Will Proton Pump Inhibitors Increase the Risk of Diabetes Mellitus? A Systemic Review and Meta-Analysis

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ABSTRACT

Background: *Proton pump inhibitor use was reported to potentially provide benefits to prevent diabetes mellitus. This study aims to investigate the association between proton pump inhibitor use and the risk of developing diabetes mellitus.*

Methods: *This study was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42021238481). A systematic literature search was conducted to identify eligible studies up to February 2021. Quality assessment was conducted according to Jadad Scoring Scale and Newcastle–Ottawa Scale. The heterogeneity among studies was tested and estimated by Q test and I^2. Pooled hazard ratio with 95% CI was calculated using the random-effects or fixed-effects model depending on the heterogeneity. Subgroup analyses, sensitivity analysis, and publication bias assessment were also performed.*

Results: *Eight studies including 850 019 participants were included. We found that proton pump inhibitor use was associated with a statistically non-significant increased risk of diabetes mellitus (pooled hazard ratio was 1.06, 95% CI = 0.89-1.28, P = .50). In subgroup analysis, 5 studies conducted in North America confirmed the overall result; however, one study conducted in Europe demonstrated a statistically significant increased risk, while one study in Asia revealed a statistically significant decreased risk.*

Conclusion: *Proton pump inhibitor use is not associated with either increased or decreased risk of diabetes mellitus. However, more well-designed studies focusing on proton pump inhibitor use and the risk of diabetes mellitus, especially among populations with different backgrounds, are still needed.*

Keywords: *Diabetes mellitus, meta-analysis, proton pump inhibitors, systematic review*

INTRODUCTION

Diabetes mellitus (DM) is a set of metabolic diseases characterized by hyperglycemia. Hyperglycemia, in turn, is caused by defective insulin secretion or impairment of its biological activity, or both.[1] The long-term presence of hyperglycemia leads to chronic damage and dysfunction of various tissues.[1] Among different types of DM, type 2 diabetes (T2DM) accounts for the majority of cases, and the number of people with T2MD is expected to reach 366 million by 2030.[2] It is known that β cells in the pancreas are critical in maintaining glucose homeostasis during the progression to T2DM, generating compensatory hyperinsulinemia to counteract insulin resistance.[3] In vitro studies found that gastrin increases β-cell mass by inducing β-cell neogenesis and regeneration, and treatment with gastrin was found to induce the formation of new β cells in animal models.[4-7]

Proton pump inhibitor (PPI) decreases gastric acid secretion by blocking its secretion system and consequently increases blood concentration of gastrin by lowering somatostatin.[8-10] As mentioned above, gastrin has the

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potential to induce the formation of new β cells; therefore, the use of PPI may have a potential impact on the development of T2DM. But, whether it increases or decreases the risk of T2DM still remains controversial. A recent cohort study of 204 689 participants found that PPI use was associated with an increased risk of diabetes.[11] In contrast, a population-based retrospective cohort study found that the use of PPI might reduce the risk of diabetes in patients with upper gastrointestinal disease.[12] However, a randomized trial suggested no association between PPI use and the risk of DM.[13] Given the high incidence of DM and the widespread use of PPI and the inconsistent findings of the association between PPI use and risk of T2DM, it is of great value to conduct a meta-analysis to assess this association.

MATERIALS AND METHODS

We followed the standard Preferred Reporting Project declared by the Systematic Review and Meta-Analysis (PRISMA) when performing this meta-analysis. It has been signed up on the International Prospective Register of Systematic Reviews (PROSPERO). The number was CRD42021238481.[14]

Search Strategy

A comprehensive search strategy was conducted for articles on PPI use and the risk of diabetes. The literature search was performed from inception till February 2021 in Embase, PubMed, Web of Science, Cochrane Library, China National Knowledge Infrastructure, China Biomedical Database, Wanfang Data, and VIP (Chinese) database. The following terms were used: (Esomeprazole OR Dexlansoprazole OR Omeprazole OR Ilaprazole OR Pantoprazole OR Rabeprazole OR proton pump inhibitor OR proton pump inhibitors OR PPI OR PPIs) AND (Diabetes OR Diabetes mellitus OR Type 2 diabetes OR Type 2 diabetes mellitus OR T2DM OR DMT2). Chinese phrases replaced English words in the Chinese database.

