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Association between dipeptidyl peptidase-4 inhibitor drugs and risk of acute pancreatitis

A meta-analysis

Shimin Chen, MD[a], Enfa Zhao, MD[b], Wenfei Li, MD[c], Jiehong Wang, MD[a,*]

Abstract

Background: Previous studies have reported conflicting results for the relationship between dipeptidyl peptidase-4 (DPP-4) inhibitor drugs and acute pancreatitis. The aim of this study was to investigate the association between DPP-4 inhibitors and an increased risk of acute pancreatitis using meta-analysis.

Methods: We conducted a comprehensive search in PubMed, Embase, Web of Science, and Cochrane library from inception to March 4, 2017. Original articles with data on DPP-4 inhibitors and acute pancreatitis were included. We used random-effects models or fixed-effects models to combine the relative risks (RRs), odds ratio (OR), and hazard ratio (HRs) with 95% confidence intervals (CIs) in randomized controlled studies, case–control study and cohort study, respectively.

Results: Five case–control studies, 5 randomized controlled studies, and 3 cohort studies were selected of the 451 retrieved abstracts. A higher risk of acute pancreatitis was observed with the following RR/OR and 95%CI: RR 1.67 (1.08–2.59) in randomized controlled studies and OR 1.45 (1.30–1.61) in case–control studies. However, the pooled HR of the 3 cohort studies failed to confirm this association.

Conclusion: There is a marginally higher risk of acute pancreatitis with DPP-4 inhibitors. However, this risk was not observed in cohort studies. Thus, further clinical trials are required to confirm this finding.

Abbreviations: CI = confidence intervals, DPP-4 = dipeptidyl peptidase-4, GLP-1 = glucagon-like peptide 1, HR = hazard ratio, OR = odds ratio, RR = relative risks.

Keywords: acute pancreatitis, dipeptidyl peptidase-4 inhibitor, meta-analysis

1. Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors are incretin-based drugs widely used in the management of type 2 diabetes mellitus.[1,2] By preventing glucagon-like peptide 1 (GLP-1) from rapid breakdown through inhibition of DPP-4, an enzyme responsible for metabolizing the gastrointestinal hormone GLP-1, the DPP-4 inhibitors enhances pancreatic endogenous insulin secretion and suppresses pancreatic glucagon secretion, resulting in the reduction blood glucose levels.[3] Acute pancreatitis is a serious condition that often results in hospitalization and even death.[4] There is a concern about DDP-4 inhibitors leading to acute pancreatitis in humans, although the evidence remains controversial.[5–7] Some authors have reported that after adjustment for available confounders, the use of DDP-4 inhibitors was not associated with an increased risk of acute pancreatitis compared with control groups;[2,8–10] other studies yielded positive results. A study from Italy concluded that the reporting odds ratio (OR) was 1.86 (95% CI: 1.54–2.24) in a case–control study of 2625 cases and 156,601 noncases.[11] Singh et al[12] reported a higher increased risk for acute pancreatitis associated with the use of DDP-4 inhibitors in patients with type 2 diabetes mellitus with an OR of 2.02 (95% CI: 1.31–3.01) in a population-based case–control study. A study conducted in France in 2013 even reported an OR of 12.08 (95% CI: 7.30–20.0) for acute pancreatitis associated with the use of DDP-4 inhibitors (sitagliptin, vildagliptin, and saxagliptin).[13] A previous study[14] found that DDP-4 inhibitors were associated with an increased risk of acute pancreatitis with an RR of 1.57; however, the study only focused on randomized clinical trials. Previous studies on this association have yielded conflicting results owing to their limited statistical power. Thus, the main aim of our study was to perform a meta-analysis on the risk of acute pancreatitis in type 2 diabetes mellitus patients who used DDP-4 inhibitors compared with a placebo-controlled population.

2. Materials and methods

2.1. Data sources and search strategy

We performed a systematic literature search of PubMed, Embase, Web of Science, and Cochrane library from inception to March 4, 2017. Human studies that reported data on DPP-4 inhibitors and risk of acute pancreatitis were included without restriction on language. The overall search strategy referred to medical subject

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SC and EZ designed this study; EZ and WL collected and collated data; SC and JW extracted and confirmed the data; SC and EZ analyzed data; SC wrote the manuscript; JW edited the manuscript.

