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META-ANALYSIS

Exposure to proton pump inhibitors and risk of diabetes: A systematic review and meta-analysis

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Abstract

BACKGROUND
Exposure to proton pump inhibitors (PPIs) has been reported to have a potential role in the development of diabetes.

AIM
To determine the association between PPIs and diabetes.

METHODS
This meta-analysis is registered on PROSPERO (CRD42022352704). In August 2022, eligible studies were identified through a comprehensive literature search. In this study, odds ratios were combined with 95% confidence intervals using a random-effects model. The source of heterogeneity was assessed using sensitivity analysis and subgroup analysis. The publication bias was evaluated using Egger's test and Begg's test.

RESULTS
The meta-analysis included 9 studies with a total of 867185 participants. Results showed that the use of PPIs increased the risk of diabetes (odds ratio = 1.23, 95% confidence interval: 1.05-1.43, n = 9, I^2 = 96.3%). Subgroup analysis showed that geographic location and study type had significant effects on the overall results. Both Egger's and Begg's tests showed no publication bias (P > 0.05). Sensitivity analysis also confirmed the stability of the results.

CONCLUSION
The results of this study indicated that the use of PPIs was related to an increased risk of diabetes. However, more well-designed studies are needed to verify these results in the future.

Key Words: Proton pump inhibitors; Diabetes mellitus; Odds ratio; Meta-analysis; Diabetogenesis

Core Tip: Exposure to proton pump inhibitors has been reported to have a potential role in the development of diabetes. There are no consistent results for the association between proton pump inhibitors use and diabetes risk. This meta-analysis aimed to provide a more reliable assessment.

INTRODUCTION

Diabetes is one of the fastest-growing chronic diseases in the 21st century and is characterized by inadequate insulin production or insulin resistance. Based on the 2021 International Diabetes Federation's Diabetes Atlas, approximately 537 million adults aged 20-79 have diabetes, which is expected to reach 783 million by 2045[1]. Drug-induced diabetes is widely reported clinically and is a global problem[2].

Proton pump inhibitors (PPIs) that act on H+/K+-ATPase and inhibit gastric acid secretion are often used in the treatment of gastroesophageal reflux disease, peptic ulcer disease, and bleeding caused by nonsteroidal anti-inflammatory drugs[3]. As one of the most widely used drugs in the world, the overuse of PPIs is increasingly prominent and may cause a variety of adverse effects, including fractures, chronic kidney disease, cancer, *etc*[3-5]. Several recent studies have shown that there is a relationship between PPIs use and diabetes risk, with the potential mechanisms including changes in gut microbiota, PPI-induced hypomagnesemia, reduction of insulin-like growth factor-1, activation of pregnane X receptor, and effects of gastrin[6].

Some studies support a link between PPI use and diabetes risk, but there have been reports of conflicting conclusions. For example, two recent case-control studies and four cohort studies confirmed that PPIs were related to an increased risk of diabetes[6-10]. By contrast, PPIs were related to a reduced risk of diabetes in another cohort study[11]. However, there was no relationship between PPI use and diabetes risk in one randomized controlled trial and one cohort study[10,12]. Moreover, a recent meta-analysis involving eight studies from six articles showed that the use of PPIs was not related to the risk of diabetes[13]. Given the high prevalence of diabetes, the widespread use of PPIs, and conflicting findings about the association between PPI use and diabetes risk, this meta-analysis aimed to provide more reliable evidence on the relationship between PPI use and diabetes risk.

MATERIALS AND METHODS

Protocol and registration

This meta-analysis was conducted according to the standard Preferred Reporting Items for Systematic Review and Meta-Analysis[14]. The study protocol has been registered on the PROSPERO International Prospective Register for Systematic Review (CRD42022352704), which provides more details.

Search strategy

A comprehensive search was performed in Web of Science, PubMed, Cochrane, and Embase to collect all eligible studies published before August 2022 (Supplementary Tables 1-4). The following retrieval strategy was used: Diabetes Mellitus, DM, T2DM, Diabetes, Type 1 Diabetes or Type 2 Diabetes, and Proton Pump Inhibitor, Proton Pump Inhibitors, PPI, PPIs, Esomeprazole, Rabeprazole, Pantoprazole, and Lansoprazole or Omeprazole.