Main Points

- *This systematic review and meta-analysis estimates the risk of diabetes mellitus (DM) in patients taking proton pump inhibitors (PPIs). Overall, PPI use is not associated with either increased or decreased risk of DM.*
- *Five studies conducted in North America confirmed the overall result; however, 1 study conducted in Europe demonstrated a statistically significant increased risk, while 1 study in Asia revealed a statistically significant decreased risk.*
- *More well-designed studies focusing on proton pump inhibitor use and the risk of DM in different geographic locations are warranted.*

Selection Criteria

Inclusion criteria developed to screen for the eligible publications were as follows: (1) study type is a randomized controlled trial (RCT), case–control study, or cohort study; (2) the exposure of interest was PPI use (no limitation on the type of PPI); (3) the outcome of interest was the risk of diabetes; (4) the risk estimates, such as hazard ratios (HRs), odds ratios (ORs), or relative risks (RRs), with 95% CIs were reported or enough data were provided for calculation. The exclusion criteria were as follows: (1) the subject of the study is not human, like in vitro and in vivo studies; (2) the articles are in the review category; (3) risk estimates cannot be calculated and (4) duplicate.

Data Extraction and Quality Assessment

Two participants (Y. Chen and C. Sun) extracted data separately and independently according to a predefined data form, after which the quality of the articles was evaluated. If disagreements were encountered, discussions were held to reach an agreement or to consult a third person (J. Liu) for the recommendation. The extracted data included the author's name, year, country, study design, comparison, total population, incident diabetes, HRs or ORs with 95% CI, quality, and adjustment factors.

For RCTs, the modified Jadad Scoring Scale was used for evaluation. The modified Jadad Scale was scored according to literature random sequence generation, allocation concealment, blinding, and whether details of study participant withdrawal or dropout were described. A total score of 4-7 was considered a high-quality study and 1-3 as a low-quality study.[15,16] The quality of observational studies was assessed through the Newcastle–Ottawa Scale, which has 3 columns: selection, comparability, and outcomes/exposure. The total score is 9 stars, with 6 or more stars for high-quality literature and 4-5 stars for moderate quality.[17]

Statistical Analysis

The association between PPI use and the risk of diabetes was evaluated by the pooled HRs with 95% CIs. Odds ratios were transformed into relative risk (RRs) which yielded similar estimates as ORs. To perform OR to RR conversion, the following formula was used: $RR = OR/[(1 - P0) + (P0 \times OR)]$. ($P0$ represents the incidence of the outcome in the non-exposed group).[18-20] Data processing was

performed using the statistical software Stata 15.0 (Stata Corp., College Station, Tex, USA) and RevMan software (version 5.3; Cochrane library). The heterogeneity among studies was tested by Q test at the level of $P = .1$, and then the degree of heterogeneity was estimated according to the I^2 statistics: $I^2 < 50\%$ indicated no significant statistical heterogeneity, a fixed-effect model was selected for the combined analysis, and $I^2 > 50\%$ indicated statistical heterogeneity, a random-effect model was applied.[21,22] Sensitivity analysis was achieved by the leave-one-out method.[23] Publication bias was assessed by observing whether the funnel plot was symmetrical and by computing the Begg's and Egger's test values.[24,25] A P value less than .05 was considered to be statistically significant.

