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Association between autoimmune gastritis and gastric cancer adjusted for Helicobacter pylori infection: A systematic review and meta-analysis

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TITLE PAGE

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selection, and data extraction; Urrego-Díaz JA and Niño S conducted the statistical analysis; Urrego-Díaz JA, Frías-Ordóñez JS, and Otero-Regino W drafted the manuscript; Portillo-Miño JD, Marulanda-Fernández H, Otero-Parra L, Otero-Ramos E, Riquelme A, Lenti MV, and Shah S critically revised the manuscript and provided intellectual input. All authors approved the final version of the manuscript.

ABSTRACT

Background: The association between autoimmune gastritis and gastric adenocarcinoma remains controversial, and Helicobacter pylori infection is a major potential confounder.

Aims: To evaluate the association between autoimmune gastritis and gastric adenocarcinoma after controlling for *H. pylori* infection.

Methods: PubMed, Embase and Scopus were searched from inception to 13 April 2025 for observational studies reporting autoimmune gastritis, H. pylori infection and gastric adenocarcinoma. Data were synthesised using random-effects meta-analysis, subgroup and adjusted analyses by *H. pylori* status, and a multilevel arm-based logistic regression model when compatible study-specific estimates were unavailable. Study quality was assessed using Joanna Briggs Institute tools.

Results: Twenty-one studies were included, although only four contributed to conventional meta-analysis. After adjustment for *H. pylori*, no significant association between autoimmune gastritis and gastric adenocarcinoma was observed (OR = 1.18, 95% CI 0.61–2.26; I^2 = 86%). Subgroup analyses were also non-significant. However, a multilevel model including nine studies showed a weak but significant association independent of *H. pylori* (OR = 1.27, 95% CI 1.02–1.57). Among *H. pylori*-negative patients with autoimmune gastritis, gastric adenocarcinoma incidence reached 98.4 per 100,000 person-years.

Conclusions: Autoimmune gastritis may be modestly associated with gastric adenocarcinoma after adjustment for *H. pylori* status. The association observed in the multilevel arm-based model, together with the higher-than-expected gastric adenocarcinoma incidence reported in longitudinal autoimmune gastritis cohorts, is compatible with a possible independent contribution of autoimmune gastritis to gastric carcinogenesis. These findings should be considered hypothesis-generating given the substantial heterogeneity, potential exposure misclassification, and residual confounding.

PROSPERO registration: CRD420251275536

KEYWORDS

Gastric cancer; Autoimmune gastritis; Helicobacter pylori; Atrophic gastritis; Meta-analysis

INTRODUCTION

Globally, gastric cancer (GC) is the fifth leading cause of both cancer incidence and cancer-related mortality [1,2]. Its incidence is higher in Asia, South America and Eastern Europe owing to both genetic and environmental factors [3]. Diagnosis is frequently delayed, often resulting in a poor prognosis [3]. Histologically, GC has traditionally been classified into intestinal and diffuse types according to the Lauren classification [4]. The intestinal subtype is more common and is associated with a better prognosis [5,6]. Progression to this subtype involves a series of genetic and epigenetic alterations [7] that proceed sequentially from chronic gastritis to chronic atrophic gastritis (CAG), gastric intestinal metaplasia (GIM), dysplasia and gastric adenocarcinoma, a stepwise process known as the Correa cascade [8]. The principal established risk factor for GC is Helicobacter pylori infection, which has been classified as a Group 1 carcinogen by the World Health Organization [9,10]. This bacterium is estimated to be responsible for 75–85% of GC, making it the second leading cause of cancer worldwide, surpassed only by smoking [10,11]. Other recognised risk factors for GC include Epstein–Barr

virus infection, high salt intake, smoking, a family history of GC, alcohol consumption and socioeconomic factors [3,12,13].

Autoimmune gastritis (AIG) is characterised by immune-mediated destruction of parietal cells and subsequent atrophy of the oxyntic mucosa, involving the gastric fundus and corpus. It leads to benign, indolent type 1 gastric neuroendocrine tumours (NETs) as a result of hypergastrinaemia induced by reduced hydrochloric acid secretion [14,15]. However, there is ongoing controversy as to whether AIG per se can cause GC or whether Helicobacter pylori infection is primarily responsible for this outcome [16-23]. Some studies have suggested that AIG is associated with an increased risk of GC [18-21], whereas others have not [22,23]. Both groups of studies have important limitations and potential biases that have fuelled substantial debate as to whether AIG may also cause intestinal-type gastric adenocarcinoma independently of H. pylori infection [17,24]. In addition, up to 30% of patients infected with H. pylori have been reported to have anti-parietal cell antibodies (APC), which decline following eradication of the infection [25]. Two recent systematic reviews have demonstrated a positive association between H. pylori infection and AIG [26,27], and in one of these, elevated titres of anti-intrinsic factor antibodies (AIF) and APC were also found in infected patients, together with reductions in autoantibody titres and improvements in histological findings after bacterial eradication [26].

In this context, we aimed to conduct a systematic review and meta-analysis to examine the association between AIG and GC independently of Helicobacter pylori infection status.

