

Metformin use and the risk of gastric cancer: a systematic review and meta-analysis

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Abstract

The use of metformin may reduce the risk of gastric cancer in people with type 2 diabetes, but the evidence remains controversial. We conducted a systematic review and meta-analysis to evaluate this association based on observational cohort studies. We systematically searched the PubMed, Embase, and Web of Science databases, covering the period from the inception of each database through December 2025. A total of 9 retrospective cohort studies involving 1,271,266 participants were included. Analysis using a random-effects model showed that metformin use was associated with a significant reduction in the risk of gastric cancer (HR = 0.72; 95% CI: 0.39–0.87; P = 0.0008). Subgroup analyses indicated no significant difference in the protective effect between genders; however, a significant risk reduction was observed only among those with long-term use (≥ 3 years) (HR = 0.30; 95% CI: 0.12–0.75), while short-term use (< 3 years) did not show a significant benefit. There was heterogeneity among the included studies ($I^2 = 86\%$, $P < 0.00001$). These results suggest that metformin use, particularly long-term use, is associated with a reduced risk of gastric cancer in patients with type 2 diabetes. Given the heterogeneity among studies and potential publication bias, further high-quality prospective studies are needed to validate these findings before recommending metformin for the chemoprevention of gastric cancer.

1. Introduction

As a prevalent public health concern, gastric cancer imposes a considerable economic and clinical strain on healthcare systems worldwide.^[1] Gastric cancer ranks fifth in incidence and fourth in mortality among all cancers worldwide. According to the latest data from 2020, there are 1,089,103 new cases of gastric cancer worldwide each year, and 768,793 deaths from the disease. In China, gastric cancer ranks third in both incidence and mortality among all cancers.^[2–3] Radical surgical resection is the only curative treatment for early-stage gastric cancer; however, the majority of patients are diagnosed with locally advanced or advanced gastric cancer. For advanced gastric cancer, perioperative chemotherapy, palliative chemoradiation, targeted therapy, and immunotherapy can reduce tumor size and prolong patient survival to some extent. Nevertheless, these treatments are associated with tumor resistance, significant adverse reactions, and high rates of recurrence and metastasis, resulting in limited overall long-term therapeutic benefits. the overall 5-year survival rate for gastric cancer patients in China remains relatively low. Therefore, identifying low-cost interventions capable of intervening in the early stages of carcinogenesis to reduce the risk of gastric cancer or improve the long-term prognosis of patients has become a current research focus in the field of gastric cancer prevention and control.☐

Metformin is a classic first-line oral antidiabetic drug widely used in the long-term management of type 2 diabetes. In recent years, numerous epidemiological and basic experimental studies have found that metformin exerts a chemopreventive effect during the precancerous stage of gastric cancer through various molecular mechanisms, including regulation of the AMPK pathway, inhibition of tumor cell proliferation and invasion, improvement of the tumor microenvironment, and antagonism of chronic inflammation, thereby reducing the risk of gastric cancer in high-risk populations. At the same time,

some cohort studies also suggest that metformin may improve treatment outcomes for gastric cancer patients with concomitant diabetes. However, conclusions from existing clinical studies remain inconsistent, and there is significant heterogeneity in sample sizes and study designs. Therefore, this study aims to use meta-analysis to systematically integrate existing evidence and comprehensively evaluate the role of metformin in the early prevention of gastric cancer, thereby providing evidence-based medical guidance for the primary prevention of gastric cancer.

2. Methods

This study addresses two core questions: Question 1: Is there an association between metformin use and a reduced risk of gastric cancer in patients with type 2 diabetes? Question 2: Do subgroup analyses (including stratification by gender and duration of treatment) support the stability of the effect of the association between metformin and gastric cancer risk? This study was conducted in strict accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines. The literature screening process and the results of the inclusion and exclusion criteria are presented in Supplementary Fig. 1.

2.1. Databases and Search Strategy

This study conducted a systematic computerized search of PubMed, Embase, and Web of Science, with the search period for each database spanning from its inception to December 2025. Search terms included: gastric cancer (e.g., “gastric tumor,” “gastric adenocarcinoma,” “gastric cancer”), metformin (e.g., “metformin”), and risk of gastric cancer (e.g., “incidence,” “risk of occurrence,” “risk factors”). Additionally, the reference lists of included studies were manually searched to identify any omitted studies. The literature screening process and results are shown in Supplementary Figure S1. After data extraction, statistical analysis was performed using Review Manager 5.3 software. Heterogeneity was assessed using a forest plot, and either a fixed-effects model or a random-effects model was selected based on the degree of heterogeneity (a fixed-effects model was used when $I^2 < 50\%$; otherwise, a random-effects model was used); when heterogeneity was significant, subgroup analysis was conducted to explore its sources. Publication bias was assessed using a funnel plot. The basic characteristics of the included studies and the NOS quality assessment results are summarized in a single table (Supplementary Table 1).

2.2. Inclusion and Exclusion Criteria:

Based on the research questions proposed in this study and in accordance with the PICOS principles (population, intervention, control, outcome, and study design), the following inclusion criteria were established in advance: (1) The study design is a cohort study (including retrospective cohort studies); (2) The study population consisted of patients with type 2 diabetes, divided into two groups based on metformin exposure: the intervention group comprised patients treated with metformin alone or metformin in combination with other antidiabetic drugs, while the control group comprised patients who

did not use metformin or were treated with other antidiabetic drugs (excluding metformin);(3) The outcome measures are the incidence of gastric cancer or the risk of developing gastric cancer;(4) The full text of the study must be available, and it must be possible to extract the sample sizes of the two groups, the number of gastric cancer events, and the relative risk (RR) with its 95% confidence interval (95% CI).