RESULTS

Study Characteristics

According to the search strategy, the initial electronic search yielded 6210 articles, and after eliminating duplicates, 4080 articles were obtained. Sixty-two articles were retained after reading the titles and abstracts. Finally, the full texts were read through to filter the literature, and 6 articles[11-13,26-28] were obtained for inclusion. The detailed literature screening process was shown in Figure 1. This meta-analysis included 1 article of randomized controlled trial and 5 articles of 7 cohorts involving a total of 850 019 participants and published between 2002 and 2020. Among them, 4 were conducted in North America,[11,27,28] 1 was in Europe,[26] 1 was in Asia,[12] and 1 was conducted in mixed countries.[13] Five of them were adjusted for confounders.[11,12,26] All included studies were of high or moderate quality. More detailed information about the included studies was presented in Table 1.

Overall Meta-Analysis

Six articles with 8 studies[11-13,26-28] regarding the association between PPI use and the risk of DM were included for the overall meta-analysis. Heterogeneity was observed, and the combined effect estimation with a random-effect model was displayed in the forest plot. The pooled result indicated that PPI use was not associated with increased or decreased risk of diabetes (HR = 1.06, 95% CI = 0.89-1.28, $P = 0.50$; Figure 2).

Subgroup Analyses

In subgroup analysis, according to study type, the same result was found in the 7 cohort studies[11,12,26-28] (HR = 1.08, 95% CI = 0.88-1.32, $P = .460$), and 1 RCT[13] reported OR of 0.96 (95% CI = 0.86-1.08). When compared with corticosteroid,[27,28] PPI use was associated with a reduced risk (HR = 0.89, 95% CI = 0.83-0.95, $P < .001$); however, no statistical significance was found when compared to non-PPI use[11,12,26] or when compared to placebo.[13] In terms of geographic locations, 5 studies conducted in North America[11,27,28] have indicated that PPI use was not associated with increased or decreased risk of diabetes (HR = 1.06, 95% CI = 0.90-1.26, $P = .480$); however, 1 study conducted in Europe[26] demonstrated a statistically significant increased risk, while 1 study in Asia[12] demonstrated a statistically significant decreased risk. For adjustment factors, a statistically significant association was detected in unadjusted studies (HR = 0.91, 95% CI = 0.86-0.96, $P = .001$),[13,27,28] whereas no significant association was observed in adjusted studies (HR = 1.17, 95% CI = 0.93-1.48, $P = .190$).[11,12,26] For subgroup analysis of different study qualities, the results remained the same (high quality: HR = 1.03, 95% CI = 0.88-1.21, $P = .710$; moderate quality: HR = 1.16, 95% CI = 0.65-2.07, $P = .610$). All these results are shown in Table 2.

Sensitivity Analyses and Publication Bias

Sensitivity analysis was achieved by the leave-one-out method, which demonstrated a stable result. The funnel plot shape was symmetrically distributed and the Begg's test and Egger's test suggested no publication bias (Begg's test: $Z = 0.87$; $P = .386$; Egger's test: $t = -1.27$; $P = .251$; Figure 3).

DISCUSSION

The association between PPI use and DM risk has been a disputed topic. Based on previous studies, this meta-analysis of 1 RCT and 7 cohort studies in patients with diverse backgrounds indicated that PPI use was not associated with the change of risk for developing DM. Furthermore, subgroup analysis confirmed the irrelevance between them. The pooled estimate effect of the 7 cohort studies included in this article was virtually indistinguishable from the overall result. Even though there was only 1 RCT, the article reported the same conclusion of no association between PPI use and risk of DM. In subgroup analysis comparing PPI to non-PPI use or placebo, PPI use was not associated with a statistically significant risk of DM; however, statistical significance was found when compared with corticosteroid. This result should be treated with caution because only 2 articles were published with corticosteroids as contrast. Moreover, in Blackburn's study, 38 441 people used inhaled corticosteroids and 31 864 used oral corticosteroids, but the usage of corticosteroids in Barnett's study was not reported. According to the preclinical findings, acute use

