# Gastric Cancer Risk of Intestinal Metaplasia Subtypes: A Systematic Review and Meta-Analysis of Cohort Studies

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INTRODUCTION: **Intestinal metaplasia (IM) is an independent risk factor for gastric cancer (GC). However, the subtypes of IM as a risk factor for GC remain controversial. We performed a systematic review and meta-analysis to evaluate the relationship between IM subtypes and GC risk.**

METHODS: **Systematic searches were conducted in PubMed, EMBASE, and the Cochrane Library for published cohort studies of patients with complete IM (type I) or incomplete IM (type II or type III) from inception to May 15, 2021. We extracted relevant data and calculated pooled risk ratios (RRs) and 95% confidence intervals (CIs) comparing the GC risk with IM subtypes.**

RESULTS: **Twelve cohort studies comprising 6,498 individuals were included in the study. Compared with complete IM, the pooled relative risk of GC risk of patients with incomplete IM was 5.16 (95% CI, 3.28–8.12), and the GC risk of type III IM was the highest, with a pooled relative risk of 2.88 (95% CI, 1.37–6.04) compared with that of type II. Compared with complete IM, the pooled relative risk of dysplasia risk in patients with incomplete IM was 3.72 (95% CI, 1.42–9.72), and the dysplasia risk of type III IM was 11.73 (95% CI, 2.08–66.08) compared with that of type I.**

DISCUSSION: **Patients with incomplete IM, especially type III, were at a higher risk of GC and dysplasia than those with complete IM. The current evidence indicates a potential correlation between IM subtypes and GC risk, which may support the use of IM subtypes in GC surveillance.**

**SUPPLEMENTARY MATERIAL** accompanies this paper at http://links.lww.com/CTG/A676, http://links.lww.com/CTG/A677

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## INTRODUCTION

Gastric cancer (GC) remains a major health problem in many countries, with more than 1.22 million incident cases of GC occurring worldwide in 2017, with nearly half of the global incident cases occurring in China (1). GC is the third leading cause of cancer mortality, causing an estimated 783,000 deaths globally in 2018 (2). High mortality in GC is closely related to its silent nature (3). Therefore, early detection and treatment are important approaches to improve the survival of patients with GC.

Intestinal-type gastric adenocarcinoma is the final stage of what is known as the Correa cascade, which pertains to the carcinoma sequence of chronic gastritis to atrophy gastritis, then intestinal metaplasia (IM), to the final dysplasia (4). The stepwise progression of intestinal-type gastric adenocarcinoma allows for the early detection and resection of neoplastic lesions. Histologically confirmed IM is a precancerous condition of GC that has been suggested to be an independent risk factor for GC and is recommended as the most reliable marker of gastric mucosal atrophy in the management of epithelial precancerous conditions and lesions in the stomach (MAPS II) (5).

IM can be classified according to histologic subtypes: complete IM (type I) and incomplete IM (type II or type III) (6). Previous reviews and meta-analyses found that incomplete IM was associated with a higher risk of GC compared with complete IM (7–9); however, additional studies are required before subtyping can be routinely recommended. Previous reviews and meta-analyses were limited to descriptive reviews or subgroup analyses of IM subtypes based on multiple observational studies, including cross-sectional studies; however, incomplete IM is not always found in the gastrectomy specimens of patients with GC (10–12). Instead, a cohort study, where an outcome or disease-free study population is first identified and monitored in time until the disease or outcome of interest occurs, can provide powerful prognostic-related results (13). Thus, we aimed to systematically

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assess the relationship between IM subtypes and GC risk in cohort studies.

## METHODS

The protocol for this systematic review was based on the Meta-Analysis of Observational Studies in Epidemiology (14). The protocol was prospectively registered at PROSPERO (CRD42020176936).

### Search strategy

Two reviewers (S.D. and S.F.) independently searched electronic databases, including PubMed, EMBASE, and the Cochrane Library, from inception to May 15, 2021. The search equations were "intestinal metaplasia" AND "(gastric cancer) OR (gastric neoplasm) OR (gastric carcinoma) OR (stomach cancer) OR (stomach neoplasm) OR (stomach carcinoma)" AND "(cohort) OR (follow-up)." In addition, the references of identified articles were also searched for potentially missed articles.

### Study selection

After excluding duplicate studies, the 2 reviewers (S.D. and S.F.) screened the titles and abstracts of all retrieved articles to exclude irrelevant studies and then read the full text of the remaining studies to include eligible studies. Disagreements were resolved through discussion or by involving a third reviewer (S.G.) when necessary.

The inclusion criteria were as follows: patients (individuals diagnosed with IM), intervention (being diagnosed with incomplete IM), comparator (being diagnosed with complete IM), outcome (GC and dysplasia incidence in patients with IM subtypes confirmed by pathologic diagnosis or records from government registration), and study design (cohort studies). The exclusion criteria were as follows: (i) insufficient data in original studies, (ii) duplicate publications, (iii) conference abstracts, and (iv) studies published in a non-English language.

### Data extraction and quality assessment

Two reviewers (G.S. and C.X.) independently screened all the included studies to extract the following data: name of the first author, publication year, study design, country, study period, sample size, age, sex, duration of follow-up, number of patients with IM subtypes, and numbers of GC and dysplasia. They independently assessed the quality of the included studies according to the Newcastle-Ottawa Quality Assessment Scale. Disagreements were resolved through discussion or by involving a third reviewer (S.D.) when necessary.