Study selection

The following studies were considered to be eligible for inclusion: (1) Randomized controlled trial, cohort study, or case-control study; (2) PPI use as an exposure of interest (no limitation on the type of PPIs); (3) Studies showing the association between PPI use and diabetes risk; and (4) Studies with relative risks, odds ratios (ORs), or hazard ratios with corresponding 95% confidence intervals (CIs). The exclusion criteria included: (1) The subject of the study was not human; (2) Reviews, systematic reviews, meta-analyses, comments, reports, letters, guides, conference abstracts, books, *etc*; (3) Results of interest not provided; and (4) Data could not be extracted or calculated.
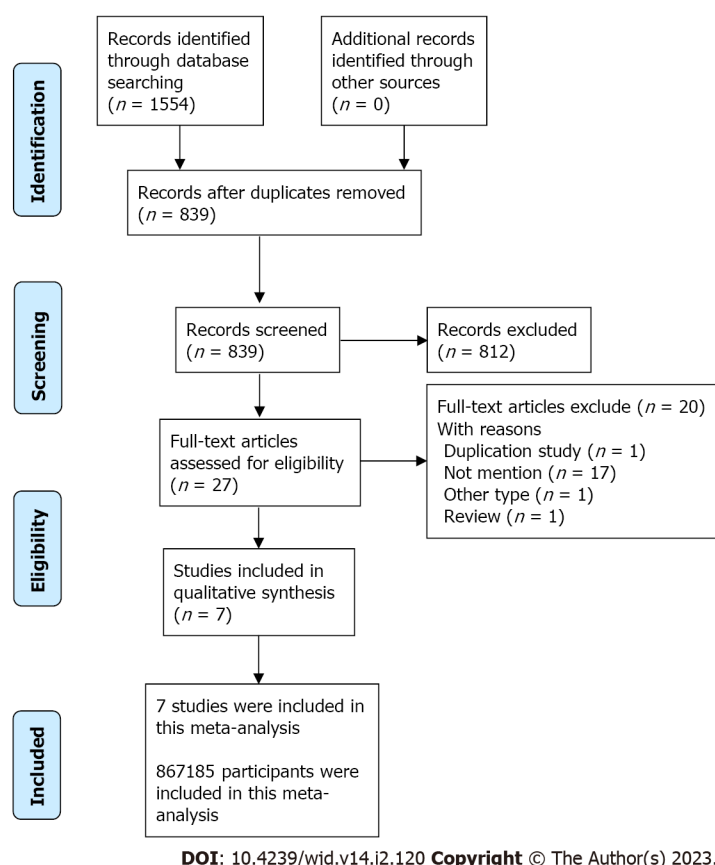
Figure 1 Flow diagram of the literature search.

Data extraction and quality assessment

Two authors separately and independently extracted data using a predesigned Excel spreadsheet. Any disagreements were resolved through discussion with the remaining authors. From the included articles, the following data were obtained: Authors' names, year of publication, country, study type, comparison, total population, age, sex, adjustment factors, and effect sizes [effect quantities (ESs), including hazard ratios or ORs] with corresponding 95%CIs.

The randomized controlled trial was assessed using the Jadad scale based on randomization and blinding and whether to describe the details of participants' exits or withdrawals from the study. The study quality was graded as follows: Low quality = 1-3 and high quality = 4-7. The Newcastle-Ottawa Scale was used to assess the quality of observational studies, including three aspects: selection, comparability, and outcome/exposure. The study quality was graded as follows: low quality = 0-3, medium quality = 4-6, and high quality = 7-9.

Statistical analysis

The data were analyzed using Stata version 15.0. (Stata Corporation, College Station, TX, United States). Due to the potential clinical heterogeneity of the studies included, multivariate-adjusted ORs were combined with 95%CIs using a random-effects model. The I^2 statistics were used to evaluate the heterogeneity between studies, and significant heterogeneity was expressed as $I^2 > 50\%$, $P < 0.1$. The subgroup analysis was conducted to further address heterogeneity. The following three aspects were considered: (1) Sex; (2) Geographic location; and (3) Study type. The sensitivity analysis was carried out by eliminating one article at a time and recalculating aggregated effect values. Egger's and Begg's tests were used to assess the publication bias, and statistical significance was expressed as the two-sided P value < 0.05.

RESULTS

Literature search and study characteristics

A total of 1554 articles were included after a comprehensive search of the four databases. After removing duplication and filtering by title and abstract, 27 articles required full-text evaluation. As shown in Figure 1, this meta-analysis contained nine studies from seven articles published from 2016 to