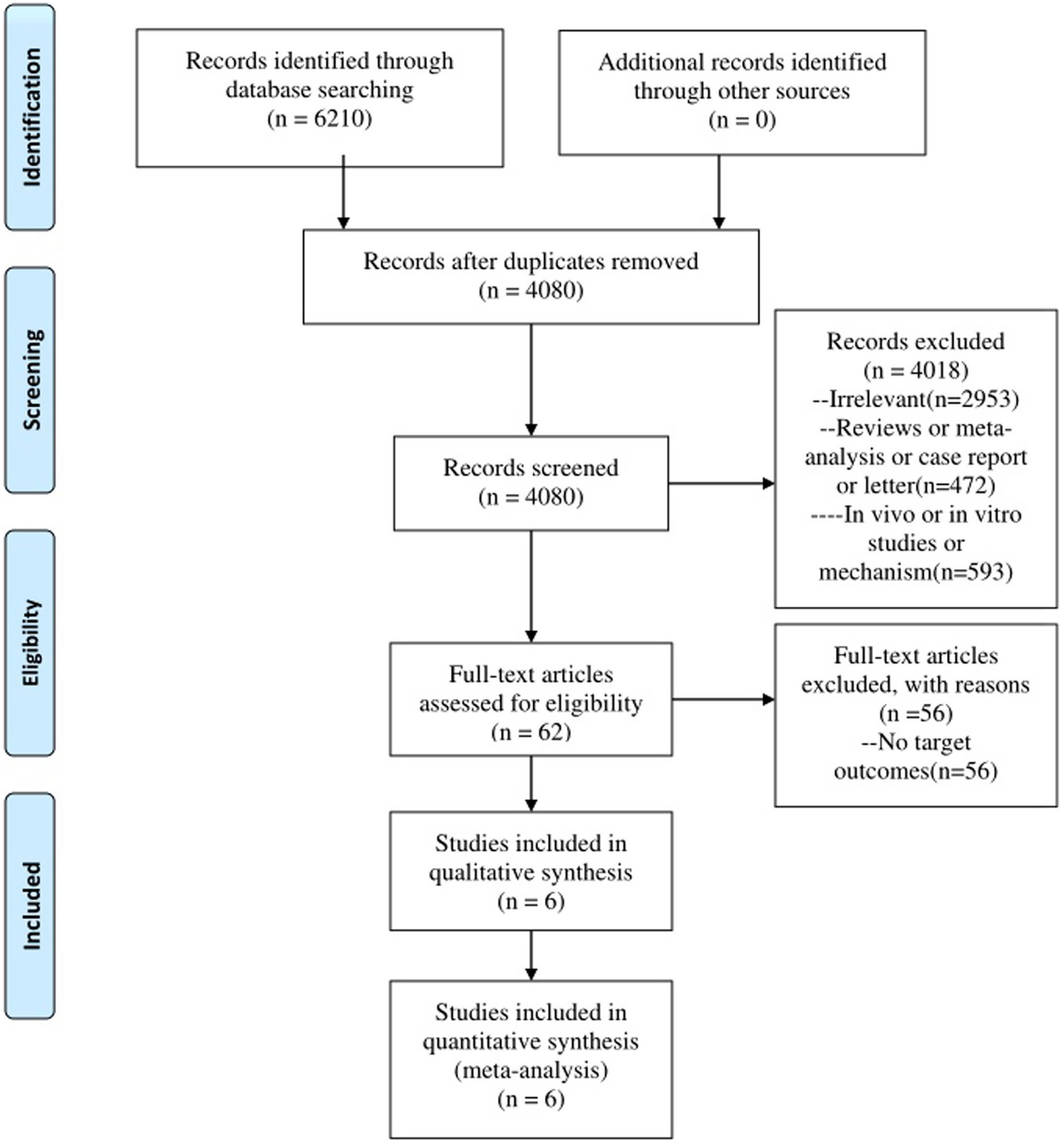

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

of corticosteroids was known to cause blood sugar disturbances. However, blood glucose fluctuations caused by corticosteroid in the acute phase are not considered as diabetes. Nevertheless, the included articles did not mention whether this part of patients was excluded. However, it is well known that steroids increase the risk of DM, which likely results from the impairment of multiple pathways including β-cell dysfunction, insulin-mediated

