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Systematic review and meta-analysis: Risk of gastric cancer in patients with first-degree relatives with gastric cancer

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Summary

Background: Gastric cancer ranks fourth in terms of global cancer-related deaths. Timely identification of high-risk populations is crucial to reduce mortality. Although a family history of gastric cancer increases risk, European and British guidelines report weak recommendations and low-quality evidence about the management of these patients.

Aim: To quantify the association in case–control studies of patients with gastric cancer with first-degree relatives with gastric cancer compared to those who do not.

Methods: We conducted a systematic review and meta-analysis of case–control studies up to November 2023. Data extraction was performed independently by two reviewers. The heterogeneity of effects across studies was quantified by I^2. We calculated odds ratios (OR) with 95% confidence intervals (CI) using random effects models.

Results: We included 30 studies in the systematic review. In all studies, a first-degree family history of gastric cancer represented a risk factor for gastric cancer. We included 21 studies on the risk of gastric cancer. There was a significantly increased association between gastric cancer and having first-degree relative(s) with gastric cancer, but with significant heterogeneity among studies (OR = 2.92; 95% CI 2.402–3.552; $p < 0.001$; $I^2 = 81.85\%$; $p < 0.001$).

Conclusion: This meta-analysis highlights the relevance of patients' family history of gastric cancer and the importance of this risk factor for the early detection of neoplastic conditions.

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Yuan. The Handling Editor for this article was Dr Colin Howden, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Gastric cancer is the fifth most common neoplasia and the fourth cause of death from neoplastic pathology worldwide.[1] Its poor prognosis is mainly due to late diagnosis at an advanced stage of cancer.[2] In high-incidence countries for gastric adenocarcinoma (e.g., Japan, China, and Korea), general population screening programmes have been shown to improve survival rates.[3] However, in low-incidence countries (e.g., European countries), gastric cancer screening is not recommended.

Among the key risk factors associated with gastric cancer, *Helicobacter pylori (H. pylori)* infection is considered a type I carcinogen for gastric cancer.[4] Another important risk factor for gastric cancer is family history. In fact, while the majority of gastric cancers are sporadic, approximately 1%–3% of cases are due to hereditary tumours, and in 10% of cases, there is a family aggregation where the pathogenesis is not clearly understood.[5] Genetic predisposition is a risk factor that has been studied in the literature with several epidemiological case–control studies that have reported Odds Ratios (ORs) of 2–10 that vary by geographical region and ethnicity.[6] Family history is considered a significant risk factor such that the guidelines of the British Society of Gastroenterology suggest that "endoscopic screening in low prevalence countries for gastric cancer should be considered in individuals aged ≥50 years old with multiple risk factors for gastric adenocarcinoma (males, smokers, pernicious anaemia) and specifically, those with a first-degree relative with gastric cancer to diagnose precancerous conditions (i.e., Atrophic Gastritis, Intestinal Metaplasia, and dysplasia)".[7] However, this statement is reported with "evidence level: low quality; grade of recommendation: weak; level of agreement: 93%".[7] Previous meta-analyses have been conducted on this topic and have evaluated the quantitative risk of gastric cancer in patients with a family history of gastric cancer. Yaghoobi et al.'s 2017 meta-analysis, which drew from 33 studies, reported an overall OR of 2.35 (95% CI: 1.96–2.81).[8] He et al.'s 2021 meta-analysis based on 35 studies reported an overall Relative Risk (RR) of 2.00 (95% CI = 1.83–2.20; $p < 0.001$), and in a subgroup analysis, it identified the risk for patients with first-degree relatives with gastric cancer (RR = 2.07, 95% CI = 1.88–2.29, $p < 0.001$).[9] Another meta-analysis by Storelli Vitelli et al. in 2021, which included 17 studies, reported an overall odds ratio of 1.84 (95% CI = 1.64–2.04 $p < 0.001$).[10] However, none of the previous analyses calculated the quantitative risk by exclusively considering studies of first-degree relatives with gastric cancer. Based on British guidelines that highlight an increased risk of gastric cancer among patients with first-degree relatives with gastric cancer, this meta-analysis evaluates the statistical association between gastric cancer patients and their first-degree relatives with gastric cancer compared to patients without first-degree relatives with the disease, specifically focusing on case–control studies.