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[a] Department of Gastroenterology, Shaanxi University of Traditional Chinese Medicine, Xian Yang, Shaanxi, China, [b] Department of Structural Heart Disease, The First Affiliated Hospital of Xi'an, Jiaotong University, Xi'an, [c] Department of Radiology, the First Hospital of Qinhuangdao, Qinhuangdao, Hebei, China.

[*] Correspondence: Jiehong Wang, Department of Gastroenterology, Shaanxi University of Traditional Chinese Medicine, Xian yang 712046, Shaanxi, China, (e-mail: wangjiehong68@163.com)

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heading terms and/or text words: (dipeptidyl peptidase-4 inhibitor or DPP-4 or sitagliptin or alogliptin or linagliptin or saxagliptin or vildagliptin) and (acute pancreatitis or pancreatitis). The reference lists of all included studies were also manually reviewed for potential studies. Abstracts and citations were screened independently by 2 authors. All the included articles need a further screening for full-text reports. Papers that only provided abstracts were also included if sufficient data were reported.

2.2. Inclusion and exclusion criteria

A study was included in the meta-analysis if it met the following criteria: (1) studies assessing DDP-4 inhibitors compared with placebo; (2) studies evaluating the association between DDP-4 inhibitors and risk of acute pancreatitis in patients with type 2 diabetes mellitus; (3) one of the outcomes is acute pancreatitis; and (4) studies with reference group. Editorials, letters, systematic reviews, comments, or reports lacking sufficient data were excluded. If the works were shared or duplicated in more than one study, the most recent publication was included. All identified papers were reviewed by 2 authors independently. Any disagreements were resolved by consensus with a third reviewer.

2.3. Data extraction

Two investigators independently extracted the following data from each study: First author, year of publication, country, study type, adjusted HR/OR, and type of DDP-4 inhibitors used. Disagreements were resolved by detailed discussion, consensus, and arbitration by the third author.

2.4. Statistical analysis

All statistical analyses were performed with stata version 11.0 software (StataCorp, College Station, TX). Relative risks (RRs), OR, or hazard ratio (HR) with 95% confidence interval (CI) were used to estimate the effect sizes. I^2 was used to describe the statistical heterogeneity among studies. $I^2 > 50\%$ was considered to exhibit severe heterogeneity. A random-effect model was used if $P > .05$ and $I^2 < 50\%$; otherwise, a fixed-effect model was selected. We used the Begg test (rank correlation method)[15] to evaluate the possible publication bias and a P value of $<.1$ was considered as significant statistical publication bias. We performed meta-analyses when relevant data were available from at least 3 studies.

3. Results

3.1. Characteristics of the subjects in the included studies

Detailed studies retrieval procedures are summarized in Figure 1. A total of 451 references were preliminarily identified according to the search strategy. Two hundred eight-nine records remained after excluding 162 duplicate articles. We screened titles and

