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ORIGINAL RESEARCH ARTICLE

Acute Pancreatitis in Patients with Type 2 Diabetes Mellitus Treated with Dipeptidyl Peptidase-4 Inhibitors: A Population-Based Nested Case-Control Study

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Abstract

Background Concern about an increasing risk of acute pancreatitis associated with incretin-based drugs, including dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 analogs, has emerged recently.

Objective This nested case-control study examined the association between the use of DPP-4 inhibitors and acute pancreatitis using Taiwan's National Health Insurance Research Database.

Methods From a study cohort of patients with type 2 diabetes mellitus, we identified 1,957 acute pancreatitis cases (patients who had been admitted with a diagnosis of acute pancreatitis) and 7,828 age-, sex-, and cohort entry year-matched controls between 2000 and 2011. Multivariate conditional regression models were used to estimate the association between the use of DPP-4 inhibitors and acute pancreatitis. Sensitivity analyses were conducted by varying the definitions of timing of exposure to DPP-4 inhibitors.

Results The risks of acute pancreatitis among current and past users of DPP-4 inhibitors were comparable with those of non-users (current users: adjusted odds ratio (aOR) 1.04; 95 % CI [0.89–1.21]; past users: aOR 1.61 [0.93–2.77]). Similar results were found in sensitivity analyses with various definitions of "current users" of DPP-4 inhibitors. Nevertheless, the adjusted risk of acute pancreatitis was found to be increased significantly in patients with gallstone disease (aOR 5.89 [4.71–7.35]), alcohol-related disease (aOR 5.36 [4.05–7.08]), hypertriglyceridemia (aOR 1.80 [1.26–2.56]), pancreatic disease (aOR 17.29 [10.60–28.19]), and a higher Diabetes Complications Severity Index (DCSI) score (DCSI 3–4: aOR 1.49 [1.21–1.84]; DCSI ≥5: aOR 1.32 [1.01–1.73]).

Conclusions This population-based study extends previous evidence by exploring the potential association between DPP-4 inhibitor use and the risk of acute pancreatitis in an ethnic Chinese type 2 diabetic cohort. We found that underlying diseases and severity of diabetes but not DPP-4 inhibitor use were associated with acute pancreatitis.

Key Points

This is the first study to investigate the association between the use of dipeptidyl peptidase-4 (DPP-4) inhibitors and risk of acute pancreatitis in a nationwide cohort representative of ethnic Chinese.

The risk of acute pancreatitis among current and past users of DPP-4 inhibitors was comparable with that of non-users.

Nevertheless, severe diabetes mellitus, gallstone disease, alcohol-related disease, hypertriglyceridemia, and pancreatic disease were associated with an increased risk of acute pancreatitis.

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1 Introduction

Recent evidence indicates that the most recently approved oral antihyperglycemic agents, including incretin-based drugs such as dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) analogs, may be associated with an increased risk of acute pancreatitis [1–3]. Since 2006, the possibility of acute pancreatitis associated with their use has been suggested in case reports [4, 5], which has resulted in subsequent labeling changes by the US FDA [6, 7]. Nevertheless, existing evidence regarding this potential safety signal has been shown to be inconsistent [2, 8–10]. In a broad range of preclinical animal studies, exposure to a DPP-4 inhibitor (sitagliptin) did not demonstrate a relationship between sitagliptin and the development of pancreatitis [2]. In contrast, another animal model has shown that incretin-based drugs may accelerate the formation of dysplastic lesions and pancreatitis [11]. In a pooled analysis of 12 double-blind randomized clinical trials of patients with type 2 diabetes mellitus treated with either sitagliptin or a comparator agent (placebo or other hypoglycemic agents), no difference in the incidence of pancreatitis between these two groups was reported [10]. Observational studies also reported inconsistent findings [8, 9, 12]. Using claims data, neither Dore et al. [8] nor Garg et al. [9] found an association between the use of sitagliptin and acute pancreatitis. Nevertheless, Singh et al. reported that sitagliptin was associated with hospitalization for acute pancreatitis [12]. Additional studies are therefore warranted as evidence surrounding the risk of pancreatitis among patients with type 2 diabetes is clinically relevant. Although the mechanism is not fully understood, patients with type 2 diabetes have been shown to have a higher incidence of pancreatitis than in the general population [13–17]. Moreover, although the incidence of severe pancreatitis is low, it carries a high mortality rate, at up to 50 % [18]. Specifically, as the risk of acute pancreatitis in Asian type 2 diabetes patients has been reported to be higher than in the Caucasian population [13–17], it is important to evaluate the association between the risk of acute pancreatitis and the use of DPP-4 inhibitors in the ethnic Chinese population. Therefore, using Taiwan's National Health Insurance (NHI) claims database, this large population-based nested case-control study was conducted to explore this potential association in patients with type 2 diabetes.

