META-ANALYSIS

Incretin-based therapies and acute pancreatitis risk: a systematic review and meta-analysis of observational studies

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Abstract Concerns raised by several animal studies, case reports, and pharmacovigilance warnings over incretin-based therapy potentially exposing type two diabetes patients to an elevated risk of pancreatitis have cast a shadow on the overall safety of this class of drugs. This systematic review evaluates the data from observational studies that compared treatment with or without incretins and the risk of pancreatitis. We searched PubMed for publications with the key terms incretins or GLP-1 receptor agonists or DPP-4 inhibitors or sitagliptin or vildagliptin or saxagliptin or linagliptin or alogliptin or exenatide or liraglutide AND pancreatitis in the title or abstract. Studies were evaluated against the following criteria: design (either cohort or case–control); outcome definition (incidence of pancreatitis); exposure definition (new or current or past incretins users); and comparison between patients receiving incretins or not for type 2 diabetes. Two authors independently selected the studies and extracted the data. Six studies meeting the inclusion criteria were reviewed. No difference was found in the overall risk of pancreatitis between incretin users and non-users (odds ratio 1.08; 95 % CI [0.84–1.40]). A risk increase lower than 35 % cannot be excluded according to the power calculation. This systematic review and meta-analysis suggests that type 2 diabetes patients receiving incretin-based therapy are not exposed to an elevated risk of pancreatitis. Limitations of this analysis are the low prevalence of incretin users and the lack of a clear distinction by the studies between therapy with DPP-4 inhibitors or with GLP-1 receptor agonists.

Keywords Incretins · Pancreatitis · Observational studies · Meta-analysis · Type 2 diabetes

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Background

Incretin-based therapies, because of their low hypoglycemic risk and apparently acceptable tolerability profile [1–3], are gaining wider use in current clinical practice for treating type 2 diabetes. However, incongruent data from experimental studies on rodents [4–6], recent case reports in humans [7–9], and pharmacovigilance analyses [10, 11] have been interpreted as providing evidence for the hypothesis that exposure to incretins may be associated with an increased risk of acute pancreatitis (AP), arousing concern about the overall safety of this drug class. Interpretations of the pharmacovigilance data in particular, based on self-reported, uncontrolled cases, supported the hypothesis for an almost 25-fold excess risk of developing AP [11, 12].

The relationship between diabetes and AP is a complex one in which many entangled factors, the disease itself, comorbidities, and medications, come into play. There is consensus that the incidence of AP is higher in patients

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with type 2 diabetes, especially among those receiving oral antidiabetic agents [13–16], and that there are known risk factors for AP, such as gallstones and obesity. Further complicating the issue is that several drugs commonly used in the treatment of type 2 diabetes have been reported to increase the risk of AP [17–19].

Involved in this association are both the glucagon-like peptide-1 (GLP-1) receptor agonist group, including injectable drugs that mimic the action of native GLP-1, such as the GLP-1 analogs exenatide and liraglutide, and the dipeptidyl peptidase 4 (DPP-4) inhibitor group, comprising oral agents that delay the catabolism of native GLP-1 mainly by inhibiting the endogenous enzyme DPP-4 [20].

Currently available randomized controlled trials (RCTs) do not suggest any increase in the risk of pancreatitis during treatment with incretins [21–23], but real-world data derived from post-marketing and observational studies leave open the possibility of an increased risk. Because AP is a relatively rare event with many possible confounders and because the current use of incretins is low, large-scale, rigorous observational studies are needed to detect this untoward effect and to define the underlying factors in the real world. In lieu of such studies, here we employed a meta-analytic approach to examine the possible association between incretin exposure and AP by gleaning salient information on available incretins from observational studies. This was done with a view to help practitioners evaluate the benefits versus risk when considering incretin-based therapy.

Methods

Search strategy and inclusion criteria

We searched the PubMed electronic database (last accessed November 15, 2013) using the key terms ("Pancreatitis"[MeSH Terms] OR "pancreatitis"[All Fields]) AND (incretin OR sitagliptin OR vildagliptin OR saxagliptin OR alogliptin OR linagliptin OR exenatide OR liraglutide OR glucagon-like peptide-1 agonist OR DPP-4 inhibitors) to identify articles published in English in the past 10 years (01/01/2003–31/10/2013) and referring to incretins and pancreatitis. The bibliographies of the retrieved publications, including reviews and meta-analyses, were also checked.