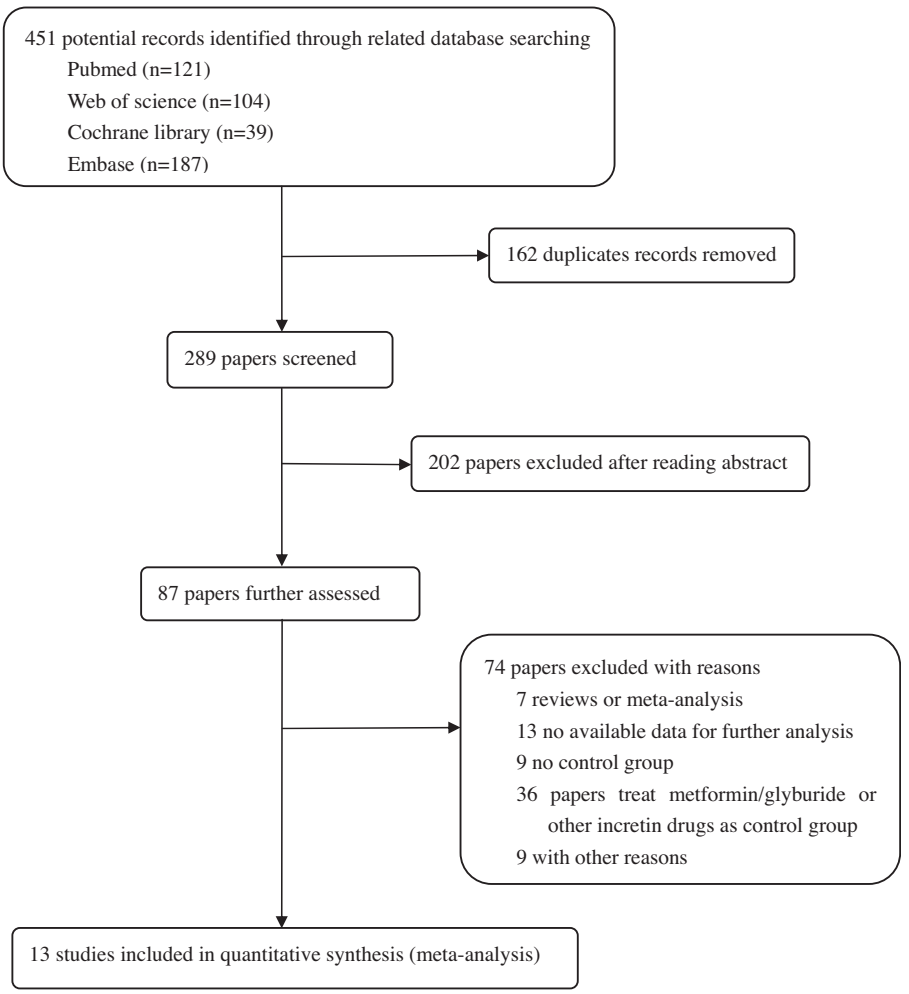

Figure 1. Flow diagram of study selection process.

Table 1

Baseline characteristic of patients in the meta-analysis.

Author	Year	Country	DPP-4		Placebo		ES (95%CI)	Research type	DPP-4
			Events	total	Events	Total			
Barnett	2013	UK	0	304	1	151	RR,0.17 (0.01–4.08)	Randomized,double-blind, parallel-group trial	Saxagliptin
White	2013	USA	12	2701	8	2679	RR,1.49 (0.61–3.63)	Randomized double-blind	Alogliptin
Hollander	2011	USA	1	381	0	184	RR,1.45 (0.06–35.40)	Randomized, double-blind, placebo-controlled trial	Saxagliptin
Scirical	2013	USA	17	8280	9	8212	RR,1.87 (0.83–4.20)	Randomized, double-blind, placebo-controlled	Saxagliptin
Green	2015	USA	23	7332	12	7339	RR,1.92 (0.95–3.85)	Randomized, double-blind study	Sitagliptin
Azoulay	2016	Canada	488	5165	7824	96,654	HR,1.09 (0.86–1.38)	Population-based cohort study	Linagliptin, sitagliptin phosphate, vildagliptin, and saxagliptin
Garg R	2010	USA					HR,1.0 (0.7–1.3)	Retrospective cohort study	Sitagliptin
Eurich	2013	Canada					HR,1.10 (0.68–1.77)	Retrospective cohort study	Sitagliptin
Chou	2014	China	322	1957	1194	7828	OR 1.04 (0.89–1.21)	Population-based nested case–control study	Sitagliptin,saxagliptin, and vildagliptin
Giorda	2014	Italy					OR 0.98 (0.69–1.38)	Population-based matched case–control study	Sitagliptin, saxagliptin, and vildagliptin
Sonal Singh	2013	USA	47	1269	31	1269	OR,2.02 (1.31–3.01)	Population-based case-control study	Sitagliptin
Faillie	2013	France	67	147	421	2962	OR,12.08 (7.3–20.0)	A case/noncase study	Saxagliptin, sitagliptin, and vildagliptin
Raschi	2011	Italy	129	2625	4227	15,6601	OR,1.86 (1.54–2.24)	A case/noncase	Saxagliptin, sitagliptin, and vildagliptin

CI = 95% confidence interval, DPP-4 = dipeptidyl peptidase-4 inhibitor, ES = effect size, HR = hazard ratio, OR = odds ratios, RR = relative risk.

abstracts of all identified papers and 202 clearly irrelevant records were excluded. After reviewing the remaining articles in detail, 74 articles were excluded with reasons. Finally, 5 case–control studies, 5 randomized controlled studies, and 3 cohort studies were included in the study. The characteristics of the 13 studies[1,2,7–13,16–19] are presented in Table 1.