Table 1. Characteristics of Individual Studies Included in the Meta-Analysis

Author	Study Design	Comparison	Country	Total Population	Incident Diabetes	HR (95% CI)	Quality	Adjustment Factors
Blackburn (2002)	Cohort	PPI versus corticosteroid	Canada	124 150	2597	0.91 (0.84-0.98)	High	Unadjusted
Barnett (2006)	Cohort	PPI versus corticosteroid/antipsychotics	USA	11 165	1496	0.86 (0.77-0.97)	Moderate	Unadjusted
Lin (2016)	Cohort	PPI versus non-PPI	China	22 152	2242	0.80 (0.73-0.88)	High	Adjusted[a]
Moayyedi (2019)	RCT	PPI versus placebo	Mixed	17 598	1045	0.96 (0.86-1.08)	High	Unadjusted
He (2020)	Cohort	PPI versus non-PPI	UK	470 265	8349	1.56 (1.46-1.66)	Moderate	Adjusted[b]
Yuan (2020a)	Cohort	PPI versus non-PPI	USA	80 500	4726	1.22 (1.12-1.33)	High	Adjusted[c]
Yuan (2020b)	Cohort	PPI versus non-PPI	USA	95 550	4631	1.22 (1.17-1.38)	High	Adjusted[c]
Yuan (2020c)	Cohort	PPI versus non-PPI	USA	28 639	748	1.12 (0.91-1.38)	High	Adjusted[c]

[a]Adjusted for age, sex, hypertension, gout and/or hyperuricemia, coronary artery disease, stroke, pancreatitis, hyperlipidemia, obesity, H2-blocker use, and clozapine or olanzapine use.
[b]Adjusted for diabetes risk factors, including age at recruitment, ethnicity, deprivation (as measured by the index of multiple deprivations), body mass index (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, including esophagitis/Barrett's esophagus, gastroesophageal reflux disease, peptic ulcer, upper gastrointestinal bleeding and histamine-2 receptor antagonists use, aspirin use and non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) use.
[c]Adjusted for race, family history of diabetes, BMI, pack-years of smoking, alcohol intake per day, physical activity, overall diet quality, total calories, multivitamin use, hypertension, hypercholesterolemia, cancer, menopausal status and postmenopausal hormone use, number of parity, breastfeeding, any use of antibiotics, regular use of non-steroidal anti-inflammatory drugs, and any use of steroids. Gastro-esophageal reflux disease, gastric or duodenal ulcer, upper gastrointestinal tract bleeding, and regular use of histamine-2 receptor antagonists.

glucose uptake with interference with glycogen synthase kinase-3, glycogen synthase, and GLUT4 translocation, and insulin resistance in various tissue.[29-32] Five studies in North America,[11,27,28] and 1 mixed study[13] all reported no statistically significant association between PPI use and diabetes risk. However, 1 study in Europe[26] found an increased risk of DM with PPI use, while 1 study from Asia[12] found a decreased risk. In subgroup analyses stratified by study quality, no protective or harmful effects of PPI use were shown for either the high-quality study[11-13,28] or moderate-quality study.[27] Also, the adjusted studies came to a generally consistent conclusion, yet the unadjusted studies[13,27,28] showed a protective effect of PPI. It is considered that the result of the adjusted studies was more convinced than the unadjusted ones because some confounding factors can affect the risk of DM.[33,34] Sensitivity analyses showed that results were not substantially altered when we adopt the leave-one-out method, indicating a robust result of this meta-analysis. Considering the widespread use of PPI in digestive diseases, this article will make considerable sense.