2 | METHODS

This systematic review and meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[11]

To evaluate the role of first-degree relatives with gastric cancer in case–control studies, two electronic databases, MEDLINE through PubMed and Embase, were searched up to November 2023 using the following search queries:

- (((gastric cancer) OR (gastric adenocarcinoma)) OR (gastric tumour)) AND (family history)
- (((gastric cancer) OR (gastric adenocarcinoma)) OR (gastric tumour)) AND (first-degree relatives)

2.1 | Search strategy, data identification and extraction

Two authors (I.L. and L.D.) independently conducted screening and data extraction. The search terms or "Text Words" included five main categories: "gastric cancer", "gastric adenocarcinoma", "gastric tumour", "family history" and "first-degree relatives". The MeSH terms used were "Stomach Neoplasms", "Medical History Taking", "Family", "Risk". The initial screening included the evaluation of titles. Subsequently, the two reviewers assessed the abstracts blindly. A full-text analysis and data extraction were finally performed. During the different phases of the selection and analysis of titles, abstracts, and full text, disagreements were resolved through discussion with a third independent author (C.S.). The references of all reviews and systematic reviews were further reviewed to identify additional appropriate papers. The following features were extracted for each selected study in the final analysis: first author, year of publication, country, type of study, journal of publication, sample size, number of cases and controls, mean age, gender, effect size, the reasons for the exclusion of each study in the meta-analysis and factors that were adjusted for OR of each study. For the meta-analysis, only case–control studies whose odds ratio could be calculated for the gastric cancer risk outcome were included. Due to the high heterogeneity of variables with which the different studies reported the adjusted odds ratio, it was decided to conduct a meta-analysis of only the unadjusted OR values to maintain consistency across the analysis.

2.2 | Study selection

Studies that evaluated the risk of first-degree relatives with gastric cancer for patients with gastric cancer with a publication date prior to November 2023 were included. Studies with missing or no extractable data, studies with no access to the full text, studies published in languages other than English, case reports, letters, comments, reviews, conference abstracts, studies on children, duplicate publications, studies that did not clearly define the degree of relatives with gastric cancer, studies that did not differentiate the risk between gastric cancers and other gastrointestinal cancers, studies that focused only on cardias cancers, studies that focused on gastric cancer within the context of hereditary syndromes and studies that exclusively focused on cases with *H. pylori* infection and/or diffuse

TABLE 1 Inclusion and exclusion criteria of the meta-analysis.

Criteria	Inclusion	Exclusion
Timeline	Published before November 2023	—
Document types	Case–control studies	Case reports; Letters; Systematic Review; Meta-analysis; Conference abstracts
Population	GC Patients with FDR with GC	Degree of relative not specified
Cancer type	Adenocarcinoma	Diffuse cancer
Cancer site	Stomach	Cardia; Others; Not specified
Hereditary syndrome	Not present	Present
Article language	English	Others
Other criteria	—	Only *Helicobacter pylori* infected population

Abbreviations: FDR, first degree relatives (father, mother, brother and sister); GC, gastric cancer.