2 Methods

2.1 Data Source

The data source was the National Health Insurance Research Database (NHIRD). The NHIRD is a nationwide database containing claims records from Taiwan's mandatory NHI program. Taiwan's NHI program was launched in 1995 and covers over 99 % of the population in Taiwan (23.12 million in 2009). Beneficiaries' demographics and healthcare utilizations including outpatient visits, hospital admissions, and prescription medications are well recorded in the NHIRD [19], and it has been the data source for numerous population-based studies in the diabetic patient population published in peer-reviewed journals [17, 18, 20–24]. Our study used three subsets of the NHIRD, the Longitudinal Health Insurance Database (LHID) 2000, 2005, and 2010, as data sources, which contained all inpatient and outpatient medical claims for approximately 1 million individuals randomly sampled from the Registry for Beneficiaries of the NHIRD in 2000, 2005, and 2010, respectively. A total of 3 million individuals, which accounted for 15 % of the total population in Taiwan, thus served as our original cohort. Because the LHID was retrieved from the NHIRD, the distributions of age, sex, and average insured payroll-related amount do not differ between the LHID and the original NHIRD [25].

Because the identification numbers of all subjects in the NHIRD were encrypted to protect the privacy of the individuals, this study was exempted from full review by the Institution Review Board of the National Taiwan University Hospital, and informed consent was waived.

2.2 Study Population

We identified a type 2 diabetic patient cohort who had at least one outpatient or inpatient diagnosis of type 2 diabetes [*International Classification of Diseases, Ninth edition, Clinical Modification* (ICD-9-CM) [26] code of 250.xx] and who filled at least one prescription of oral antihyperglycemic agents between 1 January 2001 and 31 December 2011. The cohort entry date was defined as the prescribing date of the first claim of oral antihyperglycemic agents. To be eligible for the study cohort, patients needed to be $\geq$18 years old and had claims data for a continuous period of at least 12 months before the cohort entry date and 6 months after the cohort entry date. This allowed a 12-month period for history taking and at least 6 months of observations after initiation of the oral antihyperglycemic agents.

2.3 Cases and Controls

We defined cases as patients who were hospitalized for acute pancreatitis during the study period (ICD-9-CM codes: 577.0). The positive predictive value of identifying pancreatitis by diagnosis code has been reported to be 60–80 % [27]. The date of acute pancreatitis diagnosis was defined as the index date. Using incidence–density sampling, we selected four controls for each case in the

diabetic cohort matched by age (±1 year), sex, and the cohort entry year.

2.4 Exposure to Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

The primary exposure of interest was DPP-4 inhibitors. The DPP-4 inhibitors included in this study were sitagliptin, saxagliptin, and vildagliptin. For each DPP-4 inhibitor prescribed, the prescription records of the NHIRD include information on the starting date (the date the prescription was dispensed), dosage, quantity, and prescription duration.

Based on timing relative to events, users of DPP-4 inhibitors were categorized as *current* and *past* users. The *current* users were those who had received DPP-4 inhibitors within 30 days before the index date, while the *past* users were those who had received DPP-4 inhibitors more than 30 days before the index date. *Non-users* were those who had never used DPP-4 inhibitors before the index date. Pre-planned sensitivity analyses were conducted by varying the definition of *current users* of DPP-4 inhibitors as patients who had received DPP-4 inhibitors within 60 and 90 days before the index date.