2.3. Data Extraction:

Studies that report only the hazard ratio (HR) but not the RR will also be included. Studies were excluded if they met any of the following criteria:(1) Studies that included patients with a history of gastric cancer or concurrent malignant tumors;(2) Studies that did not clearly report outcomes related to gastric cancer, or studies that duplicated previously published data, used the same database, or had overlapping samples;(3) Studies classified as reviews, abstracts, case reports, conference abstracts, commentaries, or animal studies.

2.4. Study Quality Assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of the included retrospective cohort studies. This scale, recommended by the Cochrane Handbook of Systematic Reviews of Interventions, is divided into three evaluation dimensions: (a) selection of the study population; (b) comparability between groups; and (c) definition of outcome measures. A star-rating system was used, with a maximum score of 9 stars; studies scoring 7 stars or higher were considered high-quality. Two reviewers (Y.-J. Wang and D.-Y. Sun) independently conducted the quality assessment; in cases of disagreement, a third reviewer (Z.-H. Wang) made the final decision.

2.5. Statistical Analysis

All data analyses were performed using Review Manager 5.3 software. The results of the meta-analysis were described and analyzed using the hazard ratio (HR) and its 95% confidence interval (CI). Heterogeneity was assessed using Cochran's Q test (significance level $\alpha = 0.1$) and the I^2 statistic: if $I^2 \leq 50\%$ and the P-value for the Q test was ≥ 0.1 , a fixed-effects model (Mantel-Haenszel method) was used; if $I^2 > 50\%$ or the P-value for the Q test was < 0.1 , a random-effects model (DerSimonian-Laird method) was used. The Z-test was used to test the significance of the pooled effect size, with $P < 0.05$ indicating a statistically significant difference. When heterogeneity was significant, subgroup analysis was conducted to explore its sources. In the subgroup analysis of duration of medication, if the original studies were stratified by different time periods (e.g., < 21.47 months, $21.47-45.97$ months, etc.), the data from each stratum were reclassified into two subgroups— < 3 years and ≥ 3 years—before inclusion in the meta-analysis to avoid bias resulting from inconsistent boundaries in the original groupings. Sensitivity analysis was conducted using the stepwise exclusion method to assess the impact of each study on the pooled effect size. Publication bias was qualitatively assessed using funnel plots.

3. Results

3.1. Study Selection and Characteristics

An initial search yielded a total of 414 articles. After excluding 276 duplicate articles, the remaining 138 were subjected to preliminary screening. By reviewing the titles and abstracts, 97 irrelevant articles—including reviews, meta-analyses, case reports, conference abstracts, basic research studies, and animal experiments—were excluded, leaving 41 articles for full-text screening. After evaluating the full texts, 32 articles were excluded due to unavailability of the full text or incomplete data; ultimately, 9 articles were included in the meta-analysis ^[4-12](Figure 1).

All 9 included studies were retrospective cohort studies, involving a total of 1,271,266 patients with type 2 diabetes. Among these, 6 studies were conducted in Asia (3 in Taiwan, China; 2 in South Korea; 1 in Hong Kong, China), and 3 were conducted in Europe (1 in Lithuania; 2 in Sweden). All included studies used metformin as the exposure and the risk of gastric cancer as the outcome measure; effect sizes were expressed as hazard ratios (HR) with their 95% confidence intervals. Table 1 summarizes the baseline characteristics, interventions, follow-up periods, and study quality assessments of the included studies.

3.2. Metformin Use and the Risk of Gastric Cancer

This primary outcome analysis included a total of 9 studies. The hazard ratio (HR) was used as the effect measure, and a random-effects model was employed for the meta-analysis. The results of the heterogeneity test showed $I^2 = 86\%$, $P < 0.00001$, indicating significant heterogeneity among the included studies; therefore, a random-effects model was used (Figure 2). The pooled results showed that the risk of gastric cancer among patients with type 2 diabetes who used metformin was significantly lower than among those who did not; the pooled HR was 0.72 (95% CI: 0.39–0.87), and the Z-score for the overall effect test was 3.37 ($P = 0.0008$), indicating a statistically significant difference.

The funnel plot showed an asymmetrical distribution of study points, with some points shifting to the left, suggesting that this meta-analysis may be subject to some publication bias or small-sample effects(Figure 3); therefore, the results should be interpreted with caution.