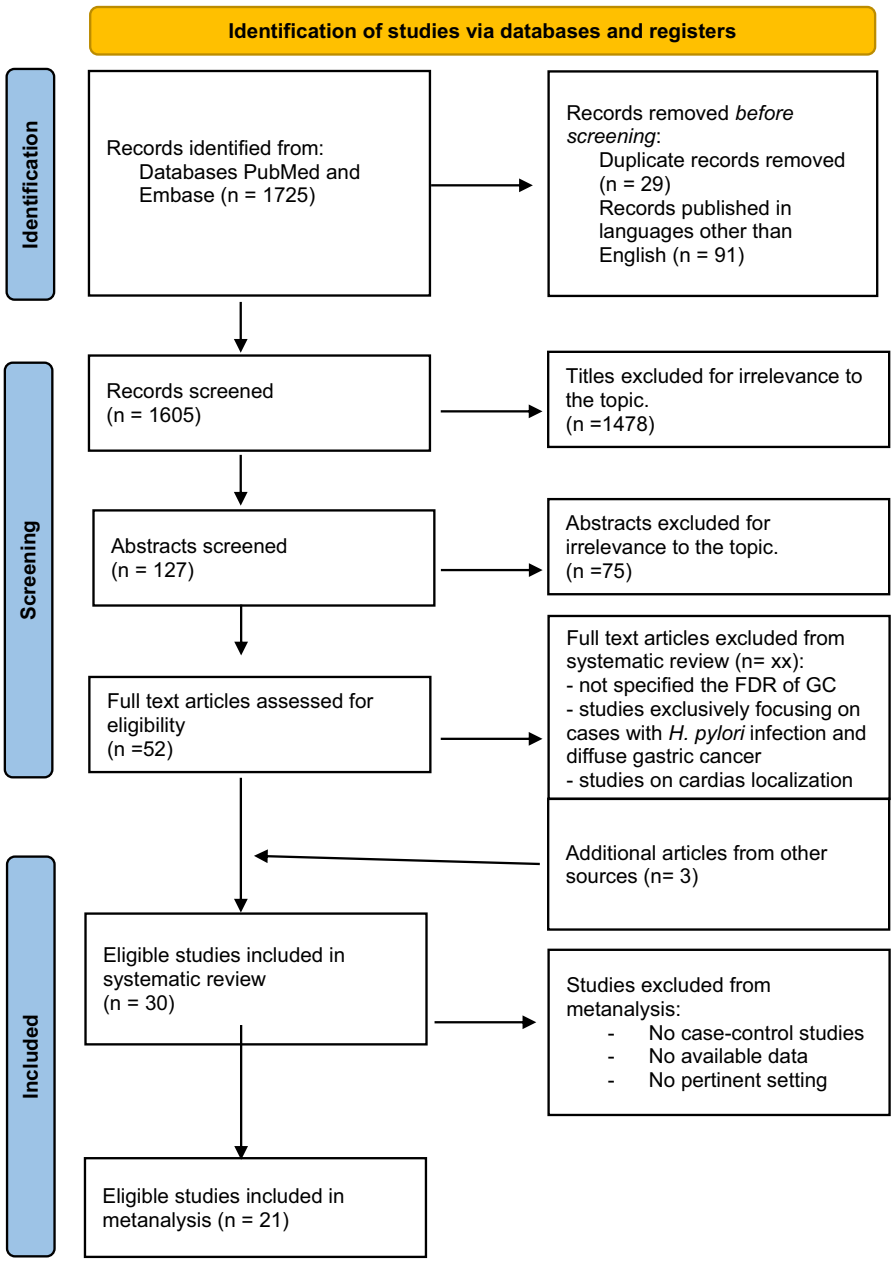

FIGURE 1 PRISMA flow diagram. Abbreviations: FDR, first-degree relatives; GC, gastric cancer; *H. pylori*, *Helicobacter pylori*.

gastric cancer were excluded to reduce bias in the selection of studies. For the meta-analysis, only case–control studies published as full papers and with complete and extractable data for OR calculation were included. Table 1 shows the inclusion and exclusion criteria.

2.3 | Statistical analysis

The probability of patients with gastric cancer having first-degree relatives with gastric cancer was expressed as ORs with a 95% confidence interval (CI). During the phase of selection studies, the reviewers' agreement was determined by calculating Cohen's κ. Egger's and Begg's regression tests and funnel plots were utilised to evaluate potential publication bias. The heterogeneity between studies was evaluated using inconsistency statistics (I^2),[12] where I^2=0%–25% was considered low heterogeneity, I^2=25%–50% was considered moderate heterogeneity, I^2=50%–75% was considered large heterogeneity, and I^2=75%–100% was considered extreme heterogeneity. The heterogeneity between nonrandomised studies of interventions (NRSI) was expected to be high because of their diversity. The random-effects meta-analysis approach should be the default choice; for this reason, a random-effects model was adopted. The level of significance was set at $p<0.05$. Statistical analyses were performed using dedicated software (MedCalc Software, Mariakerke, Belgium, version 17.4).