Table 1 Characteristics of the studies included

Ref.	Country	Study design	Quality	Population	Age in yr	Sex	Comparison	Adjustment	ESs (95%CI)
Ciardullo *et al* [7], 2022	Italian	Case-control	High	101070	≥ 40	M/F	PPIs *vs* non-PPIs	Adjusted[1]	1.56 (1.49, 1.64)
Kuo *et al*[8], 2022	China	Case-control	High	41880	55.85 ± 13.48	M/F	PPIs *vs* non-PPIs	Adjusted[2]	1.34 (1.23, 1.46)
Czarniak *et al* [6], 2022	Netherlands	Cohort	High	9531	≥ 45	M/F	PPIs *vs* non-PPIs	Adjusted[3]	1.49 (1.14, 1.95)
He *et al*[9], 2021	United Kingdom	Cohort	Moderate	470265	56.34 ± 8.11	M/F	PPIs *vs* non-PPIs	Adjusted[4]	1.56 (1.46, 1.66)
Yuan *et al* [10], 2021	United States	Cohort	High	80500	30-55	F	PPIs *vs* non-PPIs	Adjusted[5]	1.22 (1.12, 1.33)
Yuan *et al* [10], 2021	United States	Cohort	High	95550	25-42	F	PPIs *vs* non-PPIs	Adjusted[5]	1.27 (1.17, 1.38)
Yuan *et al* [10], 2021	United States	Cohort	High	28639	40-75	M	PPIs *vs* non-PPIs	Adjusted[5]	1.12 (0.91, 1.38)
Moayyedi *et al*[12], 2019	Mixed	Randomized controlled trial	High	17598	67.7 ± 8.1	M/F	PPIs *vs* placebo	Unadjusted	0.96 (0.85, 1.09)
Lin *et al*[11], 2016	China	Cohort	High	22152	55.38 ± 16.95	M/F	PPIs *vs* non-PPIs	Adjusted[6]	0.80 (0.73, 0.88)

[1]Adjusted for sex, age, and clinical status.

[2]Adjusted for age, sex, residence income, indications of proton pump inhibitor (PPI) use, obesity, dyslipidemia, hypertension, and alcohol use disorders.

[3]Adjusted for age, sex, PPI past use, body mass index (BMI), hypertension, current smoking, alcohol consumption, physical activity, and education levels.

[4]Adjusted for sex, with additional adjustment for diabetes risk factors, including age at recruitment, ethnicity, deprivation, BMI, smoking status, family history of diabetes in a first-degree relative, cardiovascular disease, treated hypertension, corticosteroids use, diagnosis of schizophrenia or bipolar affective disorder, learning disabilities, diagnosis of gestational diabetes, diagnosis of polycystic ovary syndrome, atypical antipsychotics, statins and clinical indications for PPI use.

[5]Adjusted for race, family history of diabetes, BMI, number of pack-years of smoking, alcohol intake per day, physical activity, overall diet quality, total calorie intake, multivitamin use, history of hypertension, hypercholesterolemia, cancer, menopausal status and postmenopausal hormone use in women, number of parity in women, breastfeeding in women, any use of antibiotics, regular non-steroidal anti-inflammatory drug use, any use of steroids, gastroesophageal reflux disease, gastric or duodenal ulcer, upper gastrointestinal tract bleeding, and regular use of H2 receptor agonists.

[6]Adjusted for age, sex, hypertension, gout and/or hyperuricemia, coronary artery disease, stroke, pancreatitis, hyperlipidemia, obesity, H2 blocker use, and clozapine or olanzapine use.

CI: Confidence interval; ESs: Effect quantities; F: Female; M: Male; PPI: Proton pump inhibitor.