Table 1☐Characteristics of included studies

First author (year)	Study region	Study type	Sample size (E/C)	GC cases (E/C)	Effect measure	HR (95% CI)	Adjustments	NOS score
Audrius Dulskas (2020)	Lithuania	Retrospective cohort	99,992 (total) / NR	230 / 74	SIR ($\approx$ HR)	0.75 (0.66–0.86)	Age, sex	8
Chin-Hsiao Tseng (2016)	Taiwan, China	Retrospective cohort	287,971 / 16,217	759 / 89	HR	0.448 (0.359–0.558)	Age, sex, comorbidities, medications	9
Ji Hong You (2020)	Korea	Cohort	131,877 / 131,877	2,459 / 2,872	HR	0.841 (0.797–0.887)	Age, sex, smoking, alcohol, BMI, comorbidities	9
Jiaojiao Zheng (2019)	Sweden	Retrospective cohort	334,506 / 209,624	659 / 233	HR	1.08 (0.92–1.26)	Age, sex, education, comorbidities, medications	8
Joungyoun Kim (2020)	Korea	Retrospective cohort	5,407 (M) / 10,169 (M); 4,484 (F) / 4,726 (F)	NR	HR	0.71 (0.579–0.87) [M]; 0.70 (0.499–0.981) [F]	Age, sex, smoking, alcohol, BMI, comorbidities	8
Ka Shing Cheung (2018)a	HP-eradicated cohort	Retrospective cohort	5,360 / 1,880	NR	HR	0.48 (0.24–0.98)	Age, sex, comorbidities, medications	9
Ka Shing Cheung (2018)b	Hong Kong, China	Retrospective cohort	5,368 / 1,898	20 / 17	HR	0.46 (0.23–0.93)	Age, sex, comorbidities, medications	9
Kim YI (2014)	Korea	Retrospective cohort	26,690 / 6,288	145 / 54	HR	0.73 (0.53–1.01)	Age, sex, smoking, alcohol, BMI, comorbidities	8
Yu-Lung Chen (2013)	Taiwan, China	Retrospective cohort	16,424 / 3,201	Sep-38	HR	0.82 (0.39–1.71)	Age, sex, comorbidities	9

Notes: E/C = experimental/control; GC = gastric cancer; NR = not reported; M = male; F = female; NOS = Newcastle-Ottawa Scale; HP = Helicobacter pylori; a and b denote two distinct studies by the same first author in the same year. SIR was treated as HR since the incidence rate was <10%.

3.3. Sensitivity and Subgroup Analyses

3.3.1 Sex subgroup analysis

A subgroup analysis by gender was conducted, including a total of 3 studies. (Table2)The results showed extremely low overall heterogeneity ($I^2 = 3\%$, $P = 0.40$). (Figure 4)A random-effects model was used for the meta-analysis, yielding a pooled HR of 0.78 (95% CI: 0.71, 0.86), $Z = 5.26$, $P < 0.00001$, suggesting that metformin significantly reduces the risk of gastric cancer in patients with type 2 diabetes, regardless of gender. The male subgroup included 3 studies, with moderate heterogeneity ($I^2 = 47\%$, $P = 0.15$); the pooled HR was 0.78 (95% CI: 0.66, 0.92), $Z = 2.93$, $P = 0.003$; The female subgroup included 3 studies, with no heterogeneity ($I^2 = 0\%$, $P = 0.50$); the pooled HR was 0.79 (95% CI: 0.68–0.91), $Z = 3.31$, $P = 0.0009$. Results of the subgroup interaction test showed no statistically significant difference in effect size between the male and female subgroups ($P = 0.96$, $I^2 = 0\%$), suggesting that gender has no significant impact on the effect of metformin in reducing the risk of gastric cancer. The funnel plot from the subgroup analysis showed that the distribution of study points was generally

symmetrical, with no obvious asymmetric shifts observed, suggesting a low likelihood of publication bias.(Figure 5)

Table 2:Subgroup analyses by sex and follow-up duration

First author (year)	Subgroup	Stratum	HR (95% CI)	P for interaction
Sex				
Audrius Dulskas (2020)	Sex	Male	0.74 (0.61–0.88)	NR
		Female	0.77 (0.64–0.93)	
Jiaojiao Zheng (2019)	Sex	Male	0.95 (0.75–1.21)	NR
		Female	0.90 (0.68–1.20)	
Joungyoun Kim (2020)	Sex	Male	0.71 (0.579–0.87)	NR
		Female	0.70 (0.499–0.981)	
Follow-up duration				
Jiaojiao Zheng (2019)	Follow-up duration	0–3 years	1.01 (0.76–1.33)	NR
		≥6 years	1.03 (0.71–1.49)	
Ka Shing Cheung (2018)a (HP-eradicated)	Follow-up duration	<3 years	0.78 (0.34–1.82)	NR
		≥3 years	0.36 (0.16–0.81)	
Ka Shing Cheung (2018)b (Hong Kong)	Follow-up duration	<3 years	0.75 (0.32–1.74)	NR

Notes: NR = not reported; HP = Helicobacter pylori; a and b denote two distinct studies by the same first author in the same year.

3.3.2. Medication duration subgroup analysis

Subgroup analysis based on duration of metformin use showed that this study divided participants into two groups according to duration of use: <3 years and ≥3 years.(Table2) The subgroup with a duration of <3 years included 6 studies, with no heterogeneity among them ($I^2 = 0\%$, $P = 0.98$). (Figure 6)A random-effects model was used to pool the effect sizes, yielding a pooled HR of 0.95, with a 95% CI of (0.81, 1.12). The Z-score for the overall effect test was 0.60 ($P = 0.55$), suggesting that short-term metformin use (<3 years) has no statistically significant effect on the risk of gastric cancer in patients with type 2 diabetes. The subgroup with a duration of treatment ≥3 years included 4 effect sizes and exhibited significant heterogeneity ($I^2 = 92\%$, $P < 0.00001$). The pooled HR was 0.30, with a 95% CI of (0.12, 0.75), $Z = 2.58$, $P = 0.01$, suggesting that long-term metformin use (≥3 years) significantly reduces the risk of gastric cancer, and the difference is statistically significant. The results of the subgroup interaction test showed Chi-square = 5.92, $df = 1$, $P = 0.01$, and $I^2 = 83.1\%$, indicating that the differences in effects among subgroups with different durations of use were statistically significant. This suggests that duration of use is an important moderator influencing the effect of metformin in reducing the risk of gastric cancer, and that a significant protective effect can only be observed with long-term use.