3.2. Meta-analysis results

As shown in Figure 2, the incorporated results in randomized controlled studies indicated a statistically significant increased risk for acute pancreatitis in type 2 diabetes mellitus patients who used DDP-4 inhibitors without heterogeneity with an RR of 1.67 (95% CI: 1.08–2.59; $I^2 = 0$, $P = .682$). Random-effects meta-

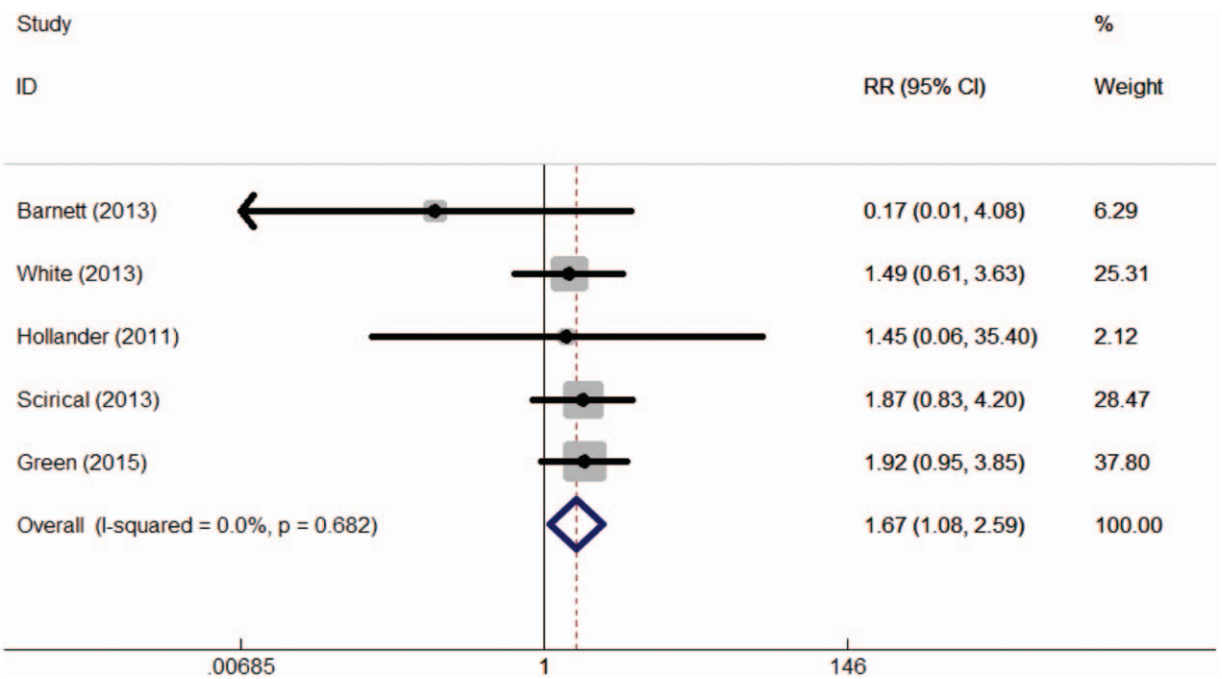

Figure 2. Relative risks (RRs) for the association between acute pancreatitis and DPP-4 inhibitor drugs in 5 randomized controlled studies. The diamond denotes the incorporated RR. Shaded rectangles suggest the RR in each study, with sizes inversely proportional to the SE of the RR. Horizontal lines indicate the 95% confidence interval (CI). CI = confidence interval, DPP-4 = dipeptidyl peptidase-4, RR= relative risks.