### Outcomes

The primary outcome was the incidence of GC in patients with IM subtypes. The secondary outcomes were the incidence of dysplasia in patients with IM subtypes and the incidence of GC and dysplasia among patients with IM subtypes in different countries and pathological quality control.

### Statistical analysis

We calculated the risk ratios (RRs) and 95% confidence intervals (CIs) using 2 × 2 table data extracted from the original studies. We pooled the results with RRs and 95% CIs using a fixed-effects or random-effects model, depending on study heterogeneity. Heterogeneity in the included studies was assessed using the Cochran Q test and quantity $I^2$. An $I^2$ greater than 50% suggested significant heterogeneity (15). To explore the source of heterogeneity, sensitivity and subgroup analyses were further performed according to the potential effect modification of factors, including country and pathological quality control. Funnel plots were generated to evaluate the possibility of publication bias (16). All statistical analyses were conducted using Review Manager, version 5.3 (Cochrane Reviews).

## RESULTS

### Literature search

As shown in Figure 1, 928 articles were identified using a search strategy from PubMed, EMBASE, and the Cochrane library, of which 295 were duplicated articles. In the remaining 633 articles, 604 irrelevant articles were excluded after reviewing the titles and abstracts; hence, 29 articles remained. Subsequently, 19 articles were excluded for the following reasons: insufficient data (n = 2), conference abstracts (n = 9), cross-sectional studies (n = 6), no diagnosis of IM subtype (n = 1), and no comparator (n = 1). Two potential articles were included from the reference list. Finally, 12 articles were included in this meta-analysis (17–28).

### Study characteristics and quality assessment

The main characteristics of the 12 articles are summarized in Table 1. Among the 12 cohort studies, 10 were prospective cohort studies (18–20,22–28) and 2 were retrospective cohort studies (17,21); 4 studies were conducted in Asia (20,22,25,28), 7 were conducted in Europe (17–19,21,23,24,26), and 1 was conducted in South America (27). In total, 6,498 individuals were included in this meta-analysis, and the sample size of the included studies ranged from 62 to 2,980. All studies included both male and female patients. All the included studies presented the numbers of IM subtypes at baseline and GC at end point, whereas 8 studies presented the numbers of dysplasia at the end point. The numbers of IM subtypes, GC, and dysplasia of the included articles are listed in Table 2. Quality assessment is also summarized in Table 1, where all studies obtained 6 or more stars.

Based on the 12 studies, the fixed-effects estimated pooled prevalence of incomplete IM among patients with IM was 42% (95% CI, 34%–49%) and complete IM was 58% (95% CI, 50%–66%), presented as forest plots in Supplementary Figures 1 and 2 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A676). In patients with incomplete IM, the fixed-effects estimated pooled prevalence of type II IM was 45% (95% CI, 41%–49%) and type III IM was 55% (95% CI, 51%–59%), presented as forest plots in Supplementary Figures 3 and 4 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A676).

### Outcomes

A total of 12 studies with 6,498 participants were included in this meta-analysis to evaluate GC risk in patients with IM subtypes. Compared with complete IM, the pooled relative risk of GC in patients with incomplete IM was 5.16 (95% CI, 3.28–8.12), and GC risk of type III IM was highest with a pooled relative risk of 2.88 (95% CI, 1.37–6.04) compared with type II and 6.42 (95% CI, 3.03–13.62) compared with type I. In addition, GC risk of type II IM was not significantly higher than type I (RR, 2.37; 95% CI, 0.84–6.72). Forest plots of GC risk in the IM subtypes are shown in Figure 2.

A total of 7 studies with 1,473 participants were included in this meta-analysis to evaluate dysplasia risk in patients with IM subtypes. Compared with complete IM, the pooled relative risk of