The funnel plot indicates some asymmetry in the distribution of study sites, suggesting that this subgroup analysis may be subject to publication bias or small-sample effects; therefore, the results

should be interpreted with caution. (Figure 7)

4. Discussion

In this updated systematic review and meta-analysis, we evaluated the association between metformin use and the risk of gastric cancer, which is currently unclear. Our findings are similar to previous evidence^[13–16] that showed metformin use is associated with a significantly reduced risk of gastric cancer.

The biological mechanisms by which metformin reduces the risk of gastric cancer remain unclear, but several pathways may explain the association. Emerging evidence suggests metformin exerts chemopreventive effects through both direct pathways, such as AMPK activation and subsequent mTOR inhibition, and indirect pathways, involving modulation of the tumor microenvironment and gut microbiota^[17]. Specifically, metformin reduces hyperglycemia by inhibiting hepatic gluconeogenesis and stimulating peripheral glucose uptake, thereby limiting gastric cancer cell proliferation. It also lowers insulin levels, which inhibits insulin binding to the insulin receptor and prevents activation of the IGF receptor signaling axis, thus suppressing tumor growth^[18–20]. From a cellular metabolism perspective, metformin inhibits gastric cancer cell development by suppressing cellular autophagy, glutaminase activity, mitochondrial function^[21], and NADH dehydrogenase, while inducing phosphorylation of epigenetic enzymes^[22]. At the molecular level, the AMPK pathway plays a crucial role and is activated in two ways: metformin directly activates AMPK to inhibit the downstream Akt/mTOR signaling pathway, or it impairs mitochondrial complex I function to activate AMPK, ultimately inhibiting cellular respiration and triggering gastric cancer cell death^[17].

The results demonstrated that the risk of gastric cancer was significantly lower in type 2 diabetes patients treated with metformin than in those not receiving metformin. Sex did not significantly modify the risk-reducing effect of metformin on gastric cancer. Significant differences in the effect were observed across subgroups stratified by duration of metformin use, indicating that treatment duration is an important factor modulating the chemopreventive effect of metformin against gastric cancer, with a significant protective effect observed only with long-term use (> 3 years).

There are several strengths in this study. First, this is the most updated systematic review and meta-analysis so far that evaluated the relationship between metformin use and gastric cancer risk. Second, this meta-analysis included a large sample size and the quality of included studies were high. Therefore, the findings of this study were more reliable. Third, this study is a meta-analysis that comprehensively evaluated the duration–response relationship between metformin therapy and gastric cancer.

This study also has several limitations. First, most studies were observational and involved heterogeneous patient populations with varying baseline characteristics. Second, there was limited information regarding the dosage of metformin, follow-up, and duration of metformin; therefore, we were unable to pool effect size based on dosage, duration, and follow-up. Third, several potential

covariates/confounders related to gastric cancer risk have not been adjusted in the included study. Future studies should adjust all possible confounders to pool the effect sizes and to show a stronger association between metformin use and gastric cancer risk.

5. Conclusions

The findings of this updated meta-analysis suggest that metformin use is associated with a reduced risk of gastric cancer in patients with type 2 diabetes. Although the pooled effect size showed a significant protective effect, the substantial heterogeneity among the included observational studies and potential publication bias do not support the routine use of metformin solely for gastric cancer chemoprevention at this time. More large-scale, well-designed prospective cohort studies and randomized controlled trials with standardized definitions of metformin exposure (including dosage, duration, and adherence) and comprehensive adjustment for confounding factors are required to confirm the chemopreventive role of metformin before it can be considered as a strategy for reducing gastric cancer risk in clinical practice.

Declarations

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Ethics approval and consent to participate Not applicable. This study is a systematic review and meta-analysis based on previously published literature and publicly available databases. No human participants or animals were involved.

Consent for publication Not applicable. This manuscript does not contain any individual person's data in any form.

Availability of data and materials All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests The authors declare that they have no competing interests.

Authors' contributions Wang ZH conceived and designed the study. Wang YJ and Sun DY performed the literature search, data extraction, and drafted the manuscript. Pan ZD conducted a thorough re-check and verification of the extracted data. All authors read and approved the final manuscript.