METHODS

Protocol and Search Strategy

We conducted a systematic review using search strategies in PubMed (all fields), Embase (broad search), Scopus (TITLE–ABS–KEY) and BASE (all fields). The strategy combined database-specific terms for "*Helicobacter pylori*", "gastritis", "autoimmune" and "gastric

cancer" with study design filters, using Boolean operators (AND/OR) (**Table S1; Supplementary material**). The study was registered in PROSPERO (CRD420251275536). The search covered all records from database inception to 13 April 2025 and was restricted to articles published in English or Spanish. Reporting was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Inclusion criteria

Observational studies that simultaneously reported the presence or absence of GC, *Helicobacter pylori* infection and AIG were included. AIG had to be diagnosed by biopsy and/or by the presence of APC or AIF, whereas *H. pylori* infection had to be diagnosed by gastric biopsy, urea breath test, faecal antigen test or serology. Studies conducted in paediatric populations and studies using designs other than cohort, case–control, cross-sectional or case-series studies were excluded. The full list of inclusion and exclusion criteria is provided in the Supplementary material.

To determine the population type to be analysed, two characteristics were identified for each study: (1) the study design (case series, cross-sectional, case–control or cohort); and (2) the type of population relevant to the statistical analyses. A cross-sectional population was defined as one in which exposure to H. pylori and AIG and the outcome of GC were assessed at the same time. A longitudinal population was defined as one in which exposure status was known and participants were followed to determine the development of GC. A case–control population was defined as one in which cases with GC and controls without GC were identified and exposure to AIG was assessed retrospectively.

Selection of studies

After the removal of duplicate records and articles published in languages other than English or Spanish, two researchers (JAU and JSFO) independently screened titles and abstracts to identify studies for full-text review. The same two researchers then assessed the full texts of

the selected articles to confirm eligibility and to exclude those that were unavailable. Any discrepancies were resolved through joint review and discussion. If disagreement persisted, a third researcher (SN) was consulted.

Study Quality

For the quality assessment of the included studies, two researchers (JAU and JSFO) independently applied the Joanna Briggs Institute (JBI) Critical Appraisal Tools, with disagreements resolved through article review and discussion. These tools provide a transparent and reproducible approach based on structured checklists comprising eight questions for cross-sectional studies, ten questions for case–control and case-series studies, and eleven questions for cohort studies. Each item was rated using the mutually exclusive categories “Yes”, “No”, “Not clear” or “Not applicable”. By consensus among the authors, studies with “No” or “Not clear” responses to fewer than two items, two to three items, or more than three items were classified as having high, moderate or low overall methodological quality, respectively. Individual item responses were also reported to enhance transparency.

Data Extraction

Two researchers (JAU and JSFO) independently extracted data from the selected studies using a data extraction form developed for this purpose in Microsoft Excel (Microsoft, Redmond, WA, USA). For all studies, general information was collected, including country, year of publication, study design, years of data collection, sample size and study population characteristics (including median age, sex and hospital-based versus community-based setting), diagnostic methods for *Helicobacter pylori* and AIG, tumour histology according to the Lauren classification, and the study design relevant to the objectives of the systematic review (case–control, longitudinal or cross-sectional).

In addition, population-specific data were extracted for each relevant study type. For longitudinal populations, the number of patients who developed GC was obtained for each

stratum defined by combinations of AIG (positive or negative) and *H. pylori* (positive or negative) status, together with the corresponding follow-up times. For case–control populations, the number of patients with a history of AIG was obtained for each stratum defined by combinations of GC status (positive or negative) and *H. pylori* status. For cross-sectional populations, the number of patients with GC was extracted for each stratum defined by combinations of AIG (positive or negative) and *H. pylori* status.

Results synthesis

All studies with relevant longitudinal populations and seven studies with case–control populations lacked sufficient information for inclusion in either the conventional meta-analyses or the mixed logistic regression model. These studies were therefore synthesised narratively. The specific reasons for exclusion are presented in Table S2. Overall, studies were excluded from quantitative synthesis because they did not provide sufficient data to estimate study-specific measures of association and lacked the information required to construct both AIG-positive and AIG-negative arms within at least one *H. pylori* stratum.

Statistical analysis

The findings were initially summarised using descriptive statistics, with absolute or relative frequencies for categorical variables and medians with ranges for continuous variables, because continuous variables were non-normally distributed according to the Shapiro–Wilk test.

Odds ratios (ORs) were used as the measure of association, as only cross-sectional and case–control studies provided sufficient information to obtain a study-specific effect estimate. Owing to the absence of a control group in all longitudinal studies, it was not possible to calculate a measure of association for this population.

For studies in which an individual OR could be estimated, an initial meta-analysis was conducted without stratification by *Helicobacter pylori* status. Subsequently, to assess the role

of *H. pylori* in this potential association, two approaches were applied: (1) subgroup meta-analysis according to *H. pylori* infection status; and (2) meta-analysis of individual ORs adjusted for *H. pylori*. For the latter, ORs were estimated for each study using logistic regression, with *H. pylori* infection included as an adjustment covariate. All conventional meta-analyses were performed using random-effects models, and forest plots were used to present the results. Statistical heterogeneity was assessed using the I^2 statistic. Because only four studies provided compatible study-specific estimates, conventional pooled analyses were considered exploratory, particularly when substantial heterogeneity was present.