The potential mechanisms underlying the association between PPI use and diabetes remain obscure. Recently, an increasing number of studies have supported the role of altered intestinal flora in the pathogenesis of diabetes.[35] It has also been reported that PPI affects the gut microbial community by changing the gastrointestinal environment.[36] Given the significant effect of PPI, its use may also be associated with an elevated risk of developing DM. Previous studies have shown that the use of PPIs may lead to some adverse effects, such as fatty liver disease[37] and metabolic syndrome,[38] which may in turn increase the risk of T2DM. Additionally, PPI use is likely to increase the levels of asymmetric dimethylarginine in plasma, which are implicated in insulin resistance and DM.[39,40] However, other studies found the potential mechanism of decreased DM risk with PPI use. In clinical studies, HbA1c was found to be lower in diabetic patients who take PPI,[41] which could probably support the beneficial effect of PPI use in diabetes patients. Also, Singh et al[42] found a significant increase in gastrin and insulin levels when T2DM patients were given 12 weeks of pantoprazole treatment.[42] The same conclusion has been confirmed in animal experiments.[4,5] Previous studies demonstrated that secretion of gastrin stimulates β-cell neogenesis, regeneration, and expansion of the β-cell mass.[4-7] In brief, the use of PPI causes a decrease in acid secretion in the stomach and an increase in pH, which in turn promotes the secretion of gastrin. Gastrin triggers the formation of pancreatic β-cells, which increases

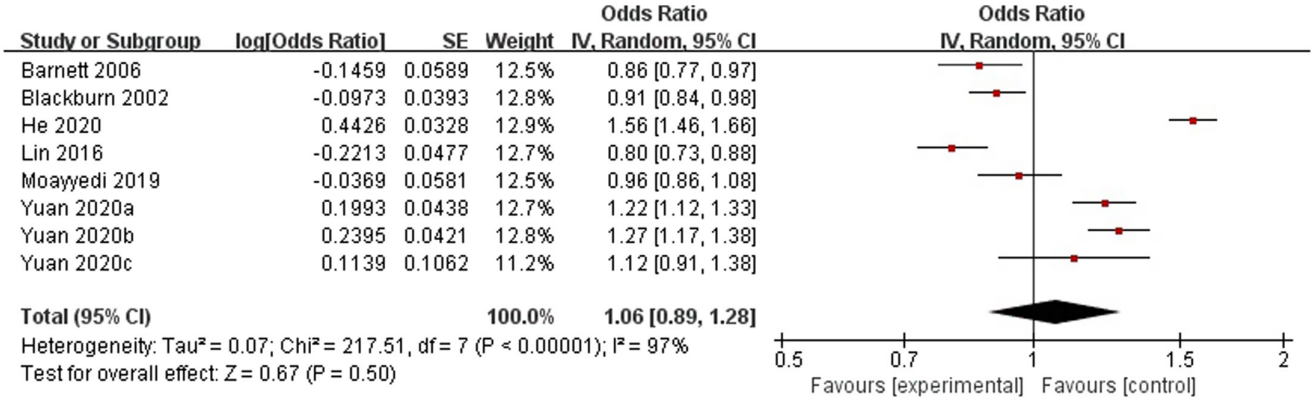

Figure 2. Forrest plot: Association between proton pump inhibitors use and the risk of diabetes mellitus.

insulin secretion. In clinical studies, HbA1c was also found to be lower in diabetic patients who take PPI,[41] which could probably support the beneficial effect of PPI use in diabetes patients. Our study found that PPI did not increase or decrease the risk of DM, and the effect of PPI on the long-term risk of diabetes in a healthy population and on blood glucose levels in a diabetic population still needs to be comprehensively explored.

There are some limitations in this meta-analysis. First, there was a heterogeneity between the included studies, so a random-effects model was applied to combine