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Figures

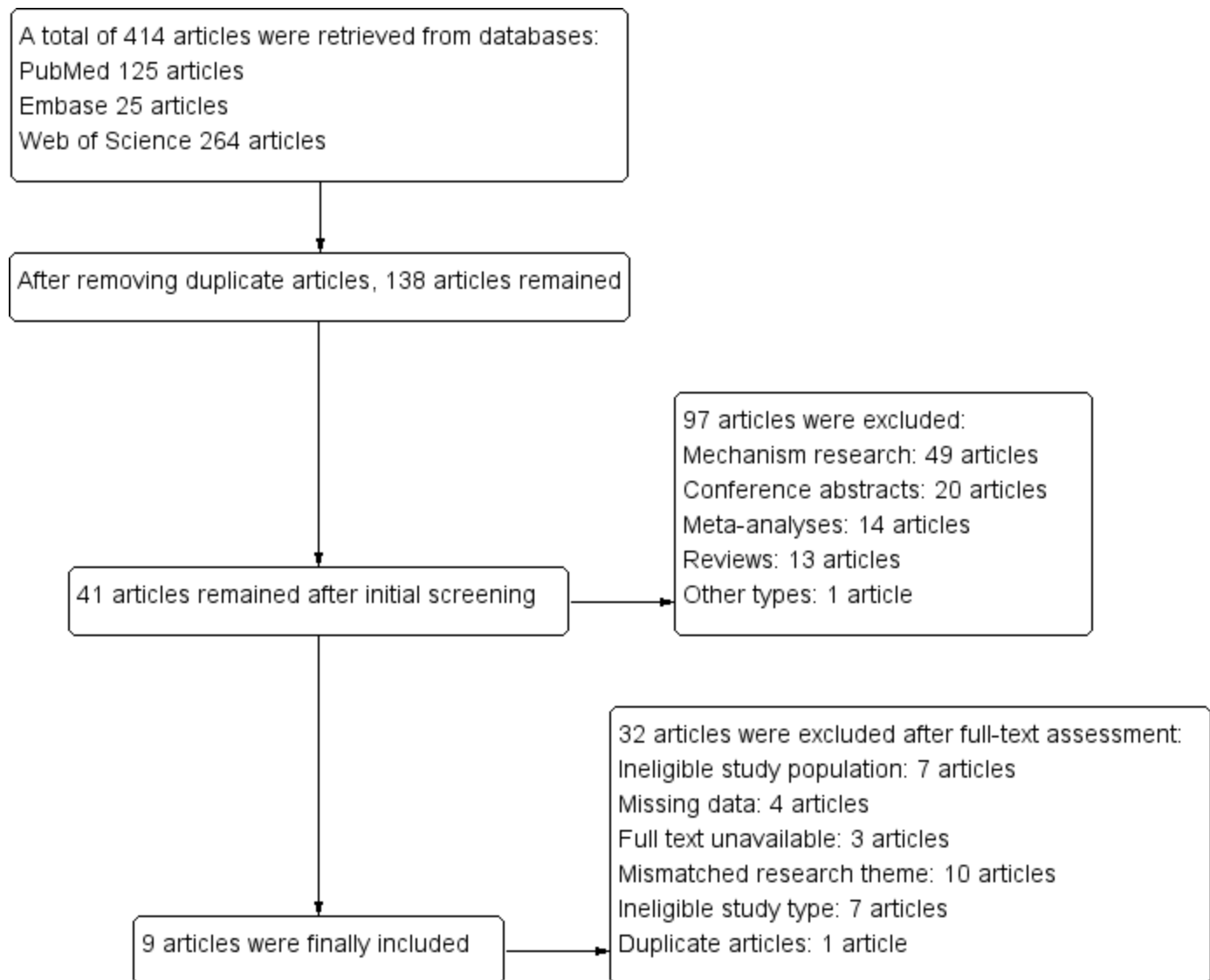


Figure 1

PRISMA flowchart for summarizing study identification and selection.