2.4 | Quality assessment

The quality of all included studies in the systematic reviews and meta-analyses was assessed using the Newcastle–Ottawa quality assessment scale (NOS).[13] This scale assigns a maximum of nine stars to each study and evaluates items related to the selection, comparability, and exposure assessment categories of cases and controls. Within the selection and exposure assessment categories, a study can receive up to one star for each numbered item, while comparability can receive up to two stars. To determine the overall quality of each study, a score of nine stars is considered high quality, seven to eight stars is medium quality, five to six stars is low quality, and four stars or less is very low quality. Any disagreements during the quality assessment were resolved through discussion among three reviewers (I.L., L.D., C.S.).

3 | RESULTS

3.1 | Search results

A flow diagram describing the process of the study selection is shown in Figure 1.

Overall, 1725 records were identified through database searching, and 127 abstracts on the risk of gastric cancer were blindly evaluated by two reviewers. The observed agreement between the reviewers for the eligibility of articles in this first screening was 96% (Cohen's κ=0.96). Finally, a full-text article evaluation was performed for 52 studies that evaluated the risk of gastric cancer. Three articles were added from the references of systematic reviews and meta-analyses. Thirty studies fulfilled the inclusion criteria and were eligible for the systematic review, and 21 studies satisfied the inclusion criteria and were eligible for the meta-analysis of the association with gastric cancer in first-degree relatives as case–control studies. The agreement between reviewers in assessing the eligibility of articles was 100% (Cohen's κ=1.0). The pooled analysis of the studies eligible for meta-analysis included a total of 97,862 patients for the association with gastric cancer. The main characteristics and results of the studies that were eligible for the systematic review but excluded from the meta-analysis with regard to the association with gastric cancer are shown in Table 2. The main characteristics and results of the studies eligible for meta-analysis with regard to the association with gastric cancer are shown in Table 3.

TABLE 2 The main characteristics and results of included studies in the systematic review and excluded from the meta-analysis.

Study, References	Journal	Country	Median Age	Female (%)	Meta-analysis exclusion	NOS
Schuman et al.[14]	*Gastrointestinal Endoscopy*	Italy	–	–	Not pertinent setting	6
Inoue et al.[15]	*International Journal of Cancer*	Japan	52.6	34.5	No available data for the cardia site	5
Bernini et al.[16]	*Gastric Cancer*	Italy	65	35.5	Cross-sectional	6
Zeegers et al.[17]	*International Journal of Cancer*	the Netherlands	–	–	Prospective cohort (RR)	6
Gong et al.[18]	*British Journal of Cancer*	Japan	64	29	Not pertinent setting	7
Song et al.[19]	*Internal Journal of Epidemiology*	Switzerland	47	51	Prospective cohort (HR) and not pertinent setting	7
Song et al.[20]	*Gastric Cancer*	Finland	–	0	Prospective cohort (HR) and not pertinent setting	7
Dondov et al.[21]	*Asian Pacific Journal of Cancer Prevention*	Mongolia	59.2	38.3	No available data	6
Sotelo et al.[22]	*Journal of Gastrointestinal Cancer*	Chile	56.8	54.5	Cross-sectional	6

Abbreviations: CI, confidence interval; HR, hazard ratio; NOS, Newcastel-Ottawa Scale; OR, odds ratio; RR, relative risk.

3.2 | Study characteristics and quality assessment results

The studies included in the meta-analysis were conducted in different countries with a good balance between Eastern and Western countries (10 vs. 11): 4 studies were conducted in Italy, 3 in Japan, 3 in China, 3 in Korea, 3 in the US, 2 in Turkey, 1 in Poland, 1 in Germany, and 1 in Venezuela. For the Newcastle–Ottawa quality assessment scale of the systematic review, 1 study was considered to be very low quality, 18 studies were low quality, 12 studies were medium quality, and 1 was high quality. For two cross-sectional studies, the Newcastle–Ottawa quality assessment scale adapted for

TABLE 3 The main characteristics and results of included studies in the meta-analysis.