2022, including one randomized controlled trial, two case-control studies, and six cohort studies, which involved 867185 participants. Table 1 shows the baseline characteristics and quality assessments of the studies included.
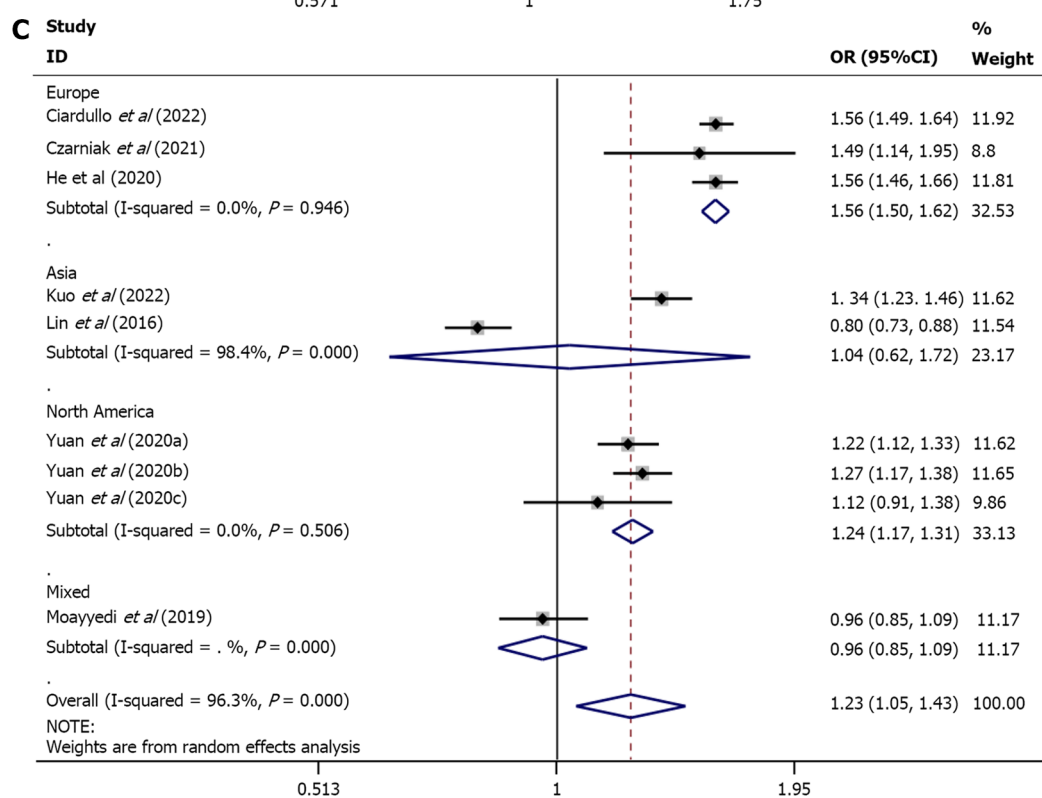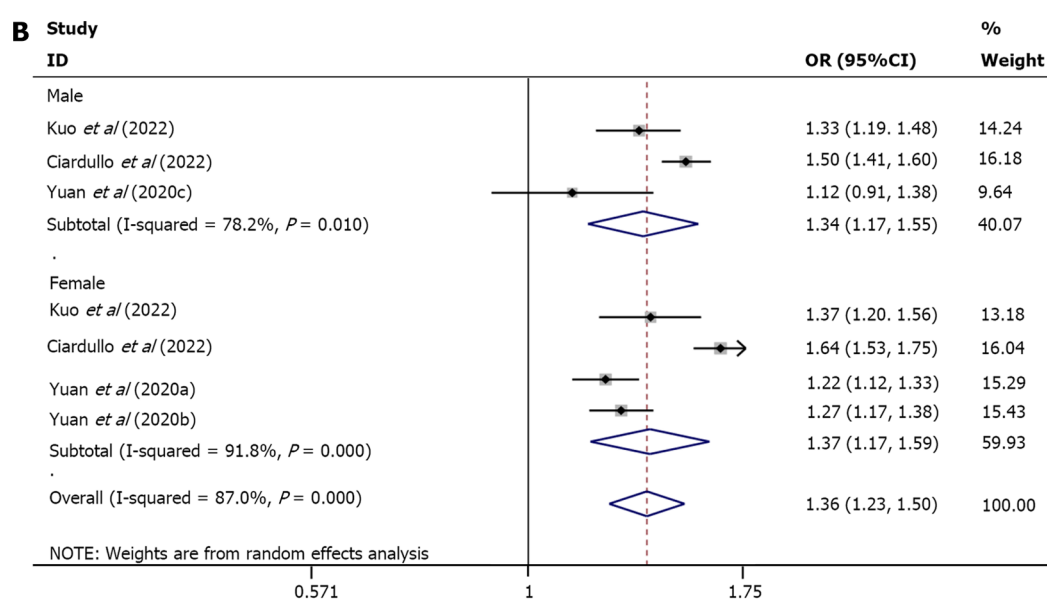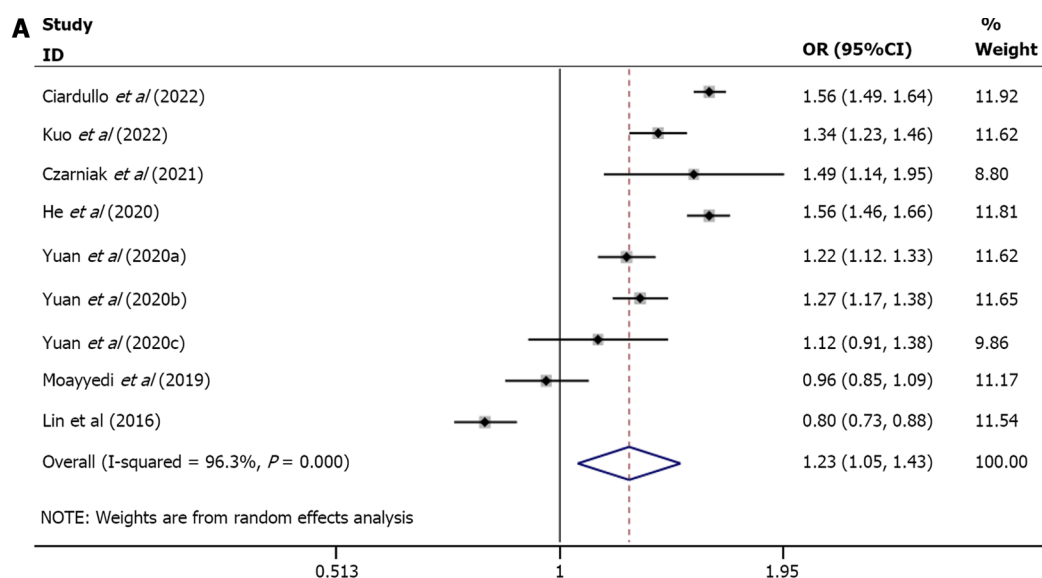
Meta-analysis
Meta-analysis using a random-effects model indicated a statistically significant association between PPI use and diabetes risk compared to placebo or no PPI use (OR = 1.23, 95%CI: 1.05-1.43, n = 9, I^2 = 96.3 %) (Figure 2A).