In addition, to include studies without extractable study-specific odds ratios, we fitted an exploratory mixed-effects arm-based logistic regression model using aggregate arm-level data. The number of GC events in each arm was modelled as a binomial outcome, with the number of participants as the denominator and a logit link function. Arms were defined according to AIG and *H. pylori* status, which were included as fixed effects, while a study-specific random intercept accounted for clustering of arms within studies and between-study differences in baseline GC risk. The model was specified as $\text{logit}(p_{ij}) = \beta_0 + u_j + \beta_1 \text{AIG}_{ij} + \beta_2 \text{HP}_{ij}$, where p_{ij} denotes the probability of GC in arm (i) of study (j), u_j is the study-specific random intercept and β_1 and β_2 are the conditional log odds ratios for AIG and *H. pylori*, respectively. The random intercept was assumed to be normally distributed with mean zero and variance τ^2. Only studies reporting both AIG-positive and AIG-negative arms within at least one *H. pylori* stratum were included. The model assumed common conditional effects across studies, conditional independence of arm-level observations after accounting for the random intercept, and no interaction between AIG and *H. pylori*. This approach allowed studies without compatible study-specific effect estimates to contribute to the analysis; however, it relied on aggregate data and did not allow the effect of AIG to vary across studies.

A sensitivity analysis of the conventional meta-analysis was performed including only high-quality studies, which corresponded exclusively to case–control designs. Additional sensitivity

analyses excluding studies with fewer than 50 participants, hospital-based studies, and studies relying solely on serology for AIG diagnosis were planned; however, these were not feasible because none of the included studies had fewer than 50 participants, only the study by Wang et al[39] was community-based, and all relied exclusively on serology for AIG diagnosis. Sensitivity analyses of the arm-based multilevel model restricted to studies with AIG ascertainment including histology, to studies using a specific *H. pylori* diagnostic method, or to a single study design (case–control or cross-sectional) were planned but could not be undertaken because of insufficient data. These restrictions resulted in too few informative arms and, in some instances, eliminated the AIG-negative comparator group, precluding identifiable and stable model estimation. Finally, because only four studies allowed estimation of individual ORs, meta-regression to account for additional confounders was not possible.

All statistical analyses were performed using Stata version 15.0 (Stata Corporation, College Station, TX, USA), except for conventional meta-analyses, which were conducted using Review Manager version 5.4 (The Cochrane Collaboration, London, UK). A two-sided *p* value <0.05 was considered statistically significant.

RESULTS

Results of the systematic search

The results of the literature search are summarised in the PRISMA flow diagram (**Figure 1**). A total of 391 records were identified. Of these, 40 articles were selected for full-text review, of which 19 were excluded, leaving 21 studies for inclusion in the final analysis. The main reasons for exclusion were lack of clarity regarding the presence or absence of AIG, lack of clarity regarding the presence or absence of GC, and failure to stratify data by *H. pylori* status.

Characteristics of the studies

A total of 21 studies met the inclusion criteria [20,22,28-46]. China and Italy contributed the largest numbers of studies, with six and four studies, respectively. The populations were

classified as case–control (eleven studies), cross-sectional (five studies) and longitudinal (four studies), whereas the study by Mahmud et al[41] included both cross-sectional and longitudinal components. The median sample size was 320 participants (range 54–24,084). Three studies were community-based (Butt et al[45], Wang et al[39], and Song et al[30]), whereas the remainder were hospital-based. Overall, 53.2% of participants were female, and the median age was 61.5 years (range 30–69 years).

In ten studies, *Helicobacter pylori* infection was defined using combinations of histology, urea breath testing, faecal antigen testing and/or serology. By contrast, six studies relied exclusively on serology and four exclusively on histology. The diagnostic approach for AIG consisted of combined histology, anti-parietal cell antibodies and/or anti-intrinsic factor antibodies in eleven studies, anti-parietal cell antibodies alone in six studies, and histology alone in four studies. The weighted proportions of patients with intestinal, diffuse, mixed and unspecified tumour histology according to the Lauren classification (all confirmed as adenocarcinomas) were 9.4%, 4.5%, 0.48% and 85.6%, respectively. Table 1 summarises the main characteristics of the included studies.

Quality of studies

Based on the JBI quality assessment, 10 studies were rated as high quality (six case series, three case–control studies and one cross-sectional study), seven as moderate quality (four case series, two case–control studies and one cross-sectional study), and four as low quality (two case–control studies, one cross-sectional study and one cohort study). **Tables S3A–D** present the item-level quality assessment for each study.