Study, References	Journal	Country	Cases	Controls	Median Age	Female (%)	OR	CI 95%	OR adjusted
Hagy et al.[23]	*American Journal of Human Genetics*	USA	106	60	63	—	9.1	0.5–162.5	Age
Zanghieri et al.[24]	*Cancer*	Italy	154	154	65	—	2.3	1.1–4.3	Parents, siblings
Yu et al.[25]	*Cancer Causes Control*	China	84	2676	—	38	6.5	3.7–11.2	No
La Vecchia et al.[26]	*Cancer Causes Control*	Italy	628	1776	60	38.1	2.79	2–3.8	Age, sex
Palli et al.[27]	*Cancer Epidemiology, Biomarkers & Prevention*	Italy	1016	1623	—	24.5	2.1	1.7–2.7	Sex, number of relatives, father, mother, siblings
Nagase et al.[28]	*Japanese Journal of Cancer Research*	Japan	136	136	57	22	2.3	1–5.1	Age, sex, paternal or maternal History
Lissowska et al.[29]	*European Journal of Cancer Prevention*	Poland	437	472	—	34.9	3.7	2.2–6.3	Age, sex, smoking, diet, mother, father, siblings
Huang et al.[30]	*Journal of Epidemiology*	Japan	887	28,619	—	32.9	2.1	1.8–2.4	Age and sex, parents, siblings or both
Bakir et al.[31]	*European Journal of Cancer Prevention*	Turkey	1240	1240	62	NR	10.1	6.2–16.3	No
Brenner et al.[32]	*America Cancer Society*	Germany	68	239	61	41	3.2	1.3–7.9	Age, sex, school education
Dhillon et al.[33]	*International Journal of Cancer*	USA	368	695	—	31	2.9	1.8–4.6	Age, sex, race, smoking, BMI, income status
Muñoz et al.[34]	*International Journal of Cancer*	Venezuela	292	483	—	—	1.7	1–2.7	No
Bakir et al.[35]	*European Journal of Cancer Prevention*	Turkey	1240	1240	56	NR	6.6	4.3–10.1	Mother, father
Yatusya et al.[36]	*British Journal of Cancer*	Japan	202	394	62	48	0.9	0.5–1.7	*Helicobacter pylori* infection, number of siblings, smoking, drinking, diet and education
Foschi et al.[37]	*International Journal of Cancer*	Italy	230	547	63	37.8	2.5	1.4–4.2	Gender, age, BMI, education, tobacco, siblings, parents
Chung et al.[38]	*World Journal of Gastroenterology*	South Korea	3242	3000	37	53.9	3.8	2.9–5.1	No
Shin et al.[39]	*Journal of Clinical Gastroenterology*	Korea	428	368	—	32.9	2.7	1.7–4.1	*Helicobacter pylori* smoking, diet, father mother, siblings, number of relatives
Jiang et al.[40]	*BMC Cancer*	USA	285	1309	52	40	1.9	1.1–3.1	Age, sex, race, education, birthplace, smoking, BMI, diabetes, other malignancies
Choi et al.[41]	*European Journal of Cancer Prevention*	Korea	930	37,200	—	—	2.6	2.2–3	Age, father, mother, siblings
Man et al.[42]	*Frontiers in Nutrition*	China	870	1928	67	30.4	1.9	1.5–2.3	Age, sex, education, family size, *H. pylori*, smoking, drinking, diet
Zhang et al.[43]	Chinese Medical Journal	China	215	645	61	42	6.8	3–15	No

Abbreviations: BMI, body mass index; CI, confidence interval; *H. pylori*, *Helicobacter pylori*; NOS, Newcatel-Ottawa Scale; OR, odds ratio.

TABLE 4 Newcastle–Ottawa quality assessment score for each study.