Subgroup analysis
The subgroup analysis was conducted based on sex, geographic location, and study type since the I^2 analysis revealed significant heterogeneity: (1) Sex. The use of PPIs was related to an increased risk of diabetes in both females (pooled ES = 1.37, 95%CI: 1.17-1.59, n = 4, I^2 = 91.8%) and males (pooled ES = 1.34, 95%CI: 1.17-1.55, n = 3, I^2 = 78.2%) (Figure 2B); (2) Geographic location. A statistical association was found in Europe (pooled ES = 1.56, 95%CI: 1.50-1.62, n = 3, I^2 = 0%) and North America (pooled ES = 1.24, 95%CI: 1.17-1.31, n = 3, I^2 = 0%) but not in Asia (pooled ES = 1.04, 95%CI: 0.62-1.72, n = 2, I^2 = 98.4%) (Figure 2C); and (3) Study type. A statistical association was detected in case-control studies (pooled ES = 1.45, 95%CI: 1.25-1.68, n = 2, I^2 = 89.1%) but not in cohort studies (pooled ES = 1.21, 95%CI: 0.98-1.50, n = 6, I^2 = 96.3%) (Figure 2D).

Sensitivity analysis
The sensitivity analysis was performed by excluding one study at a time and recalculating pooled risk estimates. The results showed no significant change in risk estimates after combination (Figure 3A). This analysis verified the robustness of the results of this study.
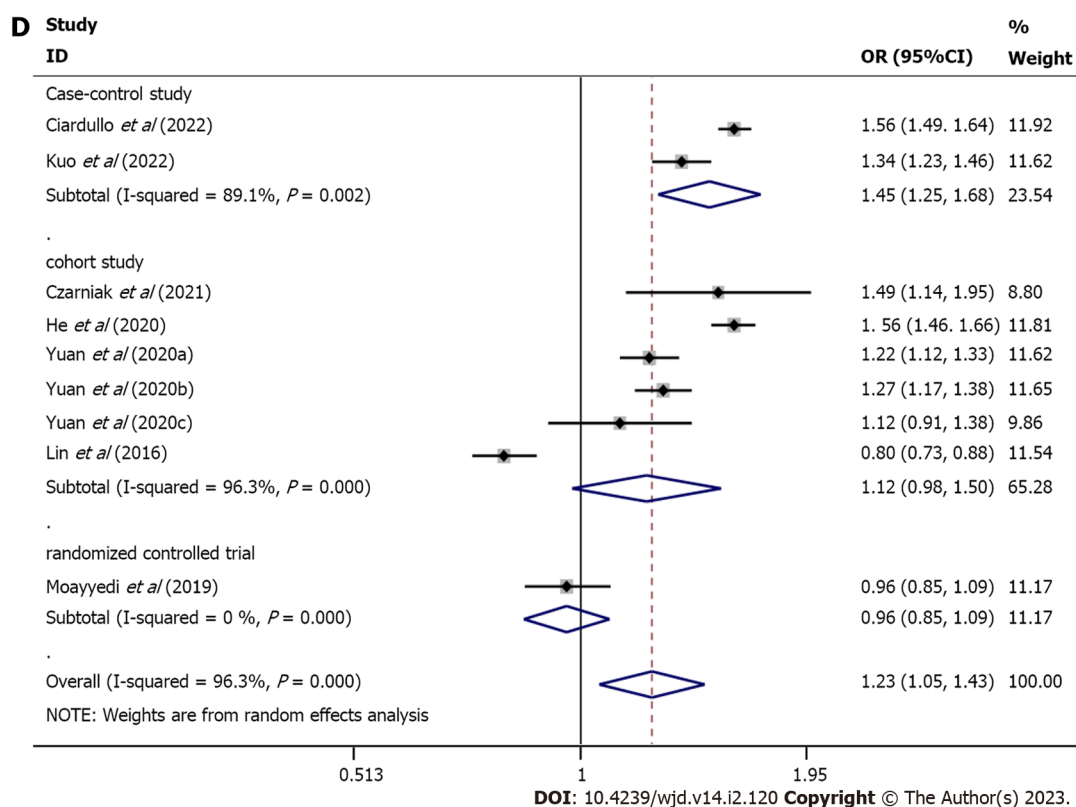
A