Studies were screened for inclusion according to the following criteria:

- Study design: cohort or case–control studies.
- Outcome definition: incidence of and/or mortality and/or hospitalization due to pancreatitis.
- Exposure definition: new or current or past incretins users: sitagliptin OR exenatide OR vildagliptin OR saxagliptin OR alogliptin OR linagliptin OR liraglutide.

- Number of subjects, association measures, confidence intervals (CI): studies had to report the CI for the association measures at each exposure level.

Starting from the paper's title and abstract, two investigators independently evaluated the study against the inclusion criteria.

Data collection

The review was performed in accordance with guidelines on meta-analyses. To diminish reporting bias and errors in data collection, two independent reviewers abstracted the data with a standardized form; disagreements were resolved through discussion and consensus.

Quality assessment

Two reviewers independently assessed the quality of each study against the Newcastle-Ottawa Scale (NOS). The NOS consists of three parameters of quality: selection, comparability, and exposure (case-control studies) or outcome (cohort studies). The NOS assigns a maximum of four points for selection, two for comparability, and three for exposure/outcome, wherein a score of nine designates the highest quality. Any scoring discrepancies were addressed by a joint re-evaluation of the original article with a third reviewer. Five was the minimum NOS score for including a study in the analysis.

Statistical analysis

The estimates of relative risks (odds ratios for case–control studies and risk ratios or hazard ratios for cohort studies) were transformed to their natural logarithm before pooling. Variances of the adjusted estimates on the log-scale are derived from the 95 % confidence intervals (95 % CI) reported in the original articles as $((\log (95\text{ \% CI upper limit}) - \log (95\text{ \% CI lower limit}))/3.92)^2$.

The analysis was stratified by study design (case–control and cohort studies) using the Der Simonian and Laird random effect model, with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model. The I^2 statistic for heterogeneity was used. Although different summary measures have different interpretations, we pooled hazard ratios (HRs) and risk ratios (RRs) since they originate from time data based on the same study design.

Because pancreatitis is a rare event and because case–control studies are nested in cohorts, we assumed that the ORs would be unbiased estimates of the RRs; hence, we report an overall estimate resulting from pooling all studies.

To assess the statistical power of the meta-analysis, we computed the power values for the two-sided Z test of no
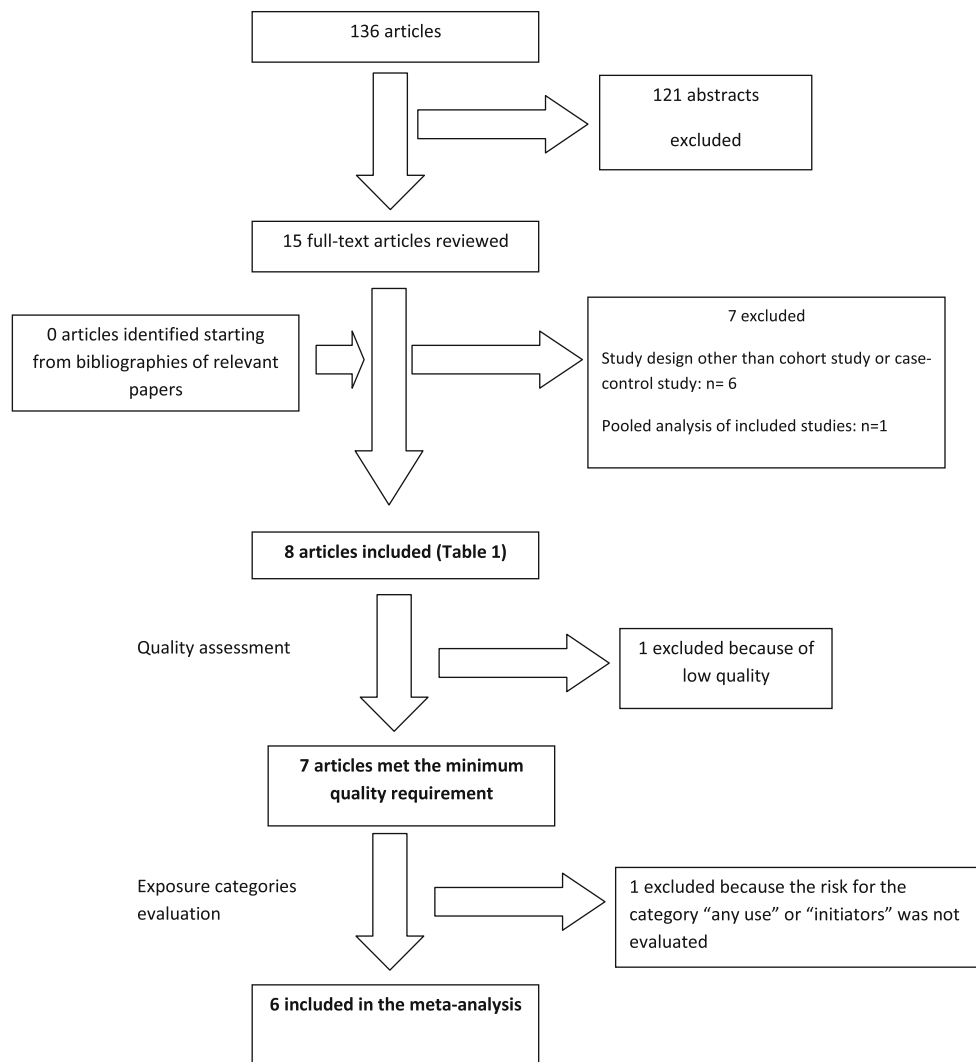
Fig. 1 Search flow, quality assesment, and exposure categories