2.5 Statistical Analysis

Multivariate conditional logistic regression models were used to estimate the association between the use of DPP-4 inhibitors and acute pancreatitis. The p value was two-sided, and α was set to 0.05. To better estimate the effect of DPP-4 inhibitors on the risk of acute pancreatitis, we adjusted for potential risk factors of acute pancreatitis in the statistical models. Using the outpatient and inpatient claims of the NHIRD, we identified the following co-morbidities based on data within 1 year prior to the index date: gallstone disease [ICD-9-CM codes: 560.31, 574.x], alcohol-related disease [291.x, 303.x, 305.0, 571.x (x = 03)], hypertriglyceridemia [272.1x], cystic fibrosis [277.0x], neoplasm [140.xx-209.xx], obesity [278.x (x = 0–1)], and tobacco use [305.1, 649.0, 989.84]. We also adjusted the Diabetes Complications Severity Index (DCSI) [28–30] to account for the potential impacts of the severity of diabetes on the risk of acute pancreatitis. Furthermore, we collected the exposure to drugs that might be potentially associated with acute pancreatitis within 1 year before the index date. Those drugs were furosemide, NSAIDs, corticosteroids, antibiotics, and cancer drugs.

Variables that were statistically significant in univariate analyses were included in the multivariate model for further adjustments. Associations are presented as adjusted odds ratios (aORs) with 95 % confidence intervals. All data in this study were analyzed using SAS® software, version 9.3 (SAS Institute, Cary, NC, USA).

3 Results

We identified 1,957 cases and 7,828 matched controls by age, sex, and cohort entry year. Overall, the distribution of age, sex, and cohort entry year in cases and controls were well-matched. Cases were more likely than control subjects to have co-morbid conditions and concomitant medications that might be associated with acute pancreatitis. A larger proportion of cases also had DCSI >0 (cases: 59.73 %, controls: 40.92 %) (Table 1). Table 2 shows that 322 cases (16.45 %) and 1,194 control subjects (15.25 %) were current users of DPP-4 inhibitors ($p = 0.19$). Among DPP-4 inhibitor users, most were prescribed sitagliptin. Compared with DPP-4 inhibitor non-users, neither current nor past users of DPP-4 inhibitors were associated with the risk of acute pancreatitis (current: aOR 1.04; 95 % CI [0.89–1.21], $p = 0.63$; past users: aOR 1.61 [0.93–2.77], $p = 0.09$). However, a higher risk of acute pancreatitis was found in patients with underlying gallstone disease (aOR 5.89 [4.71–7.35]), alcohol-related disease (aOR 5.36 [4.05–7.08]), hypertriglyceridemia (aOR 1.80 [1.26–2.56]), and pancreatic disease (aOR 17.29 [10.60–28.19]). A significantly higher risk of acute pancreatitis was found in patients with a DCSI score over 3 (DCSI 3–4: aOR 1.49 [1.21–1.84]; DCSI ≥5: aOR 1.32 [1.01–1.73]). Patients who were exposed to drugs that might potentially be associated with acute pancreatitis within 1 year before the index date had a higher risk of acute pancreatitis (NSAIDs: aOR 1.90 [1.60–2.26] and antibiotics: aOR 1.26 [1.10–1.44]) (Table 3).

We further performed a sensitivity analysis by varying the cutoffs for "current" and "past users" of DPP-4 inhibitors. Similar results were found; neither current nor past users of DPP-4 inhibitors were associated with the risk of acute pancreatitis (cutoff = 60 days, current users: aOR 1.04 [0.89–1.22], $p = 0.61$; past users: aOR 1.64 [0.93–2.89], $p = 0.09$, and cutoff = 90 days, current users: aOR 1.05 [0.90–1.22], $p = 0.57$; past users: aOR 1.58 [0.87–2.89], $p = 0.14$) (Table 4).

4 Discussion

As the first study to investigate the association between the use of DPP-4 inhibitors and the risk of acute pancreatitis using a nested matched case-control study design in a nationwide-based representative cohort of ethnic Chinese, we found that the risk of acute pancreatitis for patients with type 2 diabetes who ever used DPP-4 inhibitors was comparable with that of non-users. Nevertheless, the risk of acute pancreatitis was statistically higher in patients with severe diabetes as well as in patients with underlying gallstone disease, alcohol-related disease, hypertriglyceridemia, or pancreatic disease.