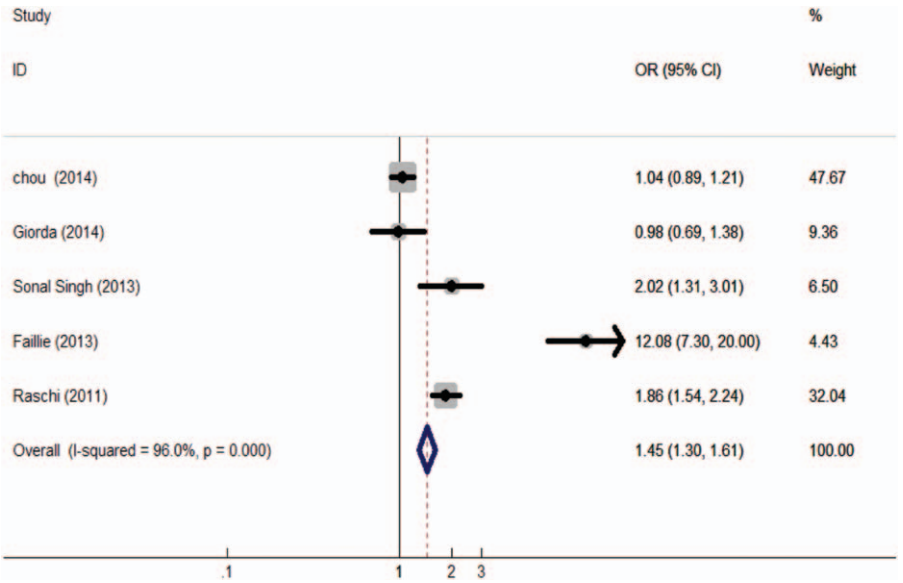

Figure 3. Odds ratio (OR) for the association between acute pancreatitis and DPP-4 inhibitor drugs in 5 case-controlled studies. The diamond denotes the incorporated OR. Shaded rectangles suggest the OR in each study, with sizes inversely proportional to the SE of the OR. Horizontal lines indicate the 95% confidence interval (CI). CI = confidence interval, OR = odds ratio, SE = standard error.

analysis showed that DDP-4 inhibitors were associated with an increased risk of acute pancreatitis with noticeable heterogeneity with OR = 1.45 (95% CI: 1.30–1.61; $I^2 = 96.0\%$, $P = .00$) (Fig. 3). However, similar results were not observed in cohort studies with HR = 1.06 (95% CI: 0.89–1.26; $I^2 = 0$, $P = .899$) (Fig. 4).

3.3. Publication bias

To evaluate potential bias across studies, the Begg test with funnel plot asymmetry was used to identify small study effects of the association between DDP-4 inhibitors and the risk of acute pancreatitis. The funnel plot of randomized controlled, case–control, and cohort studies shown in Figure 5, Figure 6, and