population effect (pooled RR = 1) against several alternative hypotheses (RR ranging from 1 to 1.5) [24]. As an estimate of the variance of population effect, we considered the one coming from pooling all studies and the other only from cohort studies, both under fixed effect models.

Statistical analyses were performed using R version 3.0.2 (R Core Team (2013). (A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org).

Results

Search results

In all, 15 articles were fully reviewed from among the 136 papers retrieved. Figure 1 illustrates the search flow.

Among the papers excluded because they did not meet the criteria for study design, Dore et al. 2013 [25] was omitted because it is a pooled analysis of two studies already included in this meta-analysis (Dore et al. 2011 and Wenten et al. 2012) [26, 27]. Tables 1 and 2 report the characteristics of the eight studies included in the final evaluation. The quality of included studies was poor, with NOS ranging from 1 to 6. The study by Elashoff et al. [10] was excluded because it did not fulfill the quality conditions, and a second study by Dore published in 2011 [26] was also excluded because it did not report the risk for the exposure category "any use" or "initiators".

At the end of selection, after excluding the two papers mentioned above, six articles [27–32] met the inclusion criteria for quality assessment and for reporting the risk estimation for the exposure category "any use" or "initiators". Only one European study reported on exposure to all the available compounds [32], two studies analyzed

Table 1 Characteristics and quality assessment of the observational studies on incretins and incidence of pancreatitis risk

First author, year, country	Study design, years	Follow-up duration	Study population	Limitations	Newcastle-Ottawa score (0–9)
Dore DD, 2009, USA	Cohort study, June 2005–June 2008	≤12 months	88,536 patients (all ages) from US commercial health insurance transaction database (Ingenix Research Datamart). Excluded: patients with previous pancreatic diseases 6 months before drug initiation	Outcome and covariate variables from administrative claims database. Not adjusted for pancreatic risk factors, diabetes duration, obesity and alcohol consumption, and medication dose and adherence. Inadequate follow-up duration. Funded by Amylin Pharmaceuticals: conflict of interest	5
Garg R, 2010, USA	Cohort study, January 2007–December 2008	≤18 months	786,656 patients (age 18–63) from US commercial health insurance transaction database (Medco National Integrated Database). Excluded: patients with acute pancreatitis 6 months before drug initiation; patients treated with Exenatide in combination with Sitagliptin; patients treated with Repaglinide, Nateglinide, Acarbose, or Miglitol	Outcome and covariate variables from administrative claims database. Not adjusted for diabetes duration, medication dose, and adherence. Inadequate follow-up duration	5
Elashoff M, 2011, USA	Nested case–control, January 2004–December 2009		US FDA database 1102 cases and 1739 controls	Data from spontaneous reports. High risk of selected cohort	1
Dore DD, 2011, USA	Cohort study, June 2005–December 2007 and nested case–control study	≤34 months Average 1.1 years for entire cohort	Cohort of 316,334 patients (all ages) from US commercial health insurance claims database (Normative Health Information database). Excluded: patients with baseline claims associated with pancreatic diseases. Case–control: 294 confirmed cases of pancreatitis and 221 controls (appendectomy)	Outcome and covariate variables from administrative claims database. Not adjusted for diabetes duration, medication dose, and adherence. Inadequate follow-up duration. Risk not estimated for "any use" or "initiators" exposure categories	5
Romley JA, 2012, USA	Cohort study, January 2007–December 2009	≤36 months	Cohort of 268,531 diabetes type 2 patients (age ≥ 18) from US administrative database of private insurance agency (31 Fortune). Excluded: Sitagliptin users and patients with pancreatic cancer	Outcome and covariate variables from administrative claims database. Not adjusted for medication dose and adherence. Inadequate follow-up duration	6
Wenten M, 2012, USA.	Cohort study, June 2005–March 2008	≤32 months Average: 1.4 years for Exenatide and 1.3 years for other antidiabetic cohort	Cohort of 482,034 patients (age ≤ 65) from US administrative database IMS LIfeLink Program Health Plan Claims Database: 24,237 initiated Exenatide twice daily and 457,797 another antidiabetes medication. Excluded: patients with previous chronic pancreatitis	Outcome and covariate variables from administrative claims database. Inadequate follow-up duration	5