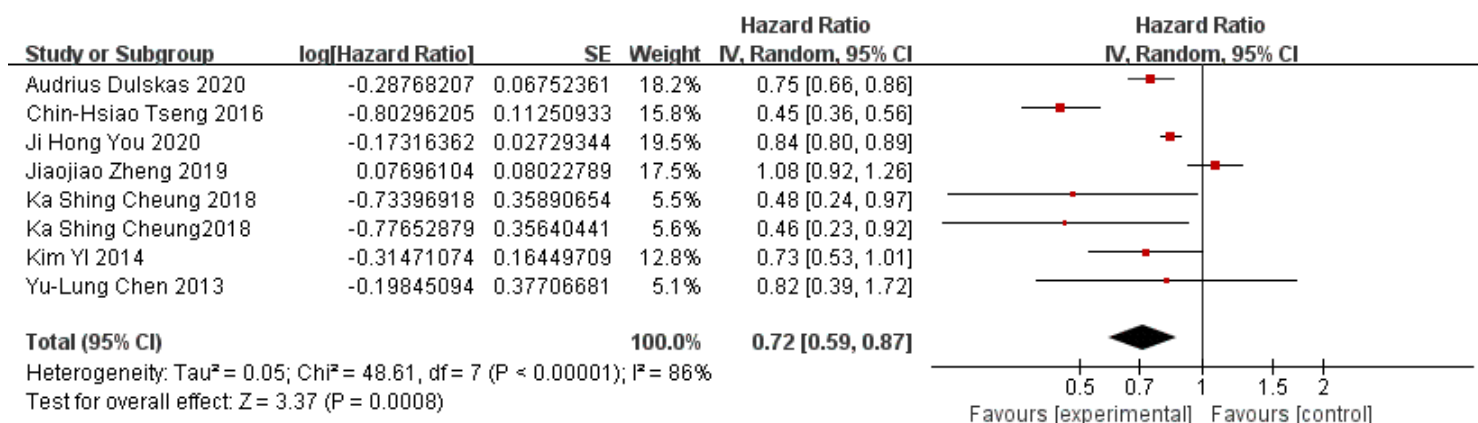


Figure 2

Association between metformin use and the risk of gastric cancer

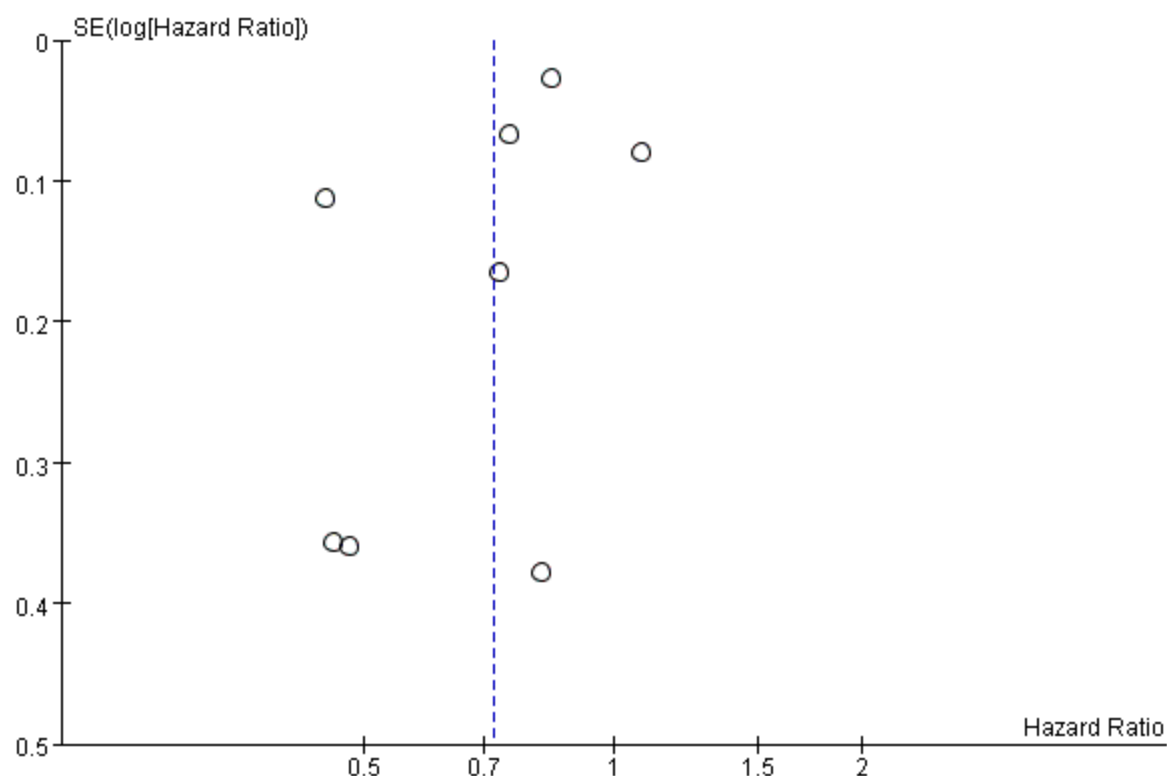


Figure 3

Funnel plot of the association between metformin use and the risk of gastric cancer