Conventional meta-analysis

Only three case–control studies (Song et al[30], Huang et al[35], and Wang et al[39]) and one cross-sectional study (Sugiu et al[42]) provided sufficient data to calculate measures of association. The three case–control studies were rated as high quality, whereas the cross-

sectional study was rated as low quality. In all four studies, AIG was defined serologically. In the conventional meta-analysis of these four studies without adjustment for *H. pylori*, no statistically significant association was observed between GC and AIG (OR = 1.07, 95% CI 0.67–1.71; I^2 = 74%) (**Figure 2**). Similarly, in a conventional meta-analysis restricted to case–control studies, no significant association was found (OR = 1.12, 95% CI 0.65–1.93; I^2 = 82%) (**Figure 3**).

Subgroup meta-analyses including the same four studies showed no statistically significant association in either *H. pylori*-positive patients (OR = 0.93, 95% CI 0.63–1.37; I^2 = 43%) or *H. pylori*-negative patients (OR = 1.72, 95% CI 0.61–4.89; I^2 = 84%) (**Figure 4**). Finally, conventional meta-analysis using odds ratios estimated by logistic regression with adjustment for *H. pylori* exposure showed no significant association across the four studies (OR = 1.18, 95% CI 0.61–2.26; I^2 = 86%) (**Figure 5**) or across the three case–control studies (OR = 1.27, 95% CI 0.59–2.72; I^2 = 90%) (**Figure S1**).

Multilevel arm-based logistic regression

Nine studies provided data for both arms (AIG-positive and AIG-negative) for at least one *H. pylori* stratum (Song et al[30], Huang et al[35], Wang et al[39], Sugiu et al[42], Zhang et al[37], Hu et al[34], Khalaf et al[40], Mahmud et al[41], and Rugge et al[44]) and were therefore included in the mixed arm-based logistic regression model used to estimate the association between GC and AIG after adjustment for *H. pylori* infection. No longitudinal population was included in this model. In this model, significant associations were observed for both AIG (OR = 1.27, 95% CI 1.02–1.57; $p = 0.033$) and *H. pylori* infection (OR = 3.23, 95% CI 2.76–3.79; $p < 0.001$).

Narrative synthesis

Longitudinal studies

Five studies reported longitudinal data from patients with AIG stratified by *H. pylori* infection status (Rugge et al[22], Zhang et al[32], Lenti et al[33], Dilaghi et al[20], and Mahmud et al[41]). None of these studies included an AIG-free control group that would have allowed estimation of an association measure. With the exception of one study (Zhang et al[32]), which did not report follow-up duration, the weighted mean follow-up was 5.95 years (minimum 1.89, maximum 7.5), corresponding to a total of 24,554.5 person-years of follow-up. During this period, 434 patients with *H. pylori*-positive AIG and 1,230 patients with *H. pylori*-negative AIG were followed, yielding GC incidence rates of 47.2 and 98.4 per 100,000 person-years, respectively. The incidence rate did not differ significantly between *H. pylori*-positive and *H. pylori*-negative patients with AIG (incidence rate ratio 0.48, 95% CI 0.05–1.98; conditional exact). Thus, although the direction of the crude incidence estimates was opposite to that expected if current *H. pylori* infection were the main determinant of risk, the wide confidence interval precludes firm conclusions regarding equivalence or the direction of the association. In the study by Zhang et al., 5,851 patients with *H. pylori*-negative AIG were followed, and GC developed in 69 (1.2%), although the duration of follow-up was not reported.

Studies including only patients with gastric cancer

Seven studies reported retrospective data exclusively on patients with GC, stratified by H. pylori status, without a GC–free control (Arai et al[28], Ahn et al[29], Krike et al[31], Zhang et al[36], Kokkola et al[38], Sipponen et al[43], and Imamura et al[46]). A total of 2,214 *H. pylori*-positive and 638 *H. pylori*-negative patients were included, of whom 213 and 127, respectively, had a history of AIG.

DISCUSSION

Several studies to date have reported contradictory findings regarding the direct association between AIG and GC. Confounding by *Helicobacter pylori* status represents a major limitation in evaluating this relationship. This bacterium appears to be a risk factor for AIG through

several mechanisms, including molecular mimicry [25, 47–49]. Its association with AIG has been demonstrated in multiple studies, as has the reversal of AIG-related histological changes, haematological abnormalities and APC titres following bacterial eradication [26, 27]. This indicates that *H. pylori* is a potential confounder in the association between AIG and GC. To the best of our knowledge, the present study is the first systematic review and meta-analysis to evaluate this association with adjustment for *H. pylori*. Using an exploratory multilevel arm-based model, we were able to include nine studies, which confirmed the well-established association between *H. pylori* and GC (OR = 3.23, 95% CI 2.76–3.79) and also suggested an association between AIG and GC independent of *H. pylori* infection (OR = 1.27, 95% CI 1.02–1.57).