Table 1 continued

First author, year, country	Study design, years	Follow-up duration	Study population	Limitations	Newcastle-Ottawa score (0–9)
Singh S, 2013, USA	Population-based case–control study nested in a cohort of diabetes patients, February 2005–December 2008		Administrative database from Blue Cross Blue Shield Association plans. Cases: all diabetes patients (age 18–64) with pancreatitis after first exposure to an antihyperglycemic drug. Controls: all diabetes patients without pancreatitis after first exposure to an antihyperglycemic drug. Included: 1269 cases and 1269 controls (incidence density matching). Excluded: patients with pancreatitis before May 2005	Outcome and covariate variables from administrative claims database	6
Giorda CB, 2013, Italy	Case-control study nested in a population-based cohort, January 2008–December 2012		Cohort of 282,000 type 2 diabetes patients (age >41) from regional administrative data from Piedmont. Included: 1003 cases and 4012 controls Excluded: type 1 diabetes patients	Outcome and covariate variables from administrative claims database	5

exposure to exenatide, and three studies to either exenatide or sitagliptin.

Contrasting estimates from the case–control studies ($I^2 = 86$ %) resulted in a pooled OR = 1.41 (95 % CI 0.68–2.94). For the sensitivity analysis, we included the nested case–control reported in the 2011 paper by Dore et al. [26], but the result was basically unchanged (OR 1.42; 95 % CI 0.75–2.69), overall OR 1.09 (95 % CI 0.86–1.38).

In contrast, individual estimates from the cohort studies were largely homogeneous—as demonstrated by the random effect models which coincided with those of the fixed effect model—and were not suggestive of an increased risk (RR = 0.94, 95 % CI 0.76–1.17) (Fig. 2). As shown by the power functions (Fig. 3), this analysis lacked sufficient statistical power to rule out positive associations measured by RRs < 1.35. As expected, the global analysis suffers from moderate heterogeneity, yielding an intermediate weighted estimate of 1.08, which was not statistically significant irrespective of the model assumptions (fixed or random effect).

Discussion

This systematic review and meta-analysis of data from observational studies suggests no alarming increase in the risk of pancreatitis during treatment with incretins. This finding is shared by those of two meta-analyses of registration trials of the DPP-4 inhibitor [21, 33], which excluded a higher risk of AP in treated patients. But because the sample size and duration of the trials were limited, the number of observed cases of incident pancreatitis was small and the final confidence intervals were too wide.

Five out of the six retrieved observational studies failed to detect a significant association between incretin exposure and an elevated risk of AP. Interpreting observational studies on the effects of drugs is always problematic owing to the possible effect of bias and confounders. The lack of randomization makes observational effect estimates vulnerable to bias by indication, due to the different prognosis of individuals between treatment groups. Despite attempts to adjust analyses for potentially relevant covariates, some parameters are difficult to measure reliably in large patient populations. For example, defining obesity or excluding cases of pre-existing milder forms of chronic pancreatitis is complicated in large datasets. Nonetheless, observational studies have the advantage that they collect vast amounts of information in a routine clinical setting, whereas RCTs involve only a limited number of patients who are not necessarily representative of those receiving prescriptions in the real world.

