.[44] In addition, a higher prevalence of Hp infection has been detected among low SES individuals.[45] In this respect, the lack of an interaction between Hp infection and SES can be explained by the fact that the effect of SES reflects, at least in part, that of Hp infection.

Salt is a risk factor of GC,[46] with possible mechanisms related to its toxic role on human cells' physiology, including a possible synergic action with nitrite.[47] A synergy has been described also with Hp infection: animal models showed a higher level of antibodies against Hp, inflammatory cells infiltration, COX-2 and iNOS upregulation when infection occurs in the presence of high-salt diet.[48] Other potential mechanisms involve potentiation of Hp colonization, Hp-mediated damage and Cag-A expression, mucous viscosity impairment, increased cell proliferation through enhanced inflammatory response and damage progression linked to induced hypergastrinemia.[49] Our results on a positive interaction between Hp infection and high salt intake are consistent with these experimental data. Higher salt intake has been described among low SES groups, and salt reduction has been proposed as preventive strategy against GC.[50] A recent simulation study from England has shown that a reduction in salt consumption from around 9 to 7 g/d would prevent nearly 5000 new GC cases, and 2000 deaths.[51]

Our study confirms the notion that history of peptic ulcer is strongly associated to GC[52] and suggested that the interaction between Hp infection and other known risk factors of GC is detectable among subjects with such history. It remains uncertain if ulcer is part of the pathogenetic pathway of the neoplasm, exerting a mediating effect on the interaction between Hp and other risk factors, or it is a correlated diagnosis, that is, reverse causation. Additional results in populations with a more precise definition on ulcer would be needed to clarify these issues.

Our study is based on a large and diverse population resulting from the inclusion in the StoP consortium of studies from different centers and countries, providing adequate statistical power of the interaction analysis. We also conducted several sensitivity analyses to assess the robustness of the results and addressed the issue of differential misclassification of Hp infection status by estimating the percentage of Hp false negatives among cases through simulation.

Besides these strengths, our study presents some limitations. The retrospective case-control design of participating studies may result in information bias, in particular with respect to tobacco smoking, alcohol drinking and salt intake. However, the fact that our results for these risk factors were consistent with previous literature corroborates the quality of the underlying data. In addition, cases of GC positive for Hp might lose the infection and result negative. Furthermore, changes in lifestyle habits might occur after the diagnosis of GC. This is particularly relevant to three studies conducted in the 1990s[9-11] in which the quality of information on Hp infection may be more limited. Anyway, a sensitivity analysis excluding these studies did not suggest that they overly influenced the results.

The source of controls differs between studies. In particular, four out of seven studies included in the analysis were hospital-based,[9-12] potentially resulting in selection bias towards the null, especially when considering tobacco smoking and alcohol drinking, two habits with higher prevalence among hospital patients than in general population.[53] A similar bias might have occurred also for Hp infection status. There were some differences between hospital-based and population-based studies, with a suggestion of stronger interacting effects among the latter, although the comparison was hampered by the small number of subjects in some strata. In general, we think results of population-based studies should be given more weight.

Similarly, we had no information on ulcer etiology or in its surgical treatment. Also, being able to date history of ulcer compared to the time of cancer diagnosis would help to understand whether it might represent an early malignant lesion.[54]

A further limitation was the relatively large proportion of missing values for the main covariates of interest: we addressed this problem by performing multiple imputations, and the results based on the imputed values confirmed those of the main analysis. For some variables, including site of origin of the cancer and Cag-A status, the relatively high proportion of subjects with missing data hampered the precision of the analysis.

While keeping these limitations into account, our results have clinical and public health implications. First, they suggest that an intervention on these modifiable risk factors can be effective in reducing GC incidence. In particular, the perspective of Hp eradication gains value, considering that eliminating the infection would also scale back the risk of cancer due to alcohol drinking or high-salt diet, for which an interaction effect emerged. This should be taken into account also with regard to low SES, a characteristic that concerns a wide part of population, in particular in low- and middle-income countries, where Hp infection is more diffuse. Another consequence is that our findings help quantifying what already represented a general health recommendation: Hp positive people should eradicate Hp, and modify their behavioral factors entailing an increased risk of GC, including cigarette smoking, alcohol drinking and high-salt diet.