Table 1 Baseline characteristics of acute pancreatitis case and their matched controls

Characteristics	Cases (n = 1,957)	Controls (n = 7,828)	p value
Age [mean (SD)]	53.55 (14.85)	53.58 (14.88)	0.91
Age (years) [n (%)]			0.97
18–30	82 (4.19)	342 (4.37)	
31–50	814 (41.59)	3,244 (41.44)	
51–64	537 (27.44)	2,174 (27.77)	
≥65	524 (26.78)	2,068 (26.42)	
Female [n (%)]	652 (33.32)	2,608 (33.32)	1.00
Cohort entry year (by 2 years) [n (%)]			1.00
2001–2002	606 (30.97)	2,424 (30.97)	
2003–2004	489 (24.99)	1,956 (24.99)	
2005–2006	363 (18.55)	1,452 (18.55)	
2007–2008	315 (16.10)	1,260 (16.10)	
2009–2011	184 (9.40)	736 (9.40)	
Duration from hospitalization date of acute pancreatitis to date of first DM medication [day, mean(SD)]	1,144.2 (903.67)	1,148.5 (897.94)	0.72
Co-morbidity in the prior year [n (%)]			
Gallstone disease	314 (16.04)	171 (2.18)	<0.0001
Alcohol-related disease	273 (13.95)	122 (1.56)	<0.0001
Hypertriglyceridemia	755 (38.58)	1,132 (14.46)	<0.0001
Pancreatic disease	187 (9.56)	25 (0.32)	<0.0001
Cystic fibrosis	702 (35.87)	979 (12.51)	<0.0001
Neoplasm	163 (8.33)	326 (4.16)	<0.0001
Tobacco abuse	713 (36.43)	1,010 (12.90)	<0.0001
Obesity	18 (0.92)	95 (1.21)	0.28
DCSI [n (%)]			<0.0001
0	788 (40.27)	4,625 (59.08)	
1–2	393 (20.08)	1,791 (22.88)	
3–4	466 (23.81)	825 (10.54)	
≥5	310 (15.84)	587 (7.50)	
Concomitant medications in the prior year [n (%)]			
Furosemide	375 (19.16)	759 (9.70)	<0.0001
NSAIDs	1,743 (89.06)	5,829 (74.46)	<0.0001
Corticosteroids	669 (34.18)	1,983 (25.33)	<0.0001
Antibiotics	1,419 (72.51)	4,351 (55.58)	<0.0001
Cancer drugs	48 (2.45)	86 (1.10)	<0.0001

DCSI diabetes complications severity index, *DM* diabetes mellitus, *SD* standard deviation

Our negative findings in the association between users of DPP-4 inhibitors and the risk of acute pancreatitis are consistent with several existing observational studies. Using a large study population derived from a US commercial health insurance database, Dore et al. [8] reported that the risk of acute pancreatitis was comparable for initiators of sitagliptin relative to the comparison cohorts (relative risk 1.0, 95 % CI 0.5–2.0). Garg et al. [9] also found that the risk of sitagliptin was similar in sitagliptin users to that in a control group using a large claims database as the data source (hazard ratio 1.0, 95 % CI 0.7–1.3). Furthermore, by exploring nationwide Taiwanese data, we had access to a large diabetes patient cohort, which allowed us to identify a larger number of cases of acute pancreatitis than those in previous studies. Our study identified 1,957 cases of acute pancreatitis, whereas Dore et al. [8] identified 92 cases and Garg et al. [9] identified 154 cases. The large number of acute pancreatitis cases may provide a more precise estimate with the appropriate power to examine relative odds for exposure to DPP-4 inhibitors. In addition, although we adopted 30 days as the cutoff for current and past use of DPP-4 inhibitors, as reported by Singh et al. [12], we examined the potential impacts of different cutoffs on the association between the risk of

Table 2 Exposure to dipeptidyl peptidase-4 inhibitors among acute pancreatitis cases and their matched controls

Use pattern of DPP-4 inhibitors	Cases (n = 1,957) [n (%)]	Controls (n = 7,828) [n (%)]	p value
Current users	322 (16.45)	1,194 (15.25)	0.19
Sitagliptin	311 (15.89)	1,155 (14.75)	0.21
Saxagliptin	11 (0.56)	44 (0.56)	1.00
Vildagliptin	11 (0.56)	22 (0.28)	0.06
Past users	30 (1.53)	52 (0.66)	<0.001
Sitagliptin	30 (1.53)	52 (0.66)	<0.001
Saxagliptin	0	0	
Vildagliptin	0	0	
Any users	352 (17.99)	1,246 (15.92)	<0.05
Sitagliptin	341 (17.42)	1,208 (15.43)	<0.05
Saxagliptin	11 (0.56)	44 (0.56)	1.00
Vildagliptin	11 (0.56)	22 (0.28)	0.06