Table 2 Outcomes of observational studies on incretins and incidence of pancreatitis risk

First author, year, country	Outcome assessment	Exposure assessment	Measure of association	Covariates
Dore DD, 2009, USA	Pancreatitis identified from health insurance claims data (primary inpatient diagnosis, outpatient diagnosis, and healthcare utilization) (ICD-9 code 577.0). Drug pair 1: Exenatide ($n = 37$), metformin or glyburide ($n = 36$); Drug pair 2: Sitagliptin ($n = 19$), metformin or glyburide ($n = 19$)	Initiators of Exenatide or Sitaglipide versus initiators of metformin or glyburide based on 6 months observation before initiation of study. Matched on exposure 1:1 by a propensity score. 27,996 exposed to Exenatide versus 27,983 to metformin or glyburide. 16,276 exposed to Sitagliptin versus 16,281 to metformin or glyburide	Drug pair 1 (Exenatide versus metformin or glyburide) RR 1.0 (95 % CI 0.6–1.7). Drug pair 2 (Sitagliptin versus metformin or glyburide) RR 1.0 (95 % CI 0.5–2.0)	Propensity score matching for age, sex, geographic region, hospital costs, pharmacy costs, total costs, total patient costs, diagnosis, drugs, physician visits, ER visits, hospital stay days, lab tests, procedures, total days of enrollment, days available for baseline period
Garg R, 2010, USA	Pancreatitis identified from claims data (ICD-9 code 577.0). Exenatide ($n = 22$), Sitagliptin ($n = 67$), other oral antihyperglycemic ($n = 65$)	Initiators of Exenatide or Sitagliptin versus initiators of sulfonylurea, metformin or thiazolidinedione versus non diabetic patients. 6545 exposed to Exenatide versus 15,826 to Sitagliptin versus 16,244 to other oral antihyperglycemic	Exenatide versus oral antidiabetic, HR adjusted for age/sex 1.0 (95 % CI 0.6–1.6); fully adjusted HR 0.9 (95 % CI 0.6–1.5). Sitagliptin versus oral antidiabetic, HR adjusted for age/sex 1.0 (95 % CI 0.7–1.4); fully adjusted HR 0.9 (95 % CI 0.7–1.3). [Diabetics versus non diabetics, HR adjusted for age/sex 2.9 (95 % CI 2.5–3.5); fully adjusted HR 2.1 (95 % CI 1.7–2.5)]	Diabetes, age, hypertriglyceridemia, pre-existing pancreatic disease, cholestatic liver disease, alcohol intake, biliary stone disease, chronic disease score
Elashoff M, 2011, USA	Pancreatitis cases reported as adverse event to FDA database. Exenatide ($n = 971$), Sitagliptin ($n = 131$), controls ($n = 43$). Controls: cases of back pain, chest pain, cough, syncope and urinary tract infection reported as adverse event to FDA database	Adverse events reported for Exenatide or Sitaglipide versus other antidiabetics. 2404 exposed to Exenatide versus 437 to Sitagliptin versus 721 to other oral antidiabetic	Exenatide OR 10.68 (95 % CI 7.75–15.1); Sitagliptin OR 6.74 (95 % CI 4.6–10.0)	Not adjusted
Dore DD, 2011, USA	Pancreatitis identified from medical records of emergency department or hospitalization claims data (ICD-9 code 577.0). Validation of cases of acute pancreatitis from clinical records. Exenatide ($n = 40$), other oral antihyperglycemic ($n = 254$)	Exenatide users classified as: current user (days supplied +31 days); recent user (current definition +31 days); and past user ($\geq$32 days beyond current definition) versus other antihyperglycemic. Matched on exposure 1:1 by propensity score. 25,719 exposed to Exenatide versus 23,4536 to other drugs	Cohort current Exenatide users versus other drugs, adjusted RR 0.5 (95 % CI 0.2–0.9); Recent Exenatide users versus other drugs, adjusted RR 1.1 (95 % CI 0.4–3.2); Past Exenatide users versus other drugs, adjusted RR 2.8 (95 % CI 1.6–4.7), case-control Past Exenatide users, unadjusted OR 1.8 (95 % CI 0.2–17.9) adjusted OR 1.6 (95 % CI 0.2–16.3)	Cohort propensity score matching for age, sex, geographic region, hospital costs, pharmacy costs, total costs, total patient costs, diagnosis, drugs, physician visits, ER visits, hospital stay days, lab tests, procedures, total days of enrollment, days available for the baseline period. case-control Overweight/obesity, alcohol use, smoking status, prior pancreatitis, cholelithiasis and cholecystectomy (multiple imputation technique for missing data)