	Selection	Comparability	Exposure/outcome	Overall star rating
Hagy 1954	+++	++	+	6
Schuman 1987	+++	++	+	6
Zanghieri 1990	+++	++	+	6
Palli 1991	+++	++	+	6
Yu 1991	+++	++	–	5
La Vecchia1992	++++	++	+	7
Nagase 1996	+++	++	+	6
Inoue 1998	++	++	+	5
Huang 1999	+++	+	+	5
Lissowska 1999	++++	++	+	7
Bakir 2000	+++	++	++	7
Brenner 2000	+++	++	+	6
Dhillon 2001	++++	++	+	7
Muñoz 2001	++++	++	+	7
Bakir 2003	+++	++	++	7
Yatsuya 2004	+++++	++	++	9
Bernini 2006[a]	++++	–	++	6
Foschi 2008	+++	++	+	6
Zeegers 2008	+++	+	+	6
Chung 2010	++++	++	+	7
Shin 2010	+++	++	+	6
Gong 2014	++++	++	+	7
Jiang 2014	+++	++	+	6
Song 2018 (25)	++++	++	+	7
Song 2018 (26)	++++	++	+	7
Choi 2020	++	++	+	5
Man 2021	++++	++	++	8
Zhang 2021	++	–	++	4
Dondov 2022	+++	++	+	6
Sotelo 2022[a]	++++	–	++	6

[a]Newcastle–Ottawa Quality Assessment Scale (adapted for cross-sectional studies).

cross-sectional studies was applicable. For the Newcastle–Ottawa quality assessment scale of the meta-analysis studies, 1 study was considered to be low quality, 11 were low quality, 8 were medium quality, and 1 was high quality. Table 4 shows the Newcastle–Ottawa quality assessment scale for each study.

3.3 | Gastric cancer

All the studies included in this systematic review indicated that a first-degree family history of gastric cancer represents a risk factor for gastric cancer.[14–43] The studies included in our systematic review provided interesting insights through subanalyses that explored various factors, such as gender, the type of family member affected (father, mother, or sibling), the specific anatomical site of cancer (corpus/antrum), geographical risk, and age considerations. Several studies highlighted a significant risk of gastric cancer specifically among women,[17,27,28,36,39] indicating a potential gender-based susceptibility to the disease. In contrast, only one study described a higher risk in male individuals.[38] Additionally, the presence of siblings affected by gastric cancer was identified as a higher risk factor than a parental history of gastric cancer.[17,19,20,21,24,27,29,30,36,37,41] Furthermore, in many studies, it was documented that having a mother affected by gastric cancer represented a higher risk than having a father affected by gastric cancer.[35,39,41] In one study, the risk of gastric cancer in family history was higher in the intestinal histotype[16]; conversely, in another study, greater familial risk was documented in the diffuse histotype.[24] *H. pylori* infection was closely associated with a higher incidence of patients having first-degree relatives with gastric cancer compared to the general population.[22,32,39] Focusing on the specific anatomical site affected within the stomach, a study revealed an increased prevalence of antrum gastric cancer in these patients[31]; in contrast,