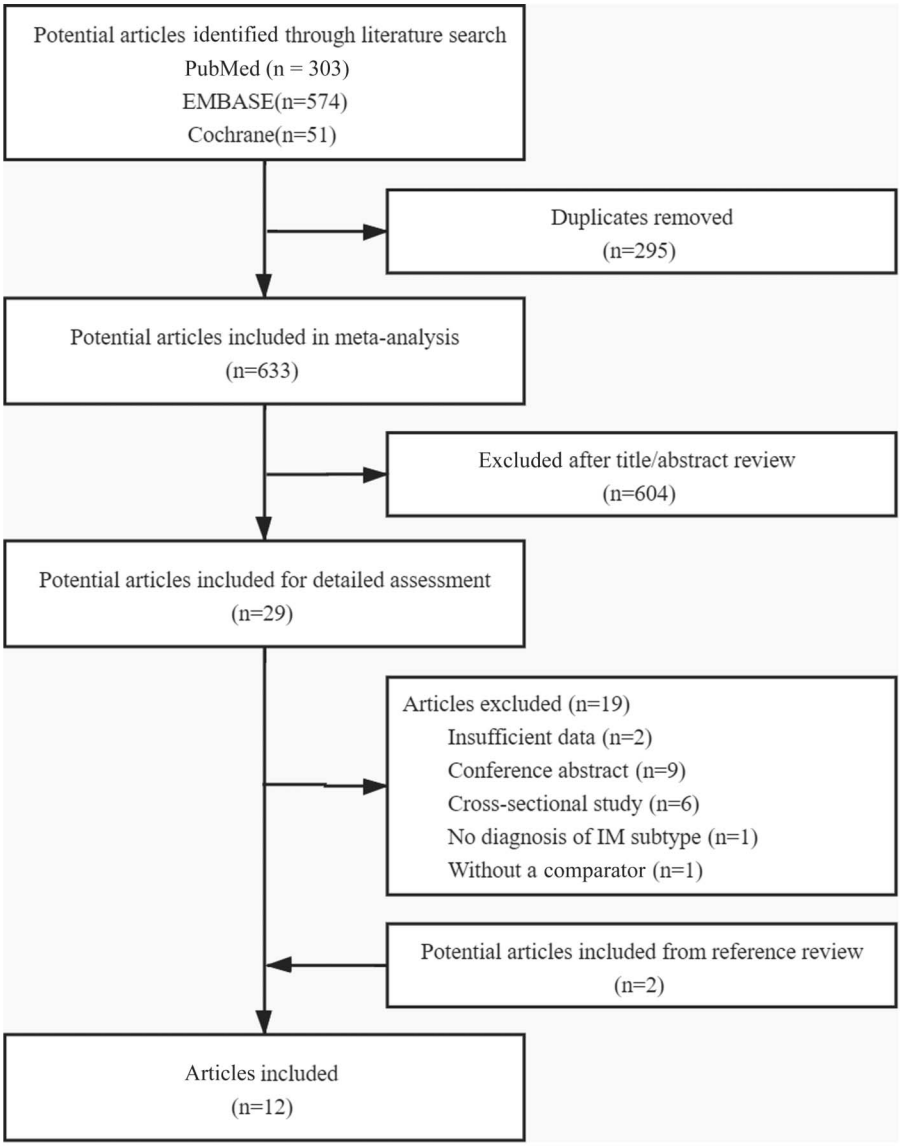


**Figure 1.** Flow diagram of literature search and study selection.

dysplasia in patients with incomplete IM was 3.72 (95% CI, 1.42–9.72), and the pooled relative risk in type III IM was 11.73 (95% CI, 2.08–66.08) compared with type I but not significantly higher than type II. Moreover, dysplasia risk of type II IM was not significantly higher than that of type I. Forest plots of GC risk in IM subtypes are shown in Figure 3.

Subgroup analysis was also performed according to the country of origin and pathological quality control (Table 2). According to the country of origin, the GC risk of incomplete IM was higher in Asia (RR, 8.83; 95% CI, 3.05–25.56), Europe (RR, 4.23; 95% CI, 2.51–7.14), and South America (RR, 8.16; 95% CI, 1.02–65.32) compared with that of complete IM. In addition, 5 studies performed pathological quality control, which indicated a significantly higher GC risk of incomplete IM compared with that of complete IM (RR, 5.45; 95% CI, 3.02–9.84). Forest plots of the subgroup analysis are shown in Figure 4. According to the country of origin, the dysplasia risk of incomplete IM was higher in Europe (RR, 4.05; 95% CI, 1.65–9.93) and South America (RR, 8.16; 95% CI, 1.89–35.14) compared with that of complete IM. Three studies performed pathological quality control, which indicated a significantly higher dysplasia risk of incomplete IM compared with that of complete IM (RR, 4.67; 95% CI, 1.11–19.63). Forest plots of the subgroup analysis are shown in Figure 5.

### Publication bias

For the risk of GC of incomplete IM vs complete IM, a funnel plot (Figure 6) suggested that publication bias may exist. The results may be related to the small sample size of some included studies and the exclusion of non-English articles and conference abstracts. However, because the abstracts do not contain complete original data, publication bias is inevitable.

## DISCUSSION

IM is an independent risk factor for GC, with an annual incidence of 12.4 (95% CI, 10.7–14.3) cases of GC per 10,000 persons with

**Table 1. Characteristics of studies included in the meta-analysis**

| First author | Year | Design | Country | Study period | Sample size | Age, y | Sex | Follow-up, mo | Quality assessment |
|---|---|---|---|---|---|---|---|---|---|
| Ramesar[17] | 1987 | RC | UK | 1976–1987 | 174 | Mean 60.8 | 53% M | 120–132 | 7 |
| Sossai[18] | 1990 | PC | Italy | None | 112 | Mean 64.2 | 57% M | 12–88 | 7 |
| Silva[19] | 1990 | PC | Portugal | 1982–1988 | 124 | 31–76 | 71% M | 12–72 | 7 |
| Fang[20] | 1991 | PC | China | 1982–1987 | 112 | 18–70 | 80% M | 15–70 | 6 |
| Filipe[21] | 1994 | RC | Slovenia | 1967–1986 | 1,281 | NR | 65% M | 126–234 | 8 |
| Sun[22] | 2009 | PC | China | 1989–2003 | 62 | NR | NR | 60–168 | 6 |
| Gonzalez[23] | 2010 | PC | Spain | 1988–1994<br>2005–2007 | 478 | Mean 50 | 47% M | Mean 153.6 | 8 |
| Gonzalez[24] | 2016 | PC | Spain | 1995–2004<br>2011–2013 | 649 | Mean 52 | 54% M | Mean 144 | 8 |
| Pittayanon[25] | 2017 | PC | Thailand | 2004–2014 | 91 | 63 ± 13.3 | 51% M | 48.6 ± 30 | 8 |
| Chapelle[26] | 2020 | PC | France | 2000–2015 | 79 | Mean 61 | 44% M | Mean 66 | 7 |
| Piazuelo[27] | 2021 | PC | Colombia | 1991–2011 | 356 | 69 ± 8 | 45% M | 240 | 8 |
| Lee[28] | 2021 | PC | Singapore | 2004–2010 | 2,980 | 59.1 ± 6.7 | 52% M | Mean 52.8 | 8 |

NR, not reported; PC, prospective cohort; RC, retrospective cohort.