Several pathophysiological mechanisms may support a causal association between AIG and GC independent of *H. pylori* infection. Patients with AIG develop progressive histological changes secondary to chronic inflammation, evolving from chronic gastritis to dysplasia [17, 50], during which multiple genetic and epigenetic alterations with carcinogenic potential may occur [51–53]. For instance, in the absence of *H. pylori*, AIG leads to CpG island hypermethylation affecting tumour suppressor genes, resulting in their repression and promoting uncontrolled cell proliferation [52]. In addition, reduced acid secretion in AIG promotes hypergastrinaemia and, consequently, histamine release from enterochromaffin-like cells, both of which stimulate proliferation of gastric epithelial and progenitor cells [54–57]. Notably, the gastrin receptor CCK2R has been found to be over-expressed in several gastrointestinal cancers [58].

There is ongoing controversy regarding the type of gastric intestinal metaplasia (GIM) associated with AIG. GIM develops as a defensive response to mucosal injury [59–61] and, when persistent, may progress to dysplasia and eventually GC in a small subset of patients [62]. Although both *H. pylori* infection and AIG induce GIM, it remains unclear whether they generate distinct metaplastic cell types with different risks of GC. For instance, incomplete-

type GIM, which carries a higher risk of GC than complete-type GIM, is less frequent in AIG [63–65]. However, factors beyond GIM subtype also influence cancer risk, including the presence of extensive GIM, defined as involvement of the corpus with or without antral involvement [66–70]. Indeed, AIG is characterised by pan-gastric GIM that is more pronounced in the corpus [67]. Moreover, a recent experimental study using murine models and human samples demonstrated that both *H. pylori* infection and AIG induce comparable GC-associated gastric metaplasias with similar histopathological and transcriptional features [71]. Both conditions also promoted a metaplastic subtype resembling incomplete GIM, closely related to cancerous tissue and characterised by ANPEP/CD13 expression, a biomarker associated with GC. These findings support the concept that AIG-induced GIM may represent a true preneoplastic condition.

Furthermore, findings derived from the ABC(D) strategy for gastritis screening are consistent with the present results and the preceding discussion. This strategy evaluates *H. pylori* serology and serum pepsinogen (PG) levels to classify patients into group A (*H. pylori*-negative and PG-negative), group B (*H. pylori*-positive and PG-negative), group C (*H. pylori*-positive and PG-positive) and group D (*H. pylori*-negative and PG-positive) [72]. The highest risk of GC has been observed in group D [73], which is compatible with both advanced gastritis caused by *H. pylori* followed by bacterial clearance and gastritis caused by AIG in the absence of *H. pylori* infection.

The present findings are further supported by a recent meta-analysis by He et al., which demonstrated a significantly increased risk of both GC and type I gastric neuroendocrine tumours in patients with AIG and, importantly, showed that the absence of *H. pylori* infection did not confer protection against GC [74]. Consistent with this, the present study found a GC incidence of 98.4 per 100,000 person-years among patients with AIG without *H. pylori* infection, which is substantially higher than that reported for the general population across different regions [2]. Notably, the meta-analysis by He et al. also reported that patients with

pernicious anaemia had the highest risk of GC [74]. As pernicious anaemia is a long-term complication of AIG, this may explain why GC risk has historically been associated primarily with this subgroup rather than with AIG alone.

The present study has several limitations. First, all meta-analyses were based on retrospective cross-sectional or case–control data and therefore do not allow causal inference [75]. Nevertheless, prospective studies included in the narrative synthesis reported a GC incidence in patients with AIG that is higher than expected in the general population, even among *H. pylori*-negative patients. Second, conventional meta-analyses included only four studies and showed substantial heterogeneity, potentially reflecting differences in study design, sampling, exposure ascertainment, participant selection, tumour histology, and control of confounding. The small number of studies precluded formal exploration of heterogeneity through meta-regression. Pooling was retained because the studies addressed the same exposure–outcome association and provided compatible ORs. Therefore, the pooled conventional estimates should be regarded as exploratory summary measures rather than as precise estimates of a common underlying effect. Third, although statistically significant, the estimated odds ratio of the exploratory multilevel arm-based model was modest (OR = 1.27). The study-specific random intercept allowed baseline GC odds to differ across studies and accounted for clustering of arms within studies; however, differences in sampling frameworks and the assumption of a common conditional AIG effect across studies remain important limitations. Therefore, the modest association observed in this model should also be regarded as exploratory and hypothesis-generating rather than causal. Additional sensitivity analyses restricting the arm-based model to studies with histological AIG ascertainment, using a specific *H. pylori* diagnostic method, or employing a single study design (case–control or cross-sectional) were not feasible because these restrictions left too few informative comparison arms for identifiable and stable model estimation. Fourth, publication bias cannot be excluded, as smaller studies or those reporting null or negative results may be less likely to be published. Formal tests could not be performed because only four studies were included in the

conventional meta-analyses [76], and because of the heterogeneity of study designs and outcome measures across the full set of 21 studies. Fifth, comparison of GC incidence in *H. pylori*-negative AIG patients with GLOBOCAN data is intended for contextual reference only, as these populations are not fully comparable. Nonetheless, the markedly higher observed incidence remains noteworthy in the absence of more appropriate comparative data.