Study ID	OR (95%CI)	% Weight
Ciardullo *et al* (2022)	1.56 (1.49, 1.64)	11.92
Kuo *et al* (2022)	1.34 (1.23, 1.46)	11.62
Czarniak *et al* (2021)	1.49 (1.14, 1.95)	8.80
He *et al* (2020)	1.56 (1.46, 1.66)	11.81
Yuan *et al* (2020a)	1.22 (1.12, 1.33)	11.62
Yuan *et al* (2020b)	1.27 (1.17, 1.38)	11.65
Yuan *et al* (2020c)	1.12 (0.91, 1.38)	9.86
Moayyedi *et al* (2019)	0.96 (0.85, 1.09)	11.17
Lin et al (2016)	0.80 (0.73, 0.88)	11.54
Overall (I-squared = 96.3%, *P* = 0.000)	1.23 (1.05, 1.43)	100.00

NOTE: Weights are from random effects analysis

0.513   1   1.95

B

Study ID	OR (95%CI)	% Weight
Male		
Kuo *et al* (2022)	1.33 (1.19, 1.48)	14.24
Ciardullo *et al* (2022)	1.50 (1.41, 1.60)	16.18
Yuan *et al* (2020c)	1.12 (0.91, 1.38)	9.64
Subtotal (I-squared = 78.2%, *P* = 0.010)	1.34 (1.17, 1.55)	40.07
Female		
Kuo *et al* (2022)	1.37 (1.20, 1.56)	13.18
Ciardullo *et al* (2022)	1.64 (1.53, 1.75)	16.04
Yuan *et al* (2020a)	1.22 (1.12, 1.33)	15.29
Yuan *et al* (2020b)	1.27 (1.17, 1.38)	15.43
Subtotal (I-squared = 91.8%, *P* = 0.000)	1.37 (1.17, 1.59)	59.93
Overall (I-squared = 87.0%, *P* = 0.000)	1.36 (1.23, 1.50)	100.00

NOTE: Weights are from random effects analysis

0.571   1   1.75

C

Study ID	OR (95%CI)	% Weight
Europe		
Ciardullo *et al* (2022)	1.56 (1.49, 1.64)	11.92
Czarniak *et al* (2021)	1.49 (1.14, 1.95)	8.8
He et al (2020)	1.56 (1.46, 1.66)	11.81
Subtotal (I-squared = 0.0%, *P* = 0.946)	1.56 (1.50, 1.62)	32.53
Asia		
Kuo *et al* (2022)	1.34 (1.23, 1.46)	11.62
Lin *et al* (2016)	0.80 (0.73, 0.88)	11.54
Subtotal (I-squared = 98.4%, *P* = 0.000)	1.04 (0.62, 1.72)	23.17
North America		
Yuan *et al* (2020a)	1.22 (1.12, 1.33)	11.62
Yuan *et al* (2020b)	1.27 (1.17, 1.38)	11.65
Yuan *et al* (2020c)	1.12 (0.91, 1.38)	9.86
Subtotal (I-squared = 0.0%, *P* = 0.506)	1.24 (1.17, 1.31)	33.13
Mixed		
Moayyedi *et al* (2019)	0.96 (0.85, 1.09)	11.17
Subtotal (I-squared = . %, *P* = 0.000)	0.96 (0.85, 1.09)	11.17
Overall (I-squared = 96.3%, *P* = 0.000)	1.23 (1.05, 1.43)	100.00

NOTE: Weights are from random effects analysis

0.513   1   1.95

Figure 2 Forest plots. A: Forest plot of the association between proton pump inhibitor use and diabetes risk; B: Forest plot of the association between proton pump inhibitor use and diabetes risk according to sex; C: Forest plot of the association between proton pump inhibitor use and diabetes risk according to geographic location; D: Forest plot of the association between proton pump inhibitor use and diabetes risk according to study design. CI: Confidence interval; OR: Odds ratio.

Publication bias

Egger's test (P = 0.149) and Begg's test (P = 0.175) indicated no publication bias (Figure 3B and C).

DISCUSSION

The meta-analysis, including nine studies with a total of 867185 participants, showed that the use of PPIs increased the risk of diabetes, which is consistent with some previous studies. A case-control study of 41880 participants in China and a cohort study of 9531 participants in Europe, after adjusting for known risk factors, showed that the use of PPIs was related to an increased risk of type 2 diabetes, and efficacy was dose-dependent[6,8]. However, the former showed an increased risk of type 2 diabetes in patients treated with pantoprazole, lansoprazole, and omeprazole, while no increased risk was found in patients treated with esomeprazole or rabeprazole[8]. Another case-control study from Europe involving 101070 participants showed that the long-term use of PPIs was related to an increased risk of diabetes and increased risk over time with treatment[7]. Similarly, there was a positive relationship between PPI use and diabetes risk in two cohort studies in North America and one in Europe but not in another study in North America[9,10].