DPP-4 dipeptidyl peptidase-4

Table 3 Unadjusted and adjusted odds ratios for acute pancreatitis and exposure to dipeptidyl peptidase-4 inhibitors

	Unadjusted OR	95 % CI		p value	Adjusted OR	95 % CI		p value
Current users	1.11	0.97	1.27	0.14	1.04	0.89	1.21	0.63
Past users	2.44	1.54	3.89	<0.001	1.61	0.93	2.77	0.09
(Reference: non-users)								
Co-morbidities in the prior year								
Gallstone disease	8.56	7.01	10.47	<0.0001	5.89	4.71	7.35	<0.0001
Alcohol-related disease	11.49	9.04	14.62	<0.0001	5.36	4.05	7.08	<0.0001
Hypertriglyceridemia	3.90	3.47	4.38	<0.0001	1.80	1.26	2.56	<0.01
Pancreatic disease	35.15	22.39	55.19	<0.0001	17.29	10.60	28.19	<0.0001
Cystic fibrosis	4.15	3.68	4.68	<0.0001	0.51	0.21	1.23	0.13
Neoplasm	2.12	1.74	2.58	<0.0001	1.27	0.99	1.63	0.06
Tobacco abuse	4.08	3.62	4.60	<0.0001	1.80	0.80	4.05	0.15
Obesity	0.76	0.46	1.25	0.28	0.96	0.55	1.68	0.89
DCSI (Reference: 0)								
1–2	1.36	1.19	1.55	<0.0001	1.03	0.89	1.20	0.67
3–4	3.59	3.11	4.14	<0.0001	1.49	1.21	1.84	<0.001
≥5	3.56	3.01	4.21	<0.0001	1.32	1.01	1.73	<0.05
Concomitant medications in the prior year								
Furosemide	2.35	2.03	2.70	<0.0001	1.12	0.94	1.35	0.21
NSAIDs	2.83	2.43	3.29	<0.0001	1.90	1.60	2.26	<0.0001
Corticosteroids	1.54	1.38	1.71	<0.0001	1.00	0.88	1.14	1.00
Antibiotics	2.13	1.90	2.37	<0.0001	1.26	1.10	1.44	<0.001
Cancer drugs	2.27	1.59	3.24	<0.0001	1.22	0.78	1.92	0.39

DCSI Diabetes Complications Severity Index, *OR* odds ratio

acute pancreatitis and the use of DPP-4 inhibitors. As similar findings were found in the sensitivity analysis, we suggest that our estimates are robust.

In contrast, a matched case-control study using administrative claims data from the USA reported a twofold increased risk of acute pancreatitis (odds ratio 2.24, 95 % CI 1.36–3.68) associated with the use of incretin-based therapies (sitagliptin and exenatide) [12]. The inconsistent findings between our study and the study performed by Singh et al. [12] may be due to several factors. First, as mentioned previously, we identified more acute pancreatitis cases than Singh et al. (1,957 vs. 1,269), which may provide a more precise estimate with stronger statistical power. Second, our 1:4 matched case-control design may

Table 4 Sensitivity analyses: unadjusted and adjusted odds ratios for acute pancreatitis and exposure to dipeptidyl peptidase-4 inhibitors (different cutoff points of "*current users*" and "*past users*")

Exposure to DPP-4 inhibitors; different cutoff points (reference: non-users)	Cases (n = 1,957) [n (%)]	Controls (n = 7,828) [n (%)]	OR	95 % CI		p value	aOR	95 % CI		p value
30 days										
Current users	322 (16.45)	1,194 (15.25)	1.11	0.97	1.27	0.14	1.04	0.89	1.21	0.63
Past users	30 (1.53)	52 (0.66)	2.44	1.54	3.89	<0.001	1.61	0.93	2.77	0.09
60 days										
Current users	325 (16.61)	1,200 (15.33)	1.11	0.97	1.28	0.12	1.04	0.89	1.22	0.61
Past users	27 (1.38)	46 (0.59)	2.45	1.51	3.97	<0.001	1.64	0.93	2.89	0.09
90 days										
Current users	329 (16.81)	1,205 (15.39)	1.12	0.98	1.28	0.09	1.05	0.90	1.22	0.57
Past users	23 (1.18)	41 (0.52)	2.33	1.39	3.90	<0.01	1.58	0.87	2.89	0.14