Table 2 continued

First author, year, country	Outcome assessment	Exposure assessment	Measure of association	Covariates
Romley JA, 2012, USA	Pancreatitis identified from medical records of hospitalization claims data (ICD-9 code 577.0). Exenatide: 13,791 patient-years with pancreatitis. Hospitalization rate 0.249 % for pancreatitis in diabetics not using Exenatide versus 0.196 % for Exenatide users	Exenatide user if at least one Exenatide prescription filled within 1 year versus other oral antidiabetics	Exenatide users versus other drugs, adjusted RR 0.926 (95 % CI 0.630–1.361)	Hypertriglyceridemia, alcohol use, gallstones, tobacco use, obesity, biliary and pancreatic cancer, cystic fibrosis and general morbidity level identified on medical claims in current or previous year of drug initiation
Wenten M, 2012, USA	Pancreatitis identified from medical records of hospitalization claims data (ICD-9 code 577.0) in primary position of claim. 24,237 patients initiated Exenatide: 46 experimented the adverse event. 457,797 patients initiated other drugs: 51 experimented the adverse event	Exposure status defined as whether patient continued or discontinued Exenatide twice daily as of end of each observed follow-up interval (31 days) versus other antidiabetics. Patients exposed to Exenatide twice daily in previous intervals who discontinued were assigned to non-exposed category in the appropriate interval. Patients assigned to current (same 31 days interval), recent (60 days beyond current exposure) or past-use (>60 days) categories	Exenatide users versus other drugs, adjusted OR 0.95 (95 % CI 0.65–1.38). Current exposure—Exenatide users versus other drugs, adjusted OR, 0.93 (95 % CI 0.63–1.36); recent exposure—Exenatide users versus other drugs, adjusted OR 0.96 (95 % CI 0.50–1.84); past exposure-Exenatide users versus other drugs, adjusted OR 0.63 (95 % CI 0.40–0.99)	Propensity score matching for 600 independent variables: demographic characteristics, clinical history, procedures, medications
Singh S, 2013, USA	Patients with inpatient code for acute pancreatitis. Excluded pancreatitis occurrence <3 months before enrollment. Controls matched 1:1 for age (±10 years), sex, insurance plan site, diabetes complication severity, follow-up duration	Patients classified as any users (174 cases and 116 controls) (exposed to Sitagliptin or Exenatide after diagnosis of diabetes and before index date of pancreatitis) Current users (110 cases and 84 controls) (exposed to Sitagliptin or Exenatide within 30 days before index date of pancreatitis); recent users (144 cases and 96 controls) (claim submitted for Sitagliptin or Exenatide from 30 days to 2 years before index date of pancreatitis). Non-users (no Sitagliptin or Exenatide prescription more than 2 years before index date of pancreatitis)	Current users, adjusted OR 2.24 (95 % CI 3.36–3.69); recent users, adjusted OR 2.01 (95 % CI 1.37–3.18); any users, adjusted OR 2.07 (95 % CI 1.36–3.13)	Comorbidity history, duration of diabetes, risk factors for pancreatitis (hypertriglyceridemia, alcohol use, gallstones, tobacco use, obesity, biliary disease)

Table 2 continued

First author, year, country	Outcome assessment	Exposure assessment	Measure of association	Covariates
Giorda CB, 2013, Italy	Patients with inpatient code for acute pancreatitis (ICD-9 code 577.0) Controls matched 1:4 for year of birth, sex, year of first exposure to antidiabetic drug	Use of incretins 6 months before date of hospital admission for pancreatitis (identical for controls)	Adjusted OR 0.98 (95 % CI 0.69–1.38) at any time (within 6 mths before hospital admission) Adjusted OR 0.99 (95 % CI 0.72–1.35) for any use any time (sensitivity analysis)	Hospitalization up to 5 years before index date for chronic pancreatitis (or acute pancreatitis, excluding index episode), gallstones diagnosis, cholelithiasis or cholangiography or cholecystectomy, alcohol use, hypertriglyceridemia, obesity, biliary tract or pancreatic cancer