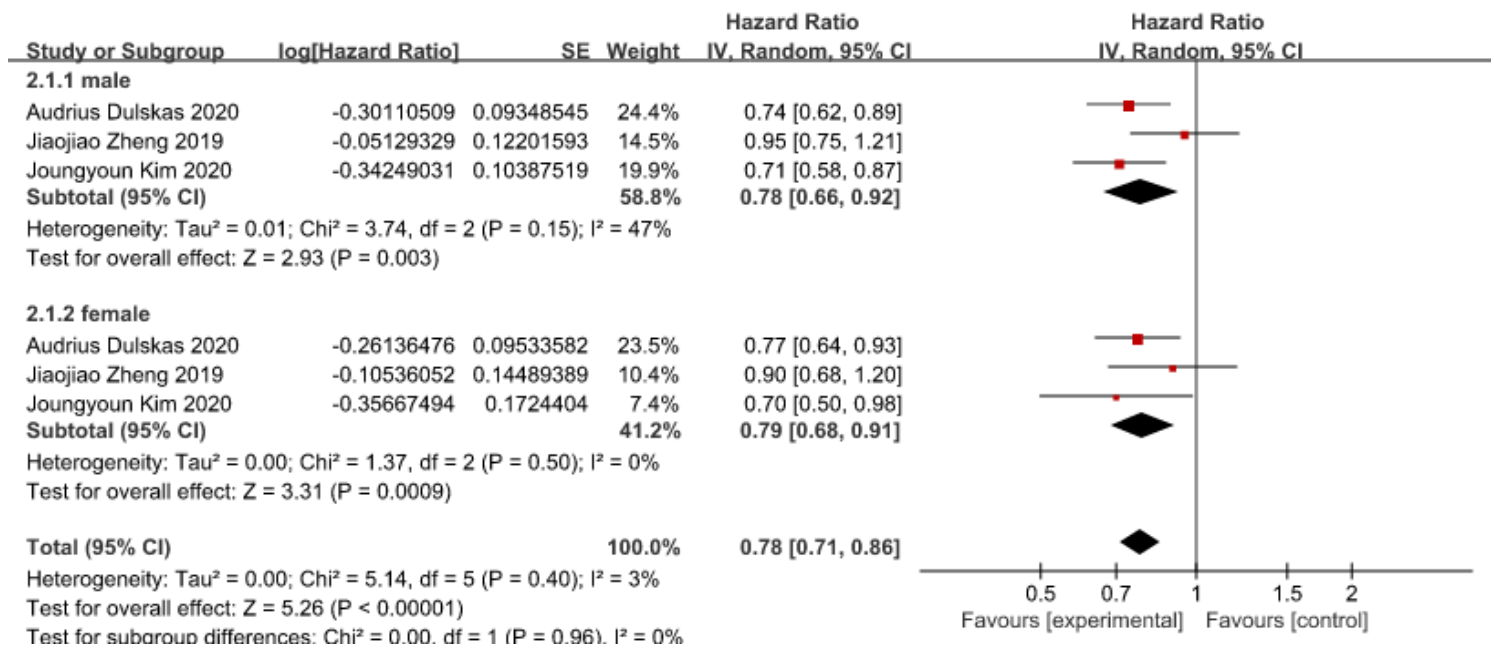


Figure 4

Forest plot of sex subgroup analysis

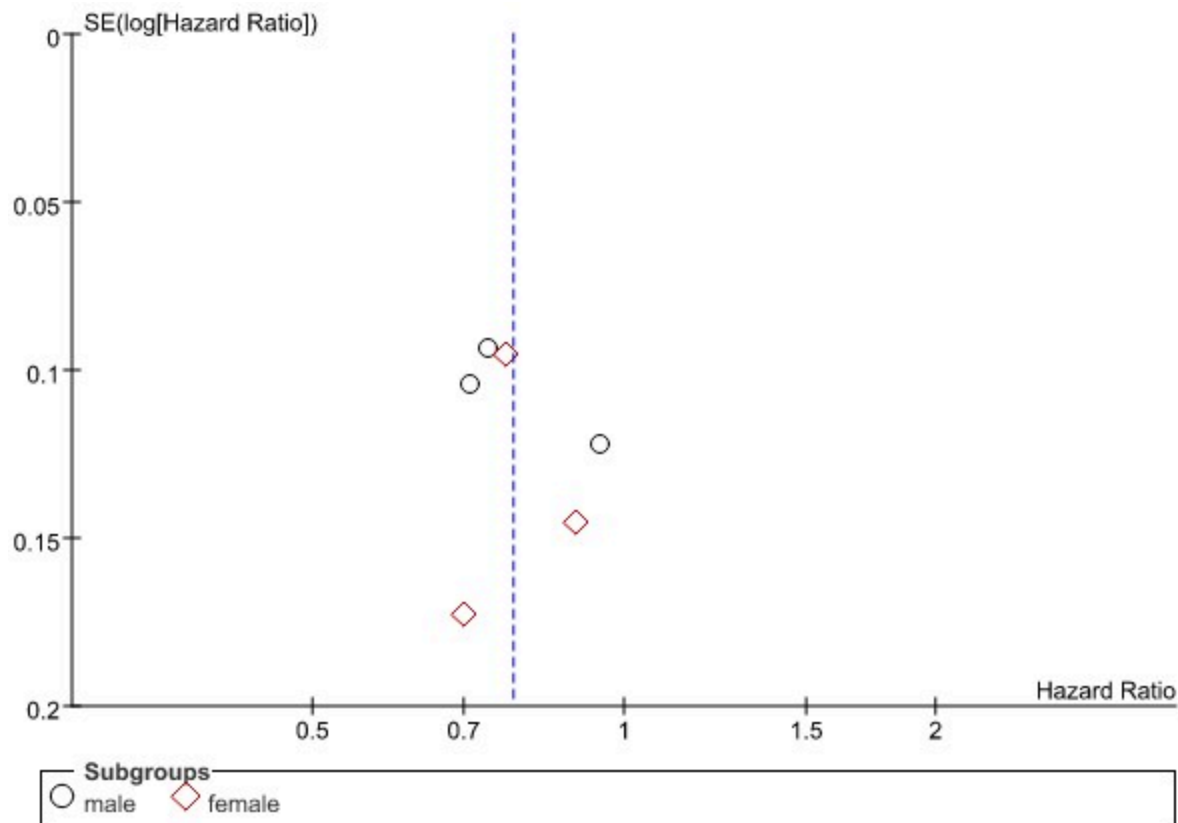


Figure 5

Funnel plot of sex subgroup analysis