Our study is the first large-scale effort to quantify the interaction between Hp infection and other modifiable risk factors in determining GC risk. They need to be replicated in other studies with prospective assessment of Hp infection, and history of past eradication. Because of limitations in the available studies, we likely underestimated the magnitude of these interactions. If confirmed, our results would imply that the benefit of combined Hp eradication and lifestyle modification on GC prevention is larger than commonly appreciated.

ACKNOWLEDGMENTS

This study was supported by the Associazione Italiana per la Ricerca sul Cancro (AIRC), Project no. 21378 (Investigator Grant), and by the Italian League for the Fight Against Cancer (LILT). The authors thank the European Cancer Prevention (ECP) Organization for providing support for the StoP meetings.

CONFLICT OF INTEREST

The authors declared no competing interests in any means or any conflicting financial interests.

ETHICS STATEMENT

The study was based on secondary use of de-identified data and was considered exempt by the International Review Board of the University of Bologna.

DATA AVAILABILITY STATEMENT

Data can be obtained from the StoP Project according to the provisions setup in the Consortium (stop-project.org). Further information is available from the corresponding author upon request.

ORCID

Giulia Collatuzzo https://orcid.org/0000-0002-2309-7365
Claudio Pelucchi https://orcid.org/0000-0003-1425-8945
Eva Negri https://orcid.org/0000-0001-9712-8526
Lina Mu https://orcid.org/0000-0003-4799-7517
Zuo-Feng Zhang https://orcid.org/0000-0002-4669-3995
Carlo La Vecchia https://orcid.org/0000-0003-1441-897X