In contrast, a randomized controlled trial of 17598 participants from mixed regions found no statistical difference between pantoprazole and diabetes risk, without adjusting for confounding factors [12]. Moreover, a cohort study from China, including 22152 participants, showed that the use of PPIs was related to a reduced risk of diabetes[11]. Recently, a systematic review and meta-analysis summarized the evidence on this topic, including eight studies of 850019 participants, showing that the use of PPIs was not related to an increased or decreased risk of diabetes. However, PPIs were only used as controls in two unadjusted included studies, with glucocorticoids and antipsychotics that have been reported to have a risk of diabetes in experimental groups[15-18]. The criteria for the included studies were standardized, and three recent high-quality studies were supplemented in the meta-analysis[6-8].

The mechanism between PPI use and diabetes risk is still unclear, and several hypotheses exist. First, the use of PPIs can alter the gut microbiome[19,20]. Changes in the gut microbiome environment play an important role in metabolism that are related to obesity, metabolic syndrome, insulin resistance, and the development of diabetic microvascular and macrovascular complications[21,22].
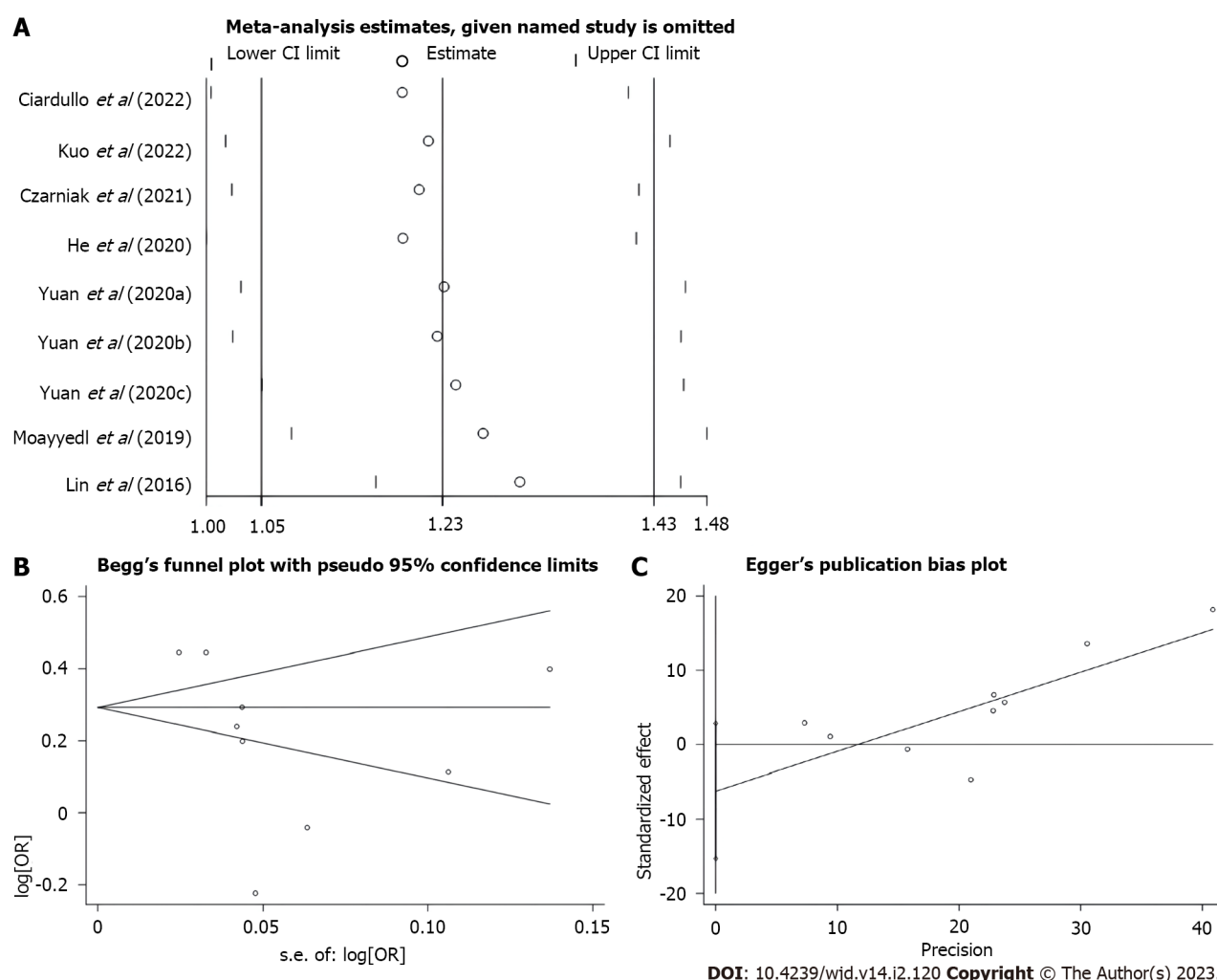
Figure 3 Plots. A: Plot of sensitivity analysis by excluding one study each time and pooling estimate for the remaining studies; B: Plot of Begg's test; C: Plot of Egger's test. CI: Confidence interval; OR: Odds ratio.