IM (9). The Operative Link on Gastritis Assessment (29) and Operative Link on Gastritis Intestinal Metaplasia Assessment (OLGIM) (30) systems have been proposed for staging of atrophy and IM. A meta-analysis revealed that stage III/IV OLGIM system was indeed associated with an increased risk of GC (31). Management of epithelial precancerous conditions and lesions in the stomach II recommended that patients with advanced stages of atrophic gastritis (Operative Link on Gastritis Assessment/OLGIM III/IV) should be followed up with a high-quality endoscopy every 3 years (5). The key issue is that the use of OLGIM has some limitations when only a few biopsies are available for examination, which always happens in clinical practice; thus, other reliable GC risk assessment systems or markers are urgently needed.

The IM subtype may be an easier way to assess the risk of GC. Since the 1970s, investigators have found that there are variants of IM that differ based on morphology and mucin secretion, and they found that some variants were more strongly associated with

**Table 2. Characteristics of the IM subtypes and GC of studies included**

| | | | | | No. of GC | | | No. of dysplasia | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. of CIM | No. of IIM | | No. of CIM at baseline | No. of IIM at baseline | | No. of CIM at baseline | No. of IIM at baseline | | |
| First author | Year | Type I | Type II | Type III | Type I | Type II | Type III | Type I | Type II | Type III | Pathological quality control |
| Ramesar[17] | 1987 | 16 | 14 | 14 | 0 | 1 | 1 | NR | NR | NR | NR |
| Sossai[18] | 1990 | 71 | 22 | 19 | 0 | 0 | 2 | 9 | 7 | 5 | NR |
| Silva[19] | 1990 | 101 | 12 | 11 | 0 | 0 | 1 | 0 | 0 | 3 | NR |
| Fang[20] | 1991 | 47 | 34 | 31 | 0 | 0 | 5 | NR | NR | NR | NR |
| Filipe[21] | 1994 | 518 | 197 | 275 | 6 | 5 | 15 | NR | NR | NR | NR |
| Sun[22] | 2009 | 19 | 22 | 21 | 0 | 1 | 3 | 6 | 4 | 3 | NR |
| Gonzalez[23] | 2010 | 104 | 88 | | 1 | 16 | | 0 | 0 | | Yes |
| Gonzalez[24] | 2016 | 248 | 219 | | 8 | 15 | | 9 | 13 | | Yes |
| Pittayanon[25] | 2017 | 81 | 10 | | 0 | 3 | | 1 | 2 | | Yes |
| Chapelle[26] | 2020 | 60 | 13 | | 0 | 2 | | 2 | 3 | | NR |
| Piazuelo[27] | 2021 | 134 | 115 | | 1 | 7 | | 2 | 14 | | Yes |
| Lee[28] | 2021 | 302 | 244 | | 2 | 13 | | NR | NR | | Yes |

CIM, complete intestinal metaplasia; GC, gastric cancer; IIM, incomplete intestinal metaplasia; NR, not reported.