Additionally, an important limitation of the present study is that advanced AIG may lead to spontaneous disappearance of *H. pylori* infection [77–80]. Even in the absence of eradication therapy, long-standing AIG is associated with declining anti-*H. pylori* antibody titres, which may even become negative in approximately one quarter of cases [81]. Consequently, some GC cases observed in patients with AIG may have been attributable to previous *H. pylori* infection despite negative faecal antigen, urea breath or serological tests. Moreover, because APC positivity may occur in patients with *H. pylori* infection and decline after eradication, serological positivity does not necessarily indicate established AIG, potentially resulting in exposure misclassification and inflation of the observed association. These residual limitations can only be addressed by long-term prospective studies with repeated assessment of *H. pylori* status and histological diagnosis of AIG; such studies are currently lacking.

CONCLUSIONS

The available evidence suggests that AIG may be modestly associated with GC after adjustment for *H. pylori* status. Although the conventional meta-analysis did not demonstrate a statistically significant association, the exploratory multilevel arm-based model showed a modest association, while longitudinal studies reported a higher-than-expected incidence of GC among patients with AIG, including those classified as *H. pylori*-negative. Although these findings do not firmly establish causality, they are compatible with the possibility that AIG itself contributes to gastric carcinogenesis beyond the effect of detectable *H. pylori* infection. Nevertheless, substantial heterogeneity, differences in study design and exposure ascertainment, the absence of appropriate control groups in longitudinal studies, and residual

confounding by previous *H. pylori* infection limit causal interpretation. Well-designed prospective studies including AIG-exposed and unexposed populations, with robust and repeated assessment of *H. pylori* exposure, are needed to determine whether AIG represents an independent causal risk factor for GC.

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Competing interests

The authors declare no competing interests to declare that are relevant to the content of this article.

Data availability

All data used in this meta-analysis are included in the published articles and their supplementary materials.

Ethics approval

Ethics approval was not required as this study was based on published data.

Consent to participate and for publication

Not applicable

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TABLES

Table 1. Characteristics of the included studies.

Reference	Country	Study type	Total population	H. pylori diagnostic method[b]	AIG diagnostic method[c]	Distribution of tumour histology (%)			
						Intestinal	Diffuse	Mixed	Not specified
Rugge M. 2023[a] [22]	Italy	CS	211	Combination	Combination	-	-	-	-
Arai J. 2022 [28]	Japan	Cohort	261	Combination	APC	78.9	21.1	0	0
Ahn S. 2025 [29]	Korea	CrS	624	Serology	Combination	70.6	26.8	0	2.6
Song M. 2022 [30]	Korea	C-C	1972	Serology	APC	0	0	0	100
Krike P. 2024 [31]	Latvia	C-C	428	Serology	Combination	50	27.1	10.3	12.6
Zhang Z. 2023 [32]	China	CS	24084	Combination	Combination	0	0	0	100
Lenti M. 2024 [33]	Italy	CS	1598	Combination	Histology	0	0	0	100

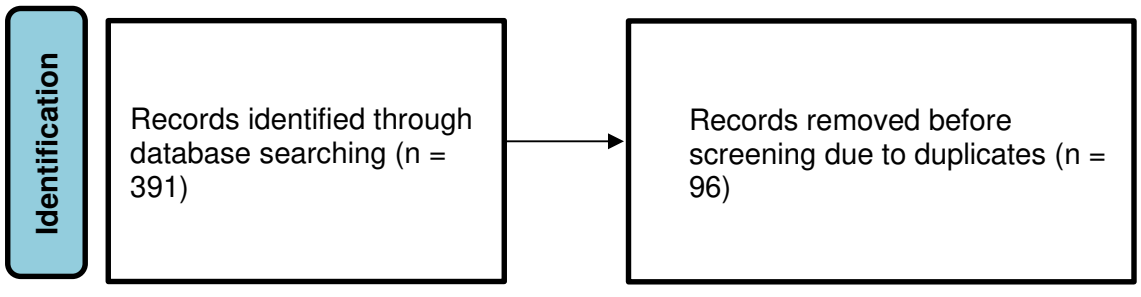
Hu H. 2022 [34]	China	CS	135	Combination	Combination	0	0	0	100
Huang Y. 2025 [35]	China	C-C	392	Combination	APC	98.5	0	0	1.5
Zhang H. 2018 [36]	China	CrS	1170	Histology	Combination	90	0	10	0
Zhang H. 2017 [37]	China	CS	320	Histology	Combination	44.4	22.2	0.1	33.3
Kokkola A. 2005 [38]	Finland	C-C	251	Serology	APC	42.7	56.6	0	0.7
Wang S. 2019 [39]	China	C-C	900	Serology	APC	0	0	0	100
Khalaf K. 2025 [40]	Canada	CS	63	NR	Combination	0	0	0	100
Dilaghi E. 2023 [20]	Italy	CS	275	Combination	Histology	0	0	0	100
Mahmud N. 2018 [41]	United States	CS	150	Histology	Histology	0	0	0	100
Sugiu K. 2006 [42]	Japan	CrS	92	Combination	APC	0	0	0	100
Sipponen P.	Finland	C-C	137	Histology	Combination	57.4	38.9	0	3.7