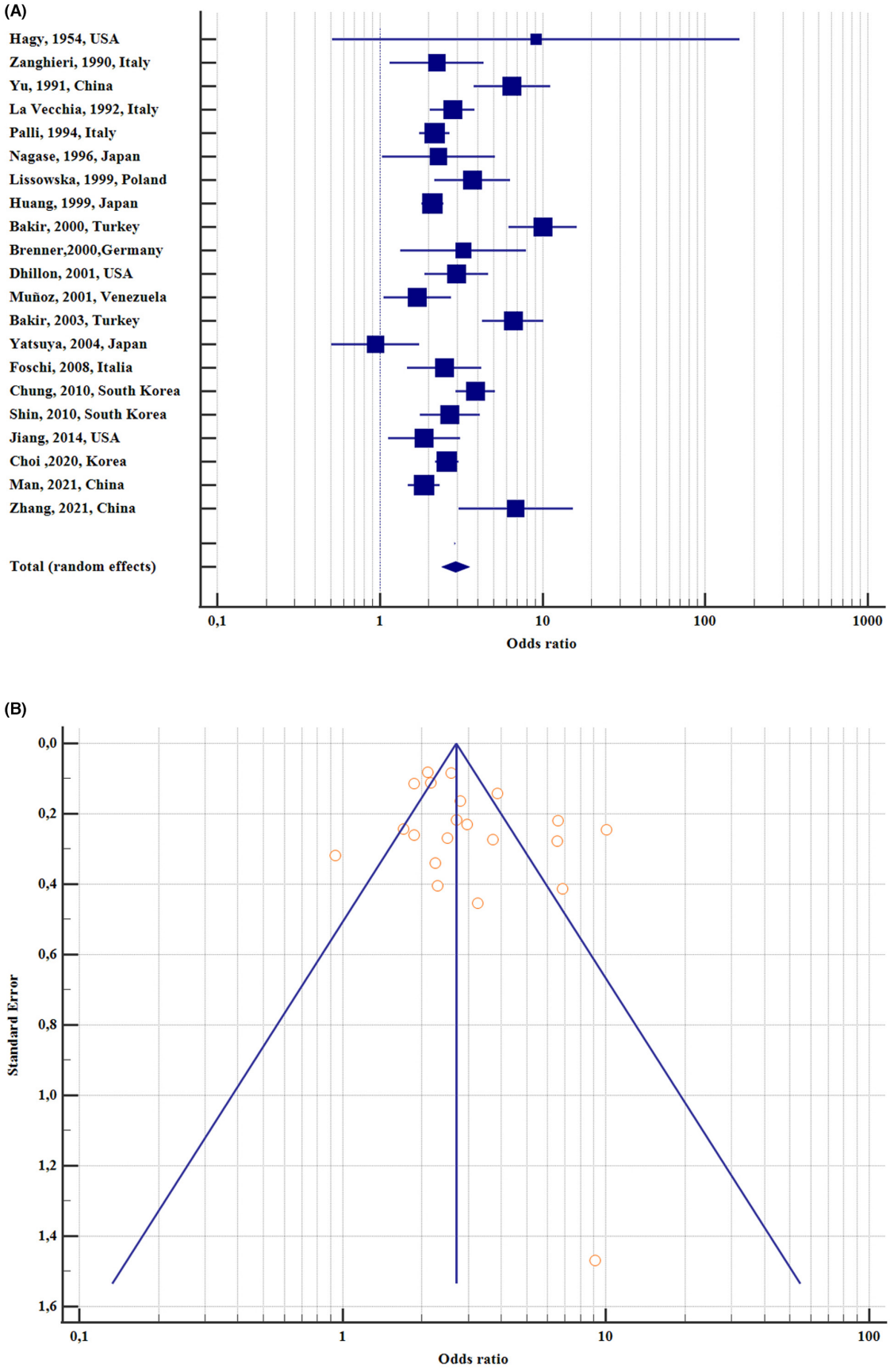

FIGURE 2 (A) Forest plot and (B) funnel plot of the risk of gastric cancer in patients with first-degree relatives with gastric cancer (OR = 2.92; 95% CI 2.402–3.552; $p < 0.001$).

another study documented a higher risk in the corpus.[15] Interestingly, low-incidence countries for gastric cancer demonstrated a more pronounced impact of family history on disease development compared to high-incidence countries,[27] emphasising the influence of geographic factors on genetic predisposition. Furthermore, age at diagnosis plays a crucial role; studies found a positive correlation between younger age at the time of gastric cancer diagnosis and an elevated risk of relatives developing the disease.[38,40,42] This finding suggests that early-onset gastric cancer in family members may be indicative of increased susceptibility within the family network. Finally in some studies, the presence of multiple family members affected by gastric cancer was found to further heighten the risk of developing the disease, with an OR ranging from approximately 5 to 12.[27,33,39] For the meta-analysis, 21 studies evaluated the risk of first-degree relatives with gastric cancer in 13,058 patients with gastric cancer (cases) in comparison to 84,804 patients without gastric cancer (controls).[23–43] In the group of patients with gastric cancer, a significantly increased presence of first-degree relatives with gastric cancer compared to controls was found, with significant heterogeneity between studies (OR = 2.92; 95% CI 2.402–3.552; $p < 0.001$; $I^2 = 81.85\%$ $Q = 110.179$, 95% CI 73.22–87.70, $p < 0.001$). Figure 2A shows the forest plot. Begg's test and Egger's test showed the absence of publication bias (Egger's regression test, $p = 0.12$; Begg's regression test, $p = 0.28$). The funnel plot, as shown in Figure 2B, reports the symmetry of the results from the individual included studies, suggesting limited evidence of potential publication bias.