REFERENCES

1. International Agency for Research on Cancer. Infection with *Helicobacter pylori*. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 61, Schistosomes, Liver Flukes and Helicobacter pylori*. Lyon, France: IARC; 1994:177-240.
2. Yusefi AR, Bagheri Lankarani K, Bastani P, Radinmanesh M, Kavosi Z. Risk factors for gastric cancer: a systematic review. *Asian Pac J Cancer Prev*. 2018;19:591-603.
3. International Agency for Research on Cancer. Consumption of alcoholic beverages. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 96, Alcohol Consumption and Ethyl Carbamate*. Lyon, France: IARC; 2010:41-1286.
4. Malfertheiner P. The intriguing relationship of *Helicobacter pylori* infection and acid secretion in peptic ulcer disease and gastric cancer. *Dig Dis*. 2011;29:459-464.
5. Pelucchi C, Lunet N, Boccia S, et al. The stomach cancer pooling (StoP) project: study design and presentation. *Eur J Cancer Prev*. 2015;24:16-23.
6. Mu LN, Lu QY, Yu SZ, et al. Green tea drinking and multigenetic index on the risk of stomach cancer in a Chinese population. *Int J Cancer*. 2005;116:972-983.
7. Pourfarzi F, Whelan A, Kaldor J, Malekzadeh R. The role of diet and other environmental factors in the causation of gastric cancer in Iran—a population based study. *Int J Cancer*. 2009;125:1953-1960.
8. Hernández-Ramírez RU, Galván-Portillo MV, Ward MH, et al. Dietary intake of polyphenols, nitrate and nitrite and gastric cancer risk in Mexico City. *Int J Cancer*. 2009;125:1424-1430.
9. López-Carrillo L, López-Cervantes M, Robles-Díaz G, et al. Capsaicin consumption, *Helicobacter pylori* positivity and gastric cancer in Mexico. *Int J Cancer*. 2003;106:277-282.
10. Nishimoto IN, Hamada GS, Kowalski LP, et al. Risk factors for stomach cancer in Brazil (I): a case-control study among non-Japanese Brazilians in São Paulo. *Jpn J Clin Oncol*. 2002;32:277-283.
11. Hamada GS, Kowalski LP, Nishimoto IN, et al. Risk factors for stomach cancer in Brazil (II): a case-control study among Japanese Brazilians in São Paulo. *Jpn J Clin Oncol*. 2002;32:284-290.
12. Machida-Montani A, Sasazuki S, Inoue M, et al. Association of *Helicobacter pylori* infection and environmental factors in non-cardia gastric cancer in Japan. *Gastric Cancer*. 2004;7:46-53.
13. Ferro A, Morais S, Pelucchi C, et al. Sex differences in the prevalence of *Helicobacter pylori* infection: an individual participant data pooled analysis (StoP Project). *Eur J Gastroenterol Hepatol*. 2019;31:593-598.
14. Rota M, Pelucchi C, Bertuccio P, et al. Alcohol consumption and gastric cancer risk—a pooled analysis within the StoP project consortium. *Int J Cancer*. 2017;141:1950-1962.
15. Praud D, Rota M, Pelucchi C, et al. Cigarette smoking and gastric cancer in the stomach cancer pooling (StoP) project. *Eur J Cancer Prev*. 2018;27:124-133.
16. Rota M, Alicandro G, Pelucchi C, et al. Education and gastric cancer risk - an individual participant data meta-analysis in the StoP project consortium. *Int J Cancer*. 2020;146:671-681.
17. Snijders TAB, Bosker RJ. *Multilevel Analysis: An Introduction to Basic and Advanced Multilevel Modeling*. 2nd ed. London, UK: Sage; 2012.
18. Rothman KJ. Measuring interactions. In: Rothman KJ, ed. *Epidemiology: An Introduction*. Oxford: Oxford University Press; 2002:168-180.
19. Judge GG, Griffiths WE, Hill RC, Lütkepohl H, Lee TC. *The Theory and Practice of Econometrics*. 2nd ed. New York, NY: Wiley; 1985.
20. Richardson DB, Kaufman JS. Estimation of the relative excess risk due to interaction and associated confidence bounds. *Am J Epidemiol*. 2009;169:756-760.
21. Smith-Warner SA, Spiegelman D, Ritz J, et al. Methods for pooling results of epidemiologic studies: the pooling project of prospective studies of diet and cancer. *Am J Epidemiol*. 2006;163:1053-1064.
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
24. Egger M, Davey-Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-634.
25. Sattar N, Preiss D. Reverse causality in cardiovascular epidemiological research: more common than imagined? *Circulation*. 2017;135:2369-2372.
26. Peleteiro B, Lunet N, Barros R, La Vecchia C, Barros H. Factors contributing to the underestimation of *Helicobacter pylori*-associated gastric cancer risk in a high-prevalence population. *Cancer Causes Control*. 2010;21:1257-1264.
27. Huang JQ, Sridhar S, Chen Y, Hunt RH. Meta-analysis of the relationship between *Helicobacter pylori* seropositivity and gastric cancer. *Gastroenterology*. 1998;114:1169-1179.
28. Helicobacter and Cancer Collaborative Group. Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut*. 2001;49:347-353.
29. StataCorp. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC; 2019.
30. Cai M, Dai S, Chen W, et al. Environmental factors, seven GWAS-identified susceptibility loci, and risk of gastric cancer and its precursors in a Chinese population. *Cancer Med*. 2017;6:708-720.
31. Capurso G, Lahner E. The interaction between smoking, alcohol and the gut microbiome. *Best Pract Res Clin Gastroenterol*. 2017;31:579-588.
32. Malaty HM, El-Kasabany A, Graham DY, et al. Age at acquisition of *Helicobacter pylori* infection: a follow-up study from infancy to adulthood. *Lancet*. 2002;359:931-935.
33. Bartpho TS, Wattanawongdon W, Tongtawee T, Paoin C, Kangwantas K, Dechsukhum C. Precancerous gastric lesions with *Helicobacter pylori vacA* $^{+}$/*babA2* $^{+}$/*oipA* $^{+}$ genotype increase the risk of gastric cancer. *Biomed Res Int*. 2020;2020:7243029.