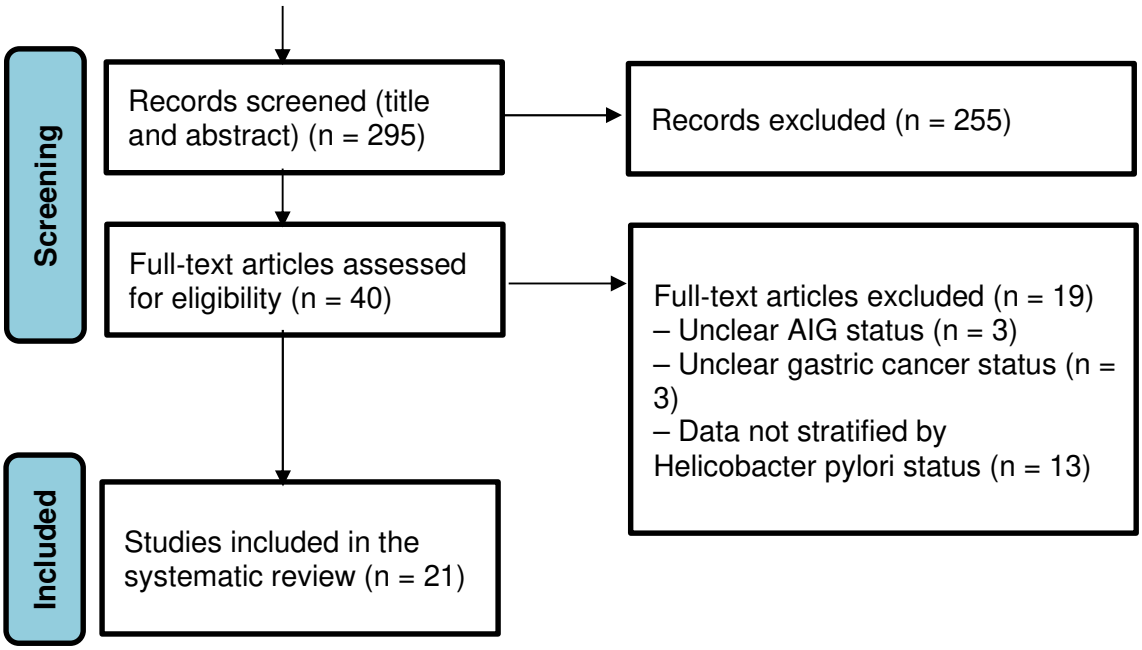
1992 [43]									
Rugge M. 2012 [44]	Italy	CS	562	Combination	Combination	100	0	0	0
Butt J. 2022 [45]	Finland	C-C	1414	Serology	Combination	4.1	67.5	0.5	27.9
Imamura K. 2024 [46]	Japan	CS	54	Combination	Histology	79.6	16.7	0	3.7

CS: Case series; C-C: Case-control; CrS: Cross-sectional; NR: Not reported; APC: Anti-parietal cell antibodies.
[a] Only study in which no cases of gastric cancer were reported.
[b] "Combination" indicates diagnostic criteria incorporating histology, serology, urea breath testing and/or *Helicobacter pylori* faecal antigen.
[c] "Combination" indicates diagnostic criteria incorporating histology, anti-parietal cell antibodies and anti-intrinsic factor antibodies.