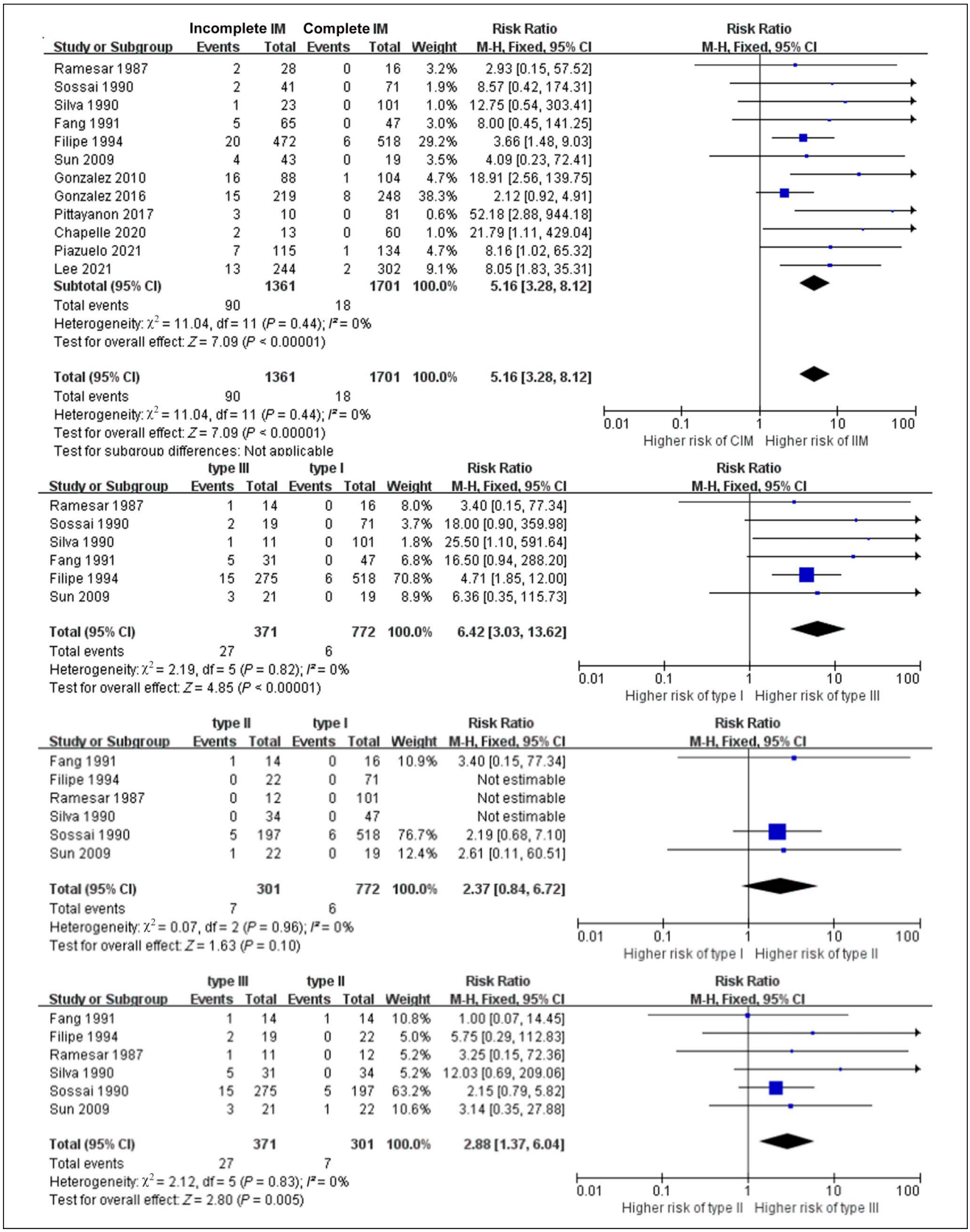


**Figure 2.** Forest plots of gastric cancer risk in IM subtypes. IIM, incomplete intestinal metaplasia; CIM, complete intestinal metaplasia; CI, confidence interval; M-H, Mantel-Haenszel.