Table 2. Summary of Pooled HRs with CI in the Meta-Analysis

			Heterogeneity		Significant		
Analysis	No. of Studies	HR (95% CI)	*P*	I^2 (%)	*Z*	*P*	M[a]
Overall	8	1.06 (0.89-1.28)	<.001	97.0	0.67	.50	R[c]
Study design							
Cohort	7	1.08 (0.88-1.32)	<.001	97.0	0.74	.46	R[c]
RCT	1	0.96 (0.86-1.08)	NA	NA	NA	NA	NA
Comparison							
PPI versus non-PPI	5	1.17 (0.93-1.48)	<.001	97.0	1.31	.19	R[c]
PPI versus corticosteroid	2	0.89 (0.83-0.95)	.230	31.0	3.44	<.001	F[b]
PPI versus placebo	1	0.96 (0.86-1.08)	NA	NA	NA	NA	NA
Geographic locations							
North America	5	1.06 (0.90-1.26)	<.001	93.0	0.71	.48	R[c]
Europe	1	1.56 (1.46-1.66)	NA	NA	NA	NA	NA
Asia	1	0.80 (0.73-0.88)	NA	NA	NA	NA	NA
Mixed	1	0.96 (0.86-1.08)	NA	NA	NA	NA	NA
Adjustment factors							
Adjusted	5	1.17 (0.93-1.48)	<.001	97.0	1.31	.19	R[c]
Unadjusted	3	0.91 (0.86-0.96)	.420	0.0	3.30	.001	F[b]
Quality							
High	6	1.03 (0.88-1.21)	<.001	94.0	0.38	.71	R[c]
Moderate	2	1.16 (0.65-2.07)	<.001	99.0	0.51	.61	R[c]

[a]Model of meta-analysis. [b]Fixed effects model. [c]Random effects model; NA: Not applicable.
HR, hazard ratio; PPI, proton pump inhibitor; RCT, randomized controlled trial.

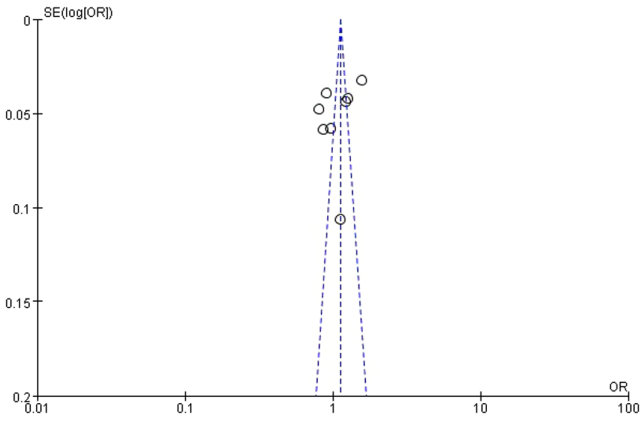

Figure 3. Funnel plot.

HRs. While subgroup analysis can interpret some causes of heterogeneity, other potential sources, such as different types of PPI, different doses of PPI use, and different cumulative durations of PPI, could not be investigated due to lack of sufficient data from the original studies included. Second, due to the limited number of included studies and the fact that most of the studies were observational, our results should be explained with caution. Notwithstanding the limitations mentioned above, the following advantages of this study should be acknowledged. To the best of our knowledge, this is the first meta-analysis to clarify the relationship between PPI use and DM risk. Moreover, sensitivity analysis showed that the results of the meta-analysis did not alter substantially when we used the leave-one-out method, as the results were robust. Besides, no publication bias existed.

In conclusion, PPI use does not change the risk of DM based on currently available evidence. However, a limited number of studies were conducted outside North America, indicating the need for more data on populations with different backgrounds. Thus, more well-designed studies focusing on PPI use and the risk of diabetes mellitus are warranted.

Ethics Committee Approval: Ethics committee approval was not received for this study as there are no human or animal subjects directly recruited.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: C.S.; Design: C.S.; Supervision: Y.C., L.H., C.S.; Materials: C.S., Y.C., L.H., J.B.; Data Collection: Y.C., L.H., C.S., J.L., S.M.; Analysis: Y.C., L.H., C.S., J.B., J.L., S.M.; Literature Search: Y.C., L.H., C.S., J.B., R.M., P.T.; Writing Manuscript: C.S., Y.C., L.H.; Critical Review: J.B., J.L., C.B., K.Y.K., S.M., M.L., X.C., C.C., Q.Z.

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