Second, studies have shown that the use of PPIs can lead to hypomagnesemia[23,24]. Magnesium, an essential mineral in the human body and the second richest cationic ion in cells, activates enzymes and plays an important role as a cofactor in various biochemical reactions[25]. It has been also reported that lower serum magnesium concentrations are associated with higher insulin resistance and diabetes risk, with a nonlinear dose-response relationship[26,27].

Third, studies have shown a negative correlation between PPIs and insulin-like growth factor-1 (IGF-1) levels[28]. IGF-1 is a polypeptide protein substance that is similar to insulin in molecular structure. It is able to enhance the absorption of glucose and amino acids, promote glycogen synthesis and lactate secretion, inhibit glycogenolysis, and increase insulin sensitivity. Studies have found that low IGF-1 levels are associated with diabetes risk[29,30].

The fourth mechanism may be associated with the use of PPIs to activate progesterone X receptor (PXR)[6]. PXR is a ligand-dependent member of the nuclear receptor family that regulates target genes and senses the chemical environment, which is activated by many clinically used drugs and environmental pollutants. When activated, it can regulate the expression of multiple drug metabolizing enzymes and transporters[31]. The true mechanism by which PXR impairs glucose metabolism is not fully understood, but its role in inducing hyperglycemia/diabetes by impairing glucose metabolism in the liver has been demonstrated[32].

The fifth mechanism is considered to be associated with gastrin. PPIs have been shown to increase endogenous gastrin levels in both animals and humans by inhibiting gastric acid secretion, which is associated with islet growth/regeneration[33]. Interestingly, there is also conflicting evidence regarding the role of PPIs in glycemic control for patients with diabetes[34,35]. Perhaps gastrin may be depleted over time, increasing the risk of diabetes[7].

It is well known that heterogeneity and study quality may influence the relationship resulting from the final analysis. Due to the high degree of heterogeneity in this study, a subgroup analysis was performed to understand the origin of heterogeneity. In the geographic location subgroup, a positive association between PPI use and diabetes risk was observed in Europe and North America but not in

Asia or other mixed regions. In addition, an association between PPI use and diabetes risk was also found in the case-control study but not in the cohort study. This suggests that more high-quality studies from diverse geographic locations may be required in the future. Adjusting for confounding factors has an important influence on the reliability of meta-analysis results, and only one randomized controlled trial of the included studies was not adjusted. Sensitivity analysis showed robust results in the present meta-analysis, and there was no published bias in this study. Taken together, the results of this meta-analysis are robust.

In summary, PPI use is associated with diabetes risk. It is expected that the inclusion of more high-quality studies with detailed data on the use of PPIs can be required in the future, such as different types of PPIs, frequency of use, duration of use, and indications. H_2 receptor antagonists could also be included in the analysis to see if there is an association between antacids and diabetes.

CONCLUSION

Based on the available evidence, it can be concluded that the use of PPIs is related to an increased risk of diabetes. In addition, this connection between the use of PPIs and the risk of diabetes is also found in both females and males. However, accounting for the limitations and the presence of bias in the primary studies, future research should still focus on the use of different types of PPIs and the risk of diabetes, especially in people with different backgrounds.

ARTICLE HIGHLIGHTS

Research background
There is a still controversial connection between the widespread use of proton pump inhibitors (PPIs) and the risk of diabetes.

Research motivation
In a previous meta-analysis, the use of PPIs was shown to not be associated with the risk of diabetes. However, three recent high-quality studies found that the use of PPIs was associated with an increased risk of diabetes. Therefore, a meta-analysis was carried out to determine the association between PPIs and diabetes.

Research objectives
To provide more reliable evidence on the relationship between PPI use and diabetes risk.

Research methods
Meta-analysis was used to realize the objectives. Statistical analyses were performed by using Stata version 15.0.

Research results
Results showed that the use of PPIs increased the risk of diabetes (odds ratio = 1.23, 95% confidence interval: 1.05-1.43, $n = 9$, $I^2 = 96.3\%$). In the subgroup analysis, geographic location and study type had significant effects on the overall results. No publication bias ($P > 0.05$) was found in Egger's or Begg's tests. Also, sensitivity analysis confirmed the stability of the results.

Research conclusions
The results of this study indicated that the use of PPIs was associated with an increased risk of diabetes.

Research perspectives
It is expected that more research from diverse geographic locations with detailed data on the use of PPIs is required in the future.

FOOTNOTES

Author contributions: Guo YR and Wang GX contributed to the study design; Guo YR and Liu XM conducted data collection and selection; Guo YR performed data analysis and wrote the manuscript; All authors read and approved the final manuscript.

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