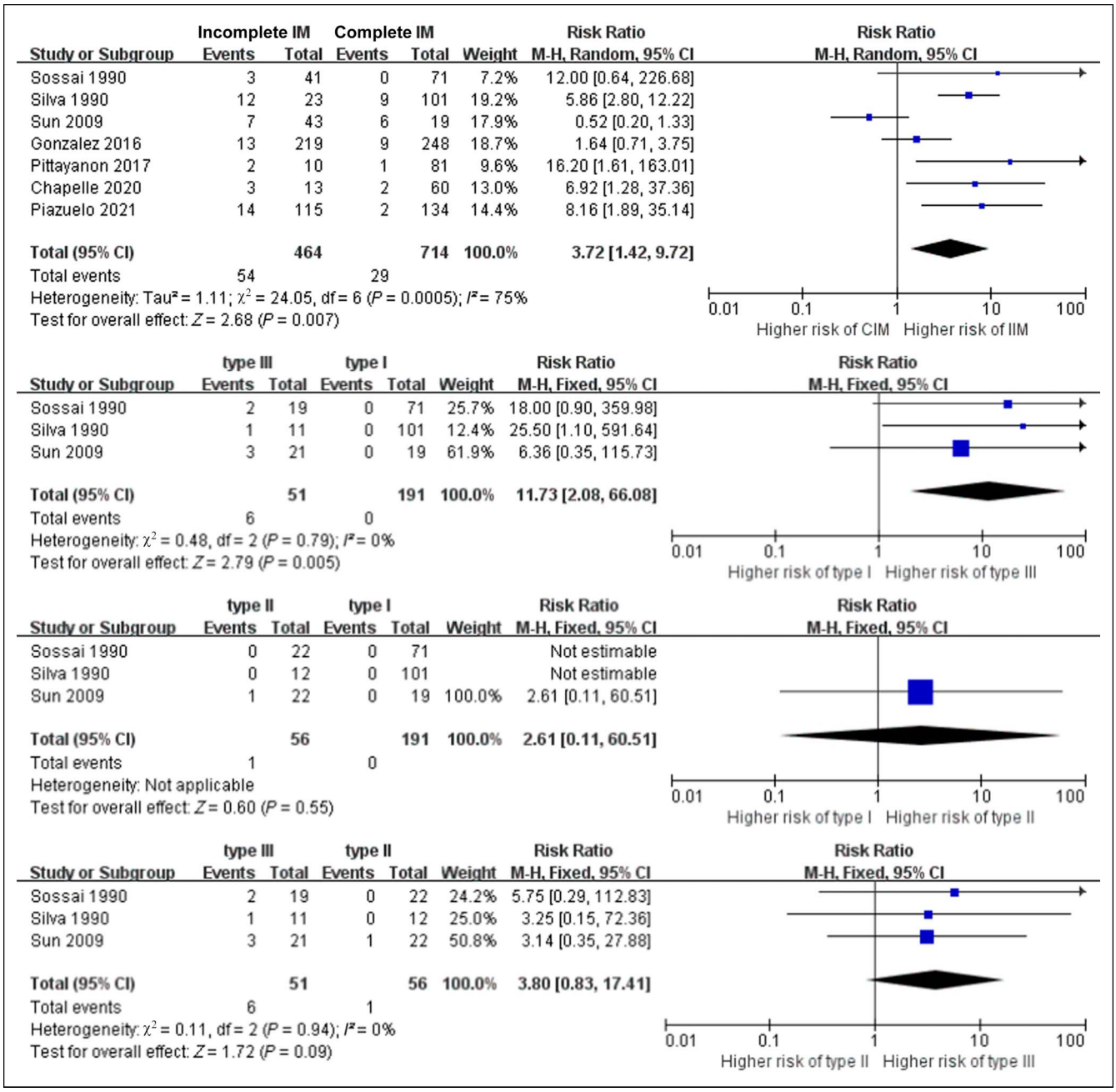


**Figure 3.** Forest plots of dysplasia risk in IM subtypes. IIM, incomplete intestinal metaplasia; CIM, complete intestinal metaplasia; CI, confidence interval; M-H, Mantel-Haenszel.

the risk of intestinal-type gastric adenocarcinoma (32–36). According to the general pathological classification criteria proposed by Jass and Filipe, IM can be classified as complete IM (type I) and incomplete IM (type II or type III) (6). In complete IM (type I), sialomucins are present in goblet cells with no mucins in columnar cells. In type II IM, sialomucins are present in goblet and columnar cells, and sulfomucins are absent in goblet cells. In type III IM, sulfomucins predominate in columnar cells, and goblet cells may contain sialomucins or sulfomucins (37).

Our study provided a comprehensive summary of the relationship between IM subtypes and GC risk and included only cohort studies with high scores of quality assessment (7.33 on average) to ensure the overall quality of evidence. This meta-analysis of cohort studies included 12 studies with 6,498 participants to evaluate the relationship between IM subtypes and GC risk. Compared with complete IM, the pooled relative risks of GC and dysplasia risk of patients with incomplete IM was 5.16 (95% CI, 3.28–8.12) and 3.72 (95% CI, 1.42–9.72), respectively, and the risk of type III IM was the highest. The abovementioned results are more significant in high-incidence areas of GC (Asia and South America). In addition, interobserver agreement between pathologists can improve the accuracy of pathological diagnosis, and research has gradually found that it is poor for AG but moderate or strong for IM (38–40). As reported in the included