34. Chiba T, Marusawa H, Seno H, Watanabe N. Mechanism for gastric cancer development by *Helicobacter pylori* infection. *J Gastroenterol Hepatol*. 2008;23:1175-1181.
35. Basset C, Holton J, Vaira D. Helicobacter: a paradigm shift in peptic ulcer disease and more? *Sci Prog*. 2002;85:13-31.
36. Nomura AM, Wilkens LR, Henderson BE, Epplein M, Kolonel LN. The association of cigarette smoking with gastric cancer: the multiethnic cohort study. *Cancer Causes Control*. 2012;23:51-58.
37. Li LF, Chan RL, Lu L, et al. Cigarette smoking and gastrointestinal diseases: the causal relationship and underlying molecular mechanisms. *Int J Mol Med*. 2014;34:372-380.
38. Wang PL, Xiao FT, Gong BC, Liu FN. Alcohol drinking and gastric cancer risk: a meta-analysis of observational studies. *Oncotarget*. 2017;8:99013-99023.
39. Wang S, Freedman ND, Loftfield E, Hua X, Abnet CC. Alcohol consumption and risk of gastric cardia adenocarcinoma and gastric noncardia adenocarcinoma: a 16-year prospective analysis from the NIH-AARP diet and health cohort. *Int J Cancer*. 2018;143:2749-2757.
40. Boffetta P, Hashibe M. Alcohol and cancer. *Lancet Oncol*. 2006;7:149-156.
41. Uthman OA, Jadidi E, Moradi T. Socioeconomic position and incidence of gastric cancer: a systematic review and meta-analysis. *J Epidemiol Community Health*. 2013;67:854-860.
42. Vohra J, Marmot MG, Bauld L, Hiatt RA. Socioeconomic position in childhood and cancer in adulthood: a rapid-review. *J Epidemiol Community Health*. 2016;70:629-634.
43. Rota M, Alicandro G, Pelucchi C, et al. Education and gastric cancer risk—an individual participant data meta-analysis in the StoP project consortium. *Int J Cancer*. 2020;146:671-681.
44. Lee K, Lim HT, Hwang SS, Chae DW, Park SM. Socio-economic disparities in behavioural risk factors for cancer and use of cancer screening services in Korean adults aged 30 years and older: the Third Korean National Health and Nutrition Examination Survey, 2005 (KNHANES III). *Public Health*. 2010;124:698-704. Erratum in: Public Health 2011;125:243.
45. Nouraie M, Latifi-Navid S, Rezvan H, et al. Childhood hygienic practice and family education status determine the prevalence of *Helicobacter pylori* infection in Iran. *Helicobacter*. 2009;14:40-46.
46. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. *Lancet*. 2020;396:635-648.
47. La Vecchia C, Negri E, Franceschi S, Decarli A. Case-control study on influence of methionine, nitrite, and salt on gastric carcinogenesis in northern Italy. *Nutr Cancer*. 1997;27:65-68.
48. Toyoda T, Tsukamoto T, Hirano N, et al. Synergistic upregulation of inducible nitric oxide synthase and cyclooxygenase-2 in gastric mucosa of Mongolian gerbils by a high-salt diet and *Helicobacter pylori* infection. *Histol Histopathol*. 2008;23:593-599.
49. Wang XQ, Terry PD, Yan H. Review of salt consumption and stomach cancer risk: epidemiological and biological evidence. *World J Gastroenterol*. 2009;15:2204-2213.
50. Faeh R. Added salt and cancer mortality: confounding by smoking. *Epidemiology*. 2014;25:615-616.
51. Kypridemos C, Guzman-Castillo M, Hyseni L, et al. Estimated reductions in cardiovascular and gastric cancer disease burden through salt policies in England: an IMPACTNCD microsimulation study. *BMJ Open*. 2017;7:e013791.
52. Bahmanyar S, Ye W, Dickman PW, Nyrén O. Long-term risk of gastric cancer by subsite in operated and unoperated patients hospitalized for peptic ulcer. *Am J Gastroenterol*. 2007;102:1185-1191.
53. Rothman KJ, Greenland S, Lash TL. Case-control studies. In: Rothman KJ, Greenland S, Lash T, eds. *Modern Epidemiology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:111-127.
54. Hwang JJ, Lee DH, Lee AR, et al. Characteristics of gastric cancer in peptic ulcer patients with *Helicobacter pylori* infection. *World J Gastroenterol*. 2015;21:4954-4960.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Collatuzzo G, Pelucchi C, Negri E, et al. Exploring the interactions between Helicobacter pylori (Hp) infection and other risk factors of gastric cancer: A pooled analysis in the Stomach cancer Pooling (StoP) Project. *Int. J. Cancer*. 2021;149(6):1228–1238. https://doi.org/10.1002/ijc.33678