FIGURES

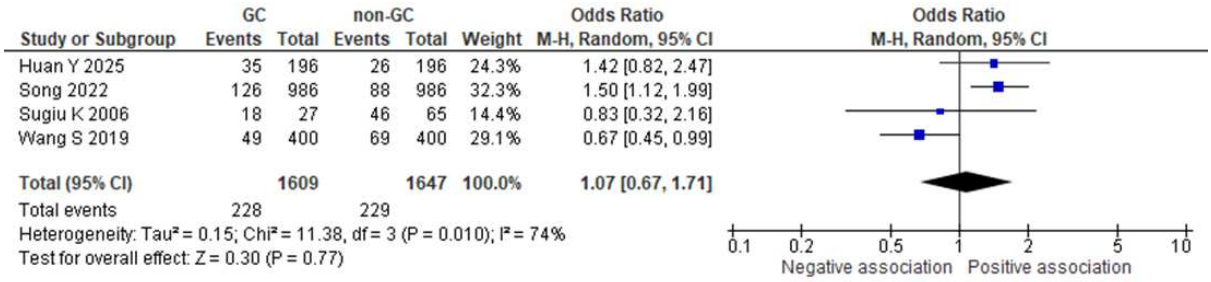
Fig. 1 PRISMA Flow diagram





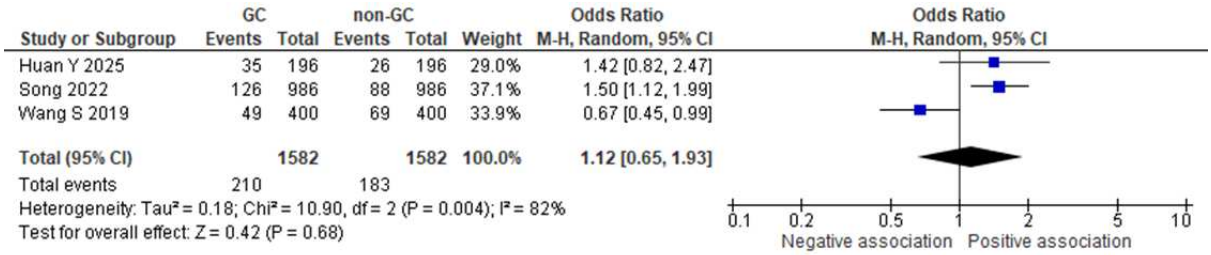
AIG: Autoimmune Gastritis; GC: Gastric cancer.

Fig. 2 Meta-analysis of the association between GC and AIG without adjustment for *H. pylori* infection



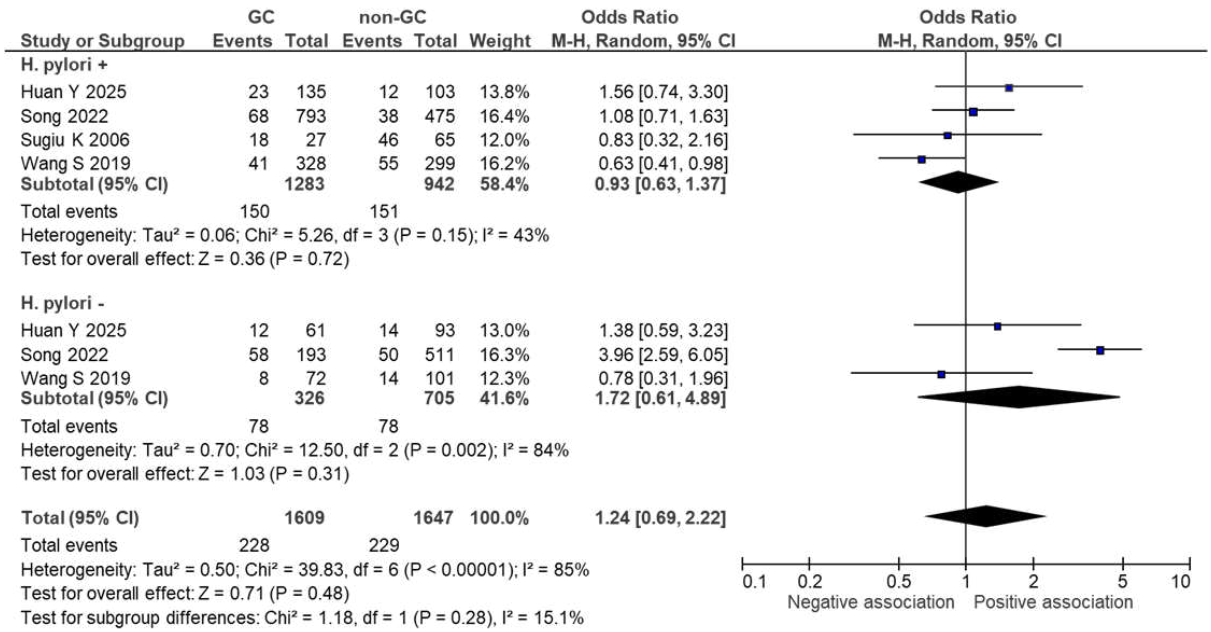
GC: gastric cancer.

Fig. 3 Meta-analysis of the association between GC and AIG in case-control populations without adjustment for *H. pylori* infection



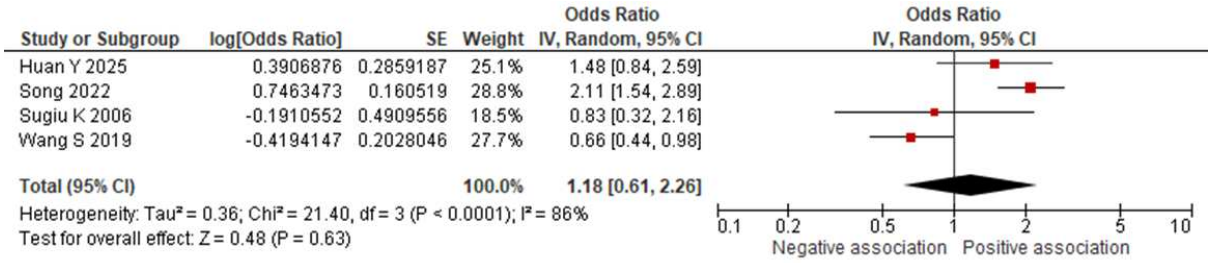
GC: gastric cancer.

Fig. 4 Subgroup meta-analysis of the association between AIG and GC stratified by *H. pylori* status



GC: gastric cancer.

Fig. 5 Meta-analysis of the association between GC and AIG after adjustment for *H. pylori* infection



GC: gastric cancer.

Supplementary Files

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- SupplementaryMaterial.docx