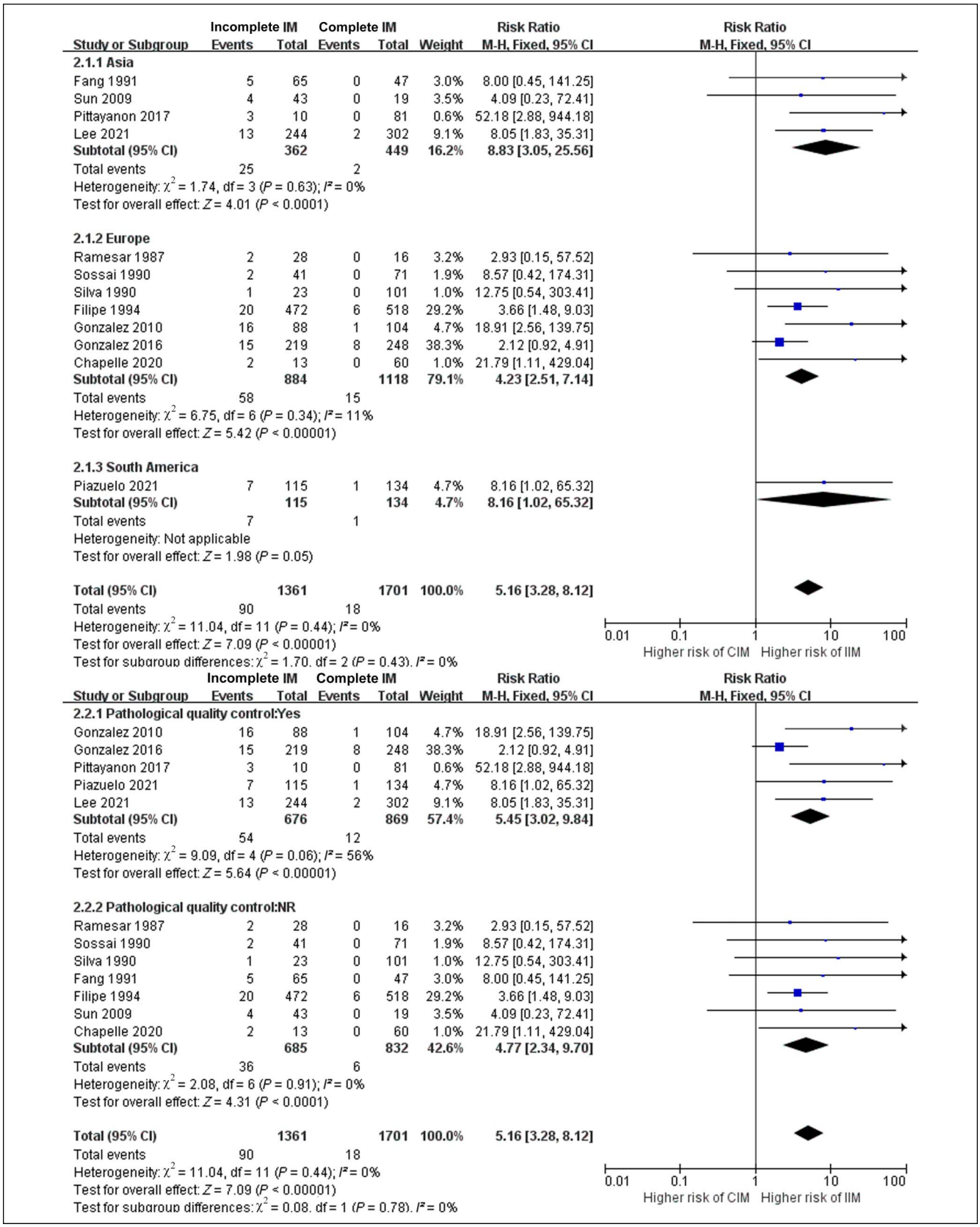


**Figure 4.** Forest plots of subgroup analysis of gastric cancer risk in IM subtypes according to country of origin and pathological quality control. IIM, incomplete intestinal metaplasia; CIM, complete intestinal metaplasia; CI, confidence interval; M-H, Mantel-Haenszel.

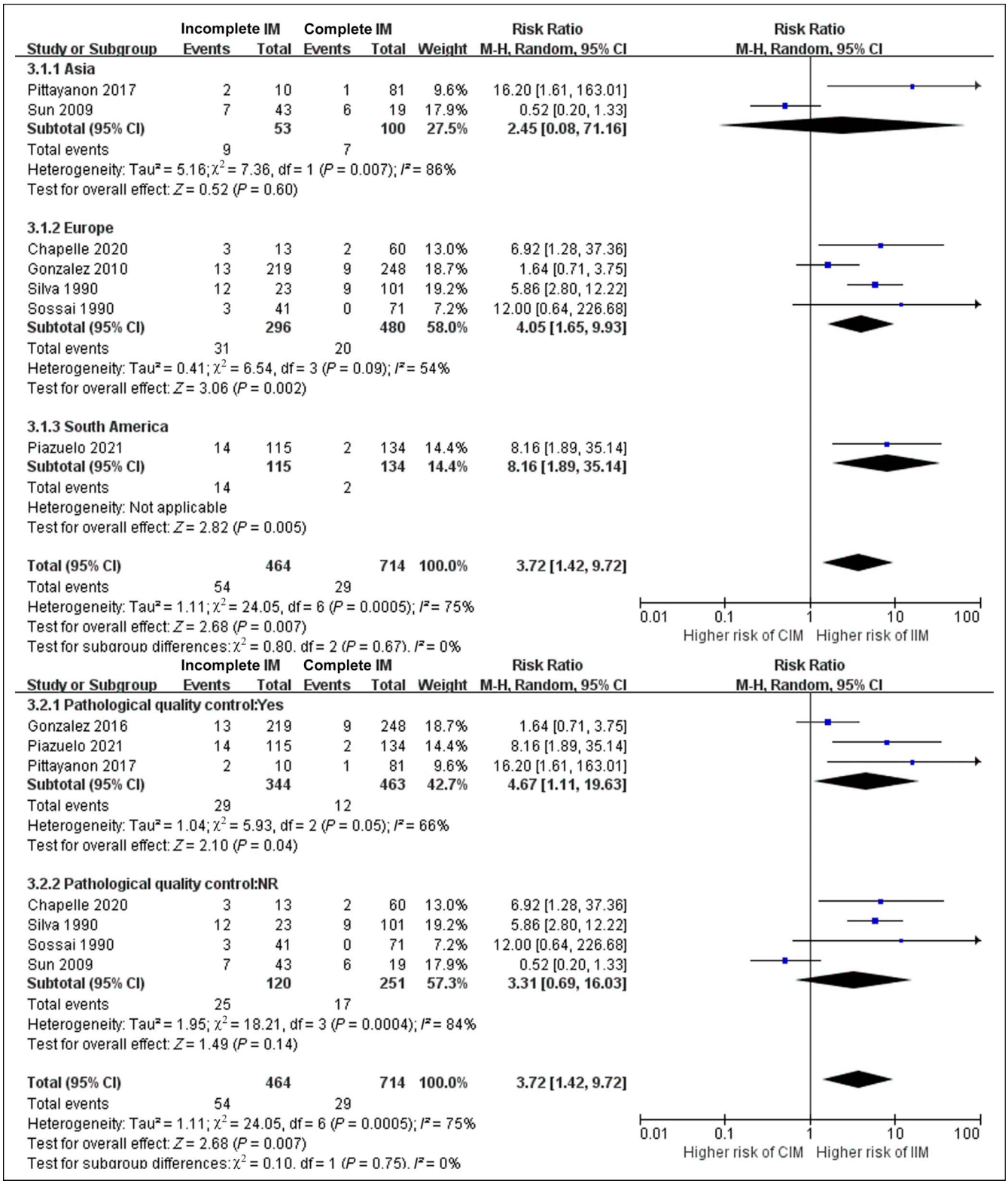


**Figure 5.** Forest plots of subgroup analysis of dysplasia risk in IM subtypes according to country of origin and pathological quality control. IIM, incomplete intestinal metaplasia; CIM, complete intestinal metaplasia; CI, confidence interval; M-H, Mantel-Haenszel.