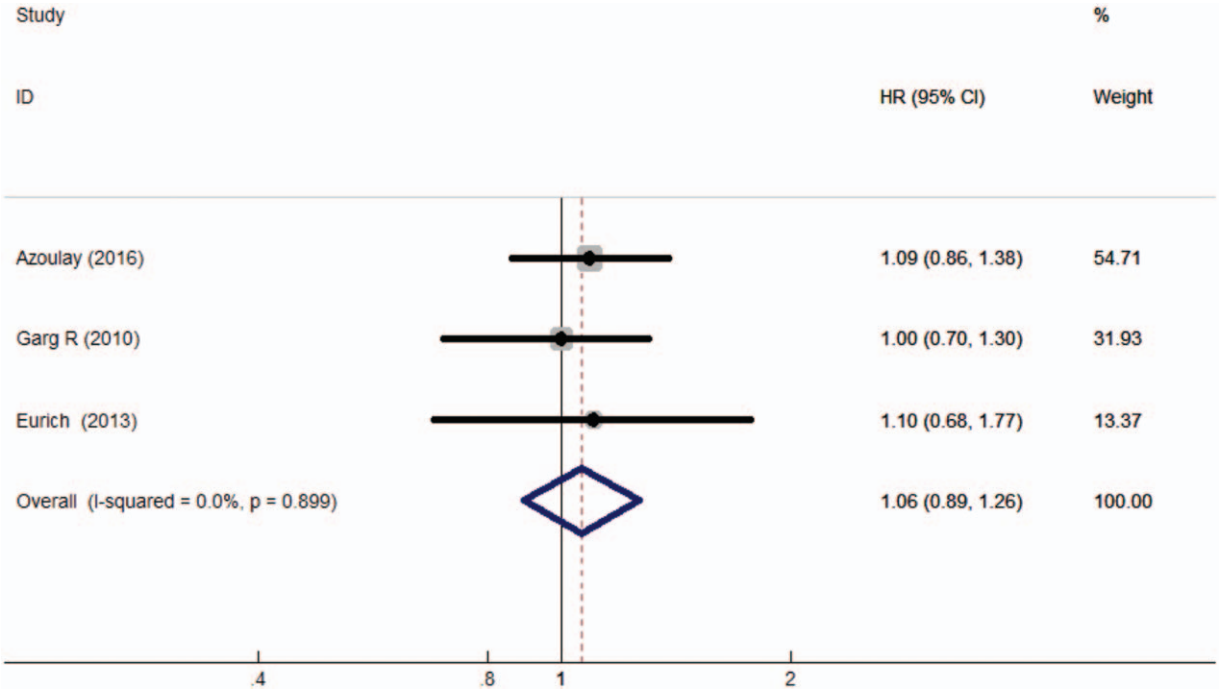

Figure 4. Hazard ratio (HR) for the association between acute pancreatitis and DPP-4 inhibitor drugs in 3 cohort studies. The diamond denotes the incorporated HR. Shaded rectangles suggest the HR in each study, with sizes inversely proportional to the SE of the HR. Horizontal lines indicate the 95% confidence interval (CI). CI = confidence interval, DPP-4 = dipeptidyl peptidase-4, HR = hazard ratios.

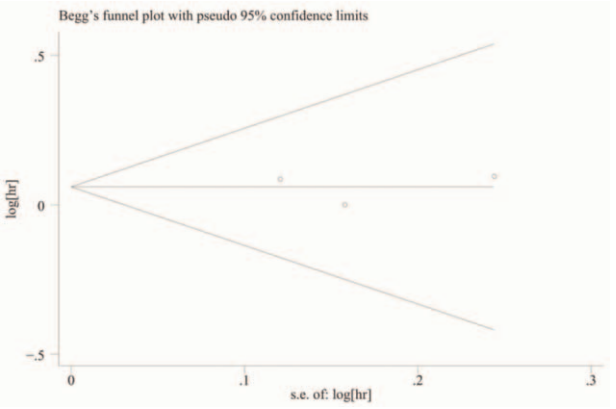

Figure 5. Funnel plot of studies evaluating the association between acute pancreatitis and DPP-4 inhibitor drugs in randomized controlled studies. The Begg regression asymmetry test ($P = .139$). DPP-4 = dipeptidyl peptidase-4.

Figure 7, respectively, was symmetrical, which indicated a low potential publication bias ($P = .139$, .253, .951, respectively).

4. Discussion

In this meta-analysis, we analyzed the risk of acute pancreatitis associated with DDP-4 inhibitors in type 2 diabetes mellitus patients. We found evidence to suggest a marginally increased risk of acute pancreatitis associated with the use of DDP-4 inhibitor drugs in patients with type 2 diabetes in randomized controlled and case–control studies.

Since the first report involving DDP-4 inhibitors drugs (sitagliptin/metformin) and its association with acute pancreatitis published by American Food and Drug Administration,[20] numerous studies related to DDP-4 inhibitors and the risk of acute pancreatitis have been reported. Our findings are in line with previous studies.[11–14] Previously, the meta-analysis of randomized clinical trials found that DDP-4 inhibitors were associated with an increased risk of acute pancreatitis (RR = 1.57, 95% CI = 1.03–2.39).[14] Positive results were not observed in meta-analysis cohort studies. A meta-analysis involving 3 retrospective cohort studies with moderate to high risk of bias did not suggest an increased risk of pancreatitis associated with sitagliptin with an adjusted HR of 1.0 (0.7–1.3).[4] The heterogeneity within the above studies was likely a result of several methodological shortcomings, including the use of inappropriate comparator groups, small sample sizes, confounding by indication, time-lag bias, and various durations of follow-up. In randomized controlled studies, there were imbalances in case number of acute pancreatitis both in DDP-4 inhibitors groups and placebo groups. In a study conducted in the United States,[18] 24 events in DDP-4 inhibitors groups and 21 in placebo groups were reported; in another study,[17] 12 events and 4 events in DDP-4 inhibitors groups and placebo groups were recorded, respectively. In yet another study, 23 events occurred in DDP-4 inhibitors groups and 12 in placebo groups. In these studies, most cases were complicated by longstanding cardiovascular disease, which does not conform to the patients using DPP-4 inhibitors in a clinical setting.[1] Singh et al[12] reported a significantly increased risk of acute pancreatitis associated with the use of the DPP-4 inhibitor–sitagliptin in type 2 diabetes mellitus with an OR of 2.02 (95% CI:1.31–3.01). In a large number of cohort studies, compared with acarbose in diabetic patients, the authors concluded that sitagliptin was not associated with an increasing risk of acute pancreatitis even in high-risk patients.[21] A recent review reported that DPP-4 inhibitors were not associated with the risk of acute pancreatitis.[22] Previous meta-analyses[23] only focused on randomized controlled studies; however, there are some case–control or cohort studies that reported the risk of acute pancreatitis.