4 | DISCUSSION

This is the first meta-analysis to examine the risk of gastric cancer only in first-degree relatives with gastric cancer. Previous meta-analyses have primarily concentrated on the risk within family history, while this analysis specifically excluded studies that did not specify the degree of relatives or considered second- or third-degree relatives. In this context, this meta-analysis revealed a higher risk of developing gastric cancer ([OR] = 2.91) compared to previous meta-analyses.[8–10] This difference could be attributed to a substantial discrepancy in the studies included. Prior meta-analyses emphasised significant heterogeneity, which was addressed by implementing stringent inclusion criteria. For these reasons, unlike previous meta-analyses, studies that examined the risk of cardias tumours (due to aetiological and pathogenic differences between cardia and non cardia tumours[44]) and "studies exclusively focusing on cases with *H. pylori* infection" were excluded. It is essential to clarify that *H. pylori* plays a predominant role in the familial predisposition to gastric cancer. Other meta-analyses have investigated the role of *H. pylori* in patients with a family history of gastric cancer and revealed that the prevalence of *H. pylori* in these patients is twice that in the general population.[45] In fact, studies that select cases only from patients positive for *H. pylori* infection report a higher OR, but this represents a selection bias. In addition, prospective studies that have expressed a hazard ratio (despite the potential advantages of prospective cohort studies in minimising biases) were excluded due to their limited availability, prioritising the analysis of case–control studies for data homogeneity. Prospective studies that present hazard ratios express the dynamic relationship between exposure and outcome over time, whereas case–control studies that provide odds ratios show the association irrespective of temporal sequence.[46] Despite the more rigorous inclusion criteria, high heterogeneity between studies remained, perhaps due to the medium/low levels of quality assessed with the Newcastle–Ottawa quality assessment scale. Another reason for the high heterogeneity is the definition of the population of controls, which in some cases is not well defined or is derived from the hospital cohort.[13] In Eastern countries such as China, Korea, and Japan, gastric cancer screening allows for the recruitment of asymptomatic individuals without a family history, whereas in Western countries, population control is established in various ways.[47] Some studies consider patients matched by age and sex who undergo gastroscopy for dyspeptic symptoms, which could be considered a symptom related to *H. pylori* infection, rather than asymptomatic individuals. Other studies consider spouses or neighbours, a population that could have a bias due to environmental factors such as smoking and diet. Regarding gastric precancerous conditions, during data extraction, it was found that numerous studies considered the risk of precancerous conditions and dysplasia in this population. However, a systematic review of the literature on this topic was not conducted, and a subanalysis of these data could be misleading. A systematic review and meta-analysis would be beneficial for quantifying the risk of these conditions in first-degree relatives with gastric cancer.

In conclusion, in a context where early identification of high-risk patients is crucial for the early diagnosis of gastric cancer, this meta-analysis has demonstrated that individuals who have a first-degree relative with gastric cancer are at an approximately threefold higher risk of developing this disease. This finding supports the British guidelines statement[7] underlining the importance of proactive endoscopic screening in this high-risk population.

AUTHOR CONTRIBUTIONS

Irene Ligato: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; writing – original draft; writing – review and editing. **Ludovica Dottori:** Data curation; formal analysis; investigation. **Caterina Sbarigia:** Data curation; formal analysis; writing – review and editing. **Emanuele Dilaghi:** Conceptualization; writing – review and editing. **Bruno Annibale:** Conceptualization; writing – review and editing. **Edith Lahner:** Conceptualization; data curation; formal analysis; writing – original draft; writing – review and editing. **Gianluca Esposito:** Conceptualization; project administration; writing – original draft; writing – review and editing.

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