aOR adjusted odds ratio, *DPP-4* dipeptidyl peptidase-4, *OR* odds ratio

have increased the statistical efficiency [31] when compared with the 1:1 matched case-control design adopted by Singh et al. [12]. Third, Singh et al. [12] used the DCSI as a matched variable, whereas we included the DCSI in the multivariate statistical model. In addition, whereas the findings from the study performed by Singh et al. [12] are not generalizable to patients older than 64 years, approximately one-quarter of our cases (26.78 %) and matched controls (26.42 %) were older than 65 years. These approaches thus enabled us to provide evidence of DPP-4 inhibitor use and the risk of acute pancreatitis that is more relevant to real-world situations. Another possible explanation is that our study cohort consisted of an ethnic Chinese population, which is different from the ethnicity of the study population recruited by Singh et al. [12].

As expected, we found that other risk factors, including the severity of diabetes, were associated with a higher risk of acute pancreatitis. Noel et al. reported a threefold higher risk of pancreatitis among patients with type 2 diabetes relative to those without diabetes, suggesting that pancreatitis may be due to underlying disease [15]. Our findings that the risk of acute pancreatitis increased with the DCSI score (DCSI 3–4: aOR 1.49 [1.21–1.84]; DCSI ≥5: aOR 1.32 [1.01–1.73]) further support the hypothesis. In addition, we found that gallstone disease, alcohol-related disease, hypertriglyceridemia, and pancreatic disease were all significantly associated with the risk of acute pancreatitis in the diabetic cohort. In addition, we have added the baseline characteristics of current, past, and non-users of DPP-4 inhibitors among cases and their matched controls in Appendix 1 (see Electronic Supplementary Material) to provide more information regarding the differences across study groups. Furthermore, Shen et al. reported that diabetic patients with acute pancreatitis had a 58 % higher risk of intensive care unit admission and a 30 % higher risk of local complications than non-diabetic patients with acute pancreatitis [17]. As diabetes may further adversely affect the disease process of acute pancreatitis, specific concern should be paid to patients with diabetes, particularly those who have underlying diseases associated with a high risk of acute pancreatitis.

As with all observational studies based on claims databases, our study has the following limitations. First, there were relatively few patients who received DPP-4 inhibitors in our study cohort. However, our study includes the largest number of DPP-4 inhibitor users in existing case-control studies. In addition, our study is the first to explore the risk of acute pancreatitis associated with DPP-4 inhibitor use in an ethnic Chinese diabetic cohort. Second, we were unable to include variables not routinely captured in claims databases, such as patients' family history or body mass index. In addition, using ICD-9-CM codes to retrieve patients' alcohol-related diseases, tobacco use, and obesity may underestimate the actual prevalence. However, we have adjusted for a broad variety of covariates associated with the risk of acute pancreatitis in our statistical models. Third, other incretin-based therapies, such as linagliptin and exenatide, were not available during the study period. These differences should be considered when comparing our findings with those of other studies. Furthermore, due to the relatively small number of patients receiving saxagliptin and vildagliptin, we were unable to compare the risk of acute pancreatitis between sitagliptin and other DPP-4 inhibitors. Further studies are needed to examine the risk associated with different DPP-4 inhibitors. The final limitation is that, as DPP-4 inhibitors and GLP-1 analogs have been reimbursed by Taiwan's NHI since 2009, our study period (end of study: 31 December 2011) may not be sufficient to identify long-term outcomes such as chronic pancreatitis or carcinoma of the pancreas.

5 Conclusions

This population-based study provides the first major report of the risk of acute pancreatitis among an ethnic Chinese population of DPP-4 inhibitor users. We found that underlying diseases and the severity of diabetes but not DPP-4 inhibitor use were associated with acute pancreatitis.

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Author contributions Dr. F.-Y. Hsiao and Ms. H.-C. Chou were responsible for the development of the study concept and design and for the preparation of the manuscript. Ms. H.-C. Chou contributed to the data acquisition and statistical analysis. All authors participated in the analysis and interpretation of the data and read and approved the manuscript for submission.

Conflict of interests Hsin-Chun Chou, Wen-Wen Chen, and Fei-Yuan Hsiao have no conflicts of interest that are directly relevant to the content of this study.

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