HR denotes hazard ratio, *OR* odds ratio, *RR* relative risk, *CI* confidence interval, *ICD-9* International Classification of Diseases, Ninth Revision

There are many reasons to remain cautious when making causal attributions between observations and interventions. Such data require circumspect interpretation. This holds particularly true for the management of information from self-reported, uncontrolled cases contained in pharmacovigilance databases, like the U.S. Food and Drug Administration (FDA) database and the very recent French one [10, 11], that may amplify public responses to risk or a risk event. The FDA Adverse Event Reporting System (FAERS, formerly AERS) has come under criticism for being based on self-reported, non-standardized adverse events, which has manifold implications for how FDA notifications and safety alerts are reported and interpreted. Consistent with the concept of a Weber effect (the so-called notoriety bias), a recent retrospective investigation applying a case/non-case method to the FDA FAERS database [34] found a significant disproportionality in the first quarter of 2008 (ROR, 1.24; 95 % CI 1.10–1.40) soon after an FDA alert was issued for exenatide and in the second quarter of 2008 (95 % CI 1.41, 1.05–1.90) for sitagliptin. The time-trend revealed a striking influence of FDA warnings on the reporting of pancreatitis, leading the authors to suspect that a pharmacovigilance alert signal had been automatically transformed into an alarm.

Two limitations of the studies included in our systematic review and meta-analysis were the low rate of incretin use (predominantly the GLP-1 receptor agonists exenatide and, to a lower extent, sitagliptin) and the relatively short study duration, which precluded ruling out less powerful associations and somehow reduced the overall accurateness of the investigation. A further weak point of our results, shared by all the observational studies on incretins, is that, owing to the low percentage of patients receiving incretin-based therapy, the two drug classes are not factored in. And because of the large differences in the mode of action of these two drug classes, future analyses need to be done separately for GLP-1 receptor agonists and DPP-4 inhibitors if the accuracy is to be improved [35, 36].

In detail, despite the inhibition of GLP-1 degradation by DPP-4 inhibitors, the pancreas might not be exposed to harmfully high GLP-1 concentrations when DPP-4 inhibitors are used. In such treatment, high concentrations of active GLP-1 in portal blood are substantially diluted before reaching the pancreatic arteries via the general circulation [35]. Furthermore, the pancreatic effects of other DPP-4 substrates (e.g., [GIP] gastric inhibitory peptide or [VIP] vasoactive, intestinal peptide) cannot be excluded because their concentrations and biological activities might also be increased by DPP-4 inhibition. By contrast, since GLP-1 receptor agonists significantly augment circulating concentrations of the incretin mimetic throughout the body, this could potentially exert a more aggressive action on pancreatic cells.

Fig. 2 Forest plot (*) The summary measures are expressed as *ORs* odd ratios for the case–control studies and as *RRs* risk ratios for the cohort studies, except for *HR* hazard ratios in Garg et al. and OR in Wenten et al

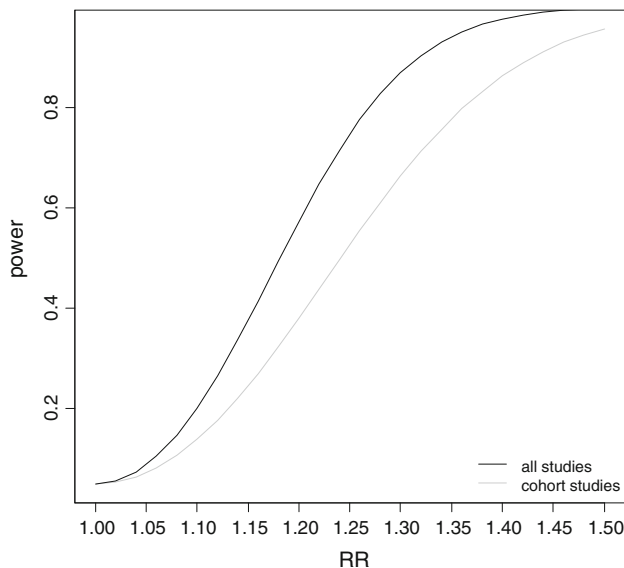