studies, the abovementioned subtype staining results are easy to identify and distinguish, so the level of interobserver agreement for the IM subtype is likely similarly high. In our study, we conducted a subgroup analysis on whether to perform pathological quality control, which showed that the pooled relative risk (5.45, 95% CI, 3.02–9.84) of pathological quality control was

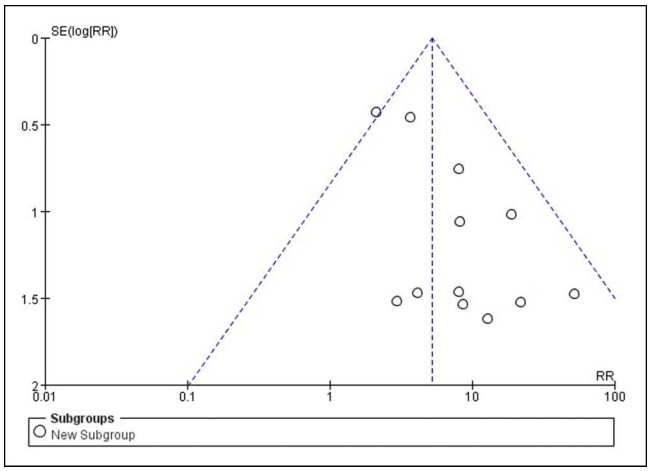


**Figure 6.** Funnel plots for the analysis of publication bias.

similar to the total pooled results, which proved that the IM subtypes have a high coincidence rate in the pathological diagnosis.

González et al. (7) conducted a review of the evidence including 14 cross-sectional studies and 10 follow-up studies assessing the risk of GC among subjects with different types of IM, and the results showed that the relative risks of GC were 4- to 11-fold higher for the presence of incomplete IM in comparison with complete IM or the absence of incomplete IM. Similarly, Shao et al. (8) observed that incomplete IM (pooled OR = 9.48, 95% CI, 4.33–20.78), but not complete IM (pooled OR = 1.55, 95% CI, 0.91–2.65), was significantly associated with a higher GC risk in a meta-analysis of GC risk among patients with gastric IM. The results of our systematic review and meta-analysis are consistent with the abovementioned research conclusions.

In addition, we found that the fixed-effects estimated pooled prevalence of incomplete IM among patients with IM was 42% (95% CI, 34–49) and complete IM was 58% (95% CI, 50–66), which is consistent with previous research results (41). The widespread distribution of incomplete IM further illustrates the necessity of clinical subtype diagnosis; however, we believe that the main barrier to clinical implementation is the limited reliable evidence-based data, which is mainly caused by the heterogeneity of the research with different study designs, periods, endoscopic and biopsy protocols, and variable follow-up statuses. Fortunately, in recent years, reports of related long-term cohort studies have gradually increased. We, therefore, chose cohort studies for the meta-analysis to obtain more objective results. In clinical practice, Correa et al. (42) suggested that a diagnosis of incomplete IM should be followed by endoscopic topographic mapping to evaluate its extension and rule out more advanced lesions, such as dysplasia or early adenocarcinoma. Shah et al. (37) also promoted the utility of the IM subtype for potential prognostic value and cost-effective pathological operation. In addition, the diagnosis of mixed complete and incomplete IM has not yet been unified, and consensus on pathological diagnosis needs to be formed later.

Our systematic review and meta-analysis had several limitations. First, only 3 electronic databases were searched, and only studies published in English were included, which may have missed potential studies in other databases or those published in other languages. Second, the included studies were from Asia, Europe, and South America; the limited generalizability to global populations cannot be ignored. Third, all the included studies were cohort studies, of which 10 were prospective cohort studies; several biases could not be avoided, particularly follow-up bias. Fourth, we calculated the RRs and 95% CIs by using the 2 × 2 table data extracted from the original studies; hence, confounding factors could not be excluded or matched, such as sex, age, family history of GC, and *Helicobacter pylori* infection. Finally, all the included studies presented the numbers of IM subtypes at baseline and GC at the end point; only 2 studies reported the hazards ratio of progression to GC for patients with incomplete IM compared with that for patients with complete IM (see Supplementary materials, http://links.lww.com/CTG/A677). However, RR and hazards ratio cannot be pooled even if we calculate the RRs of the remaining 10 studies because the absolute risk of GC in patients with IM is not low (43). A technical review reported that the annual incidence of GC is 12.4 cases per 10,000 persons with IM (9), and a Japanese study reported a higher cumulative incidence of GC at 5 years, reaching 5.3%–9.8% in patients with IM (44). Considering the abovementioned factors, we calculated the RRs and 95% CIs by using the 2 × 2 table data extracted from all the original studies and pooled the results with RRs and 95% CIs.

In conclusion, our systematic review and meta-analysis indicated that the GC risk of incomplete IM, especially type III, was higher than that of complete IM. The current evidence indicates a correlation between IM subtypes and GC risk, which may support the use of IM subtypes in GC surveillance. More population-based prospective cohort studies are warranted to confirm our findings.

## CONFLICTS OF INTEREST

**Guarantor of the article:** Wei Wei, MD.
**Specific author contributions:** S.D., S.F., P.Z., and W.W: conception and design. S.D. and S.G.: analysis and interpretation of the data. S.D. and Y.Y: drafting of the article. S.D.: critical revision of the article for important intellectual content. all authors: final approval of the article.
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**Potential competing interests:** None to report.

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