Although we included different types of studies in our meta-analysis, it has limitations. We failed to perform a meta-regression analysis to evaluate the potential variables because of unavailable data even though there was noticeable heterogeneity

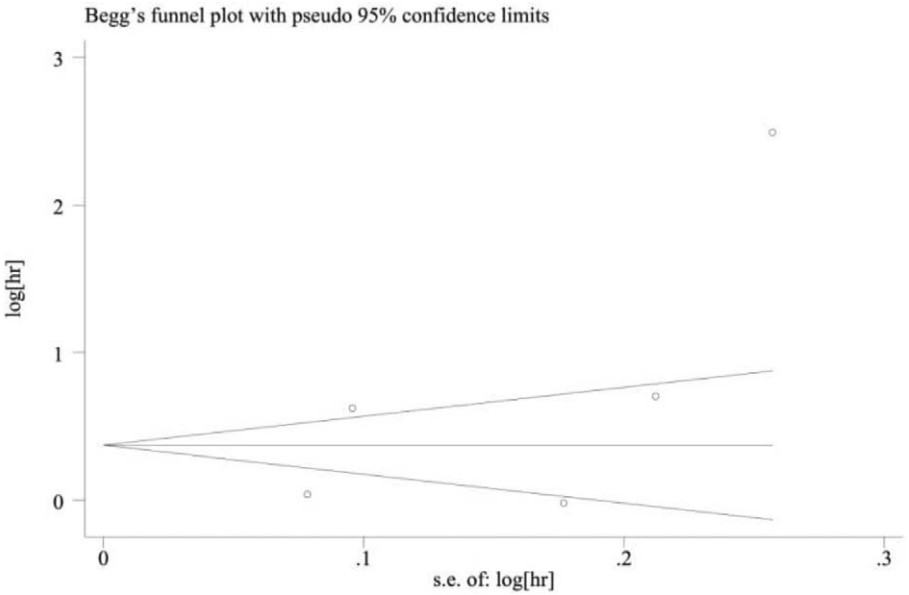

Figure 6. Funnel plot of studies evaluating the association between acute pancreatitis and DPP-4 inhibitor drugs in case-controlled studies. The Begg regression asymmetry test ($P = .253$). DPP-4 = dipeptidyl peptidase-4.

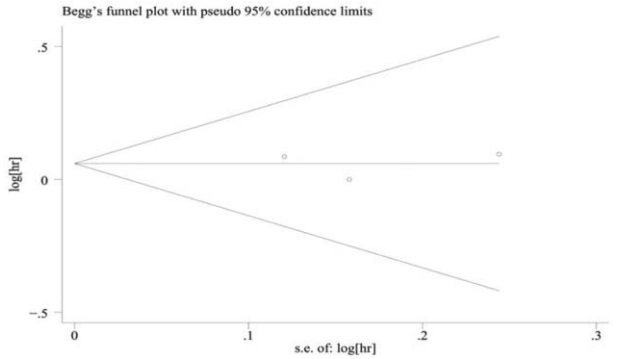

Figure 7. Funnel plot of studies evaluating the association between acute pancreatitis and DPP-4 inhibitor drugs in cohort studies. The Begg regression asymmetry test ($P = .951$). DPP-4 = dipeptidyl peptidase-4.

in case–control studies. Another limitation was related to various study designs. This can account for why our analysis failed to have a unified conclusion for different study types. Even though the Begg tests with funnel plot asymmetry suggested that there was no obvious publish bias, potentially bias may be unavoidable. Besides, in this meta-analysis, the DPP-4 inhibitors had 4 different molecular structures. This also may another source of bias. It may affect the stability of results.

Our meta-analysis shows an increased risk of acute pancreatitis in DPP-4 inhibitor drugs in randomized controlled studies or case–control studies. However, meta-analysis of cohort studies failed to confirm this association with only 3 studies included. Therefore, this finding should be interpreted cautiously. There remains a cloud of uncertainty regarding the association between the risk of acute pancreatitis and DPP-4 inhibitor. Thus, to better understand the possible association, all types of original studies encompassing whole populations are urgently warranted.

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