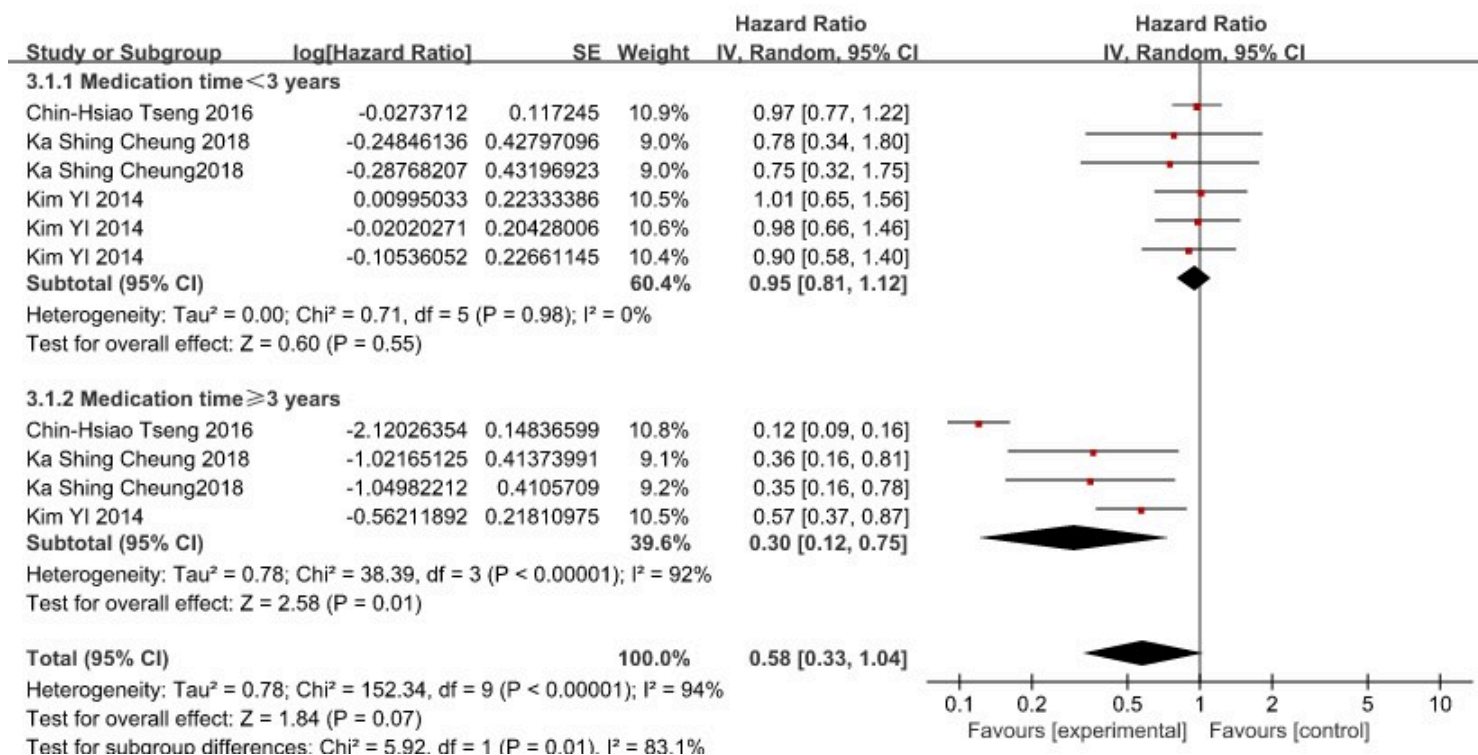


Figure 6

Forest plot of medication time subgroup analysis

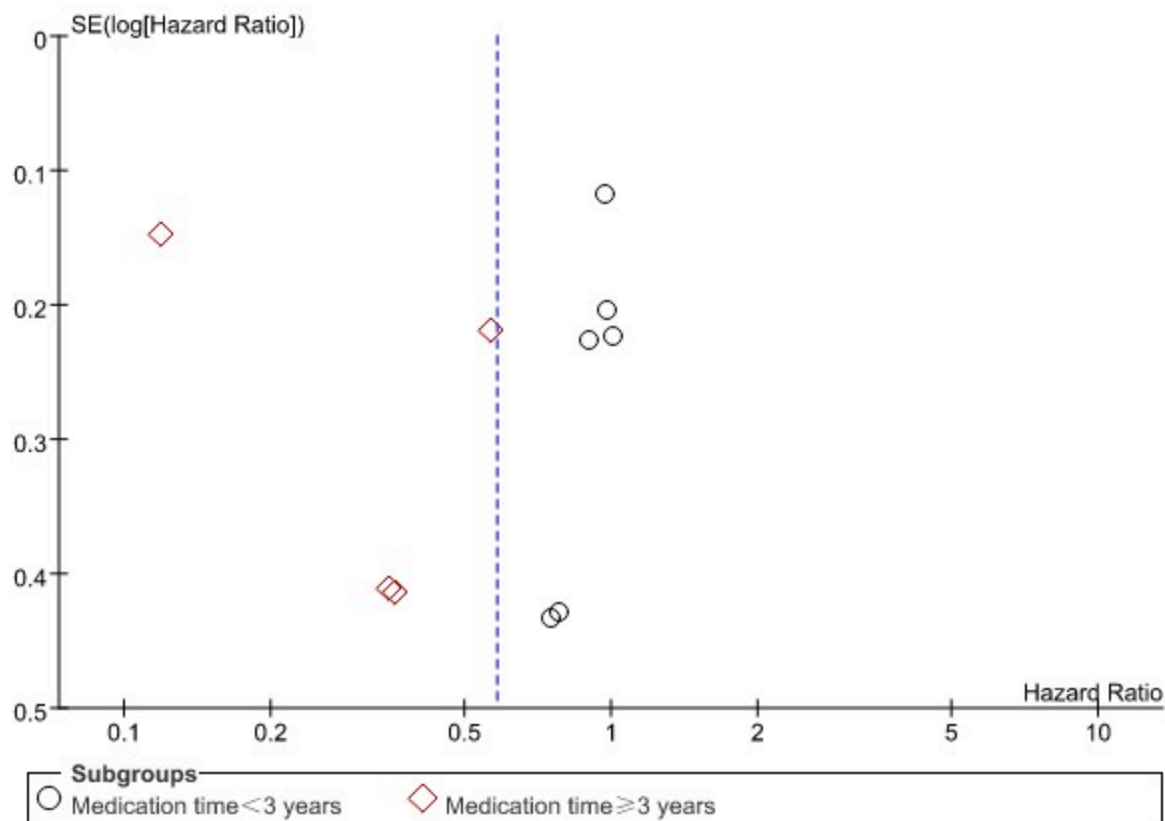


Figure 7

Forest plot of medication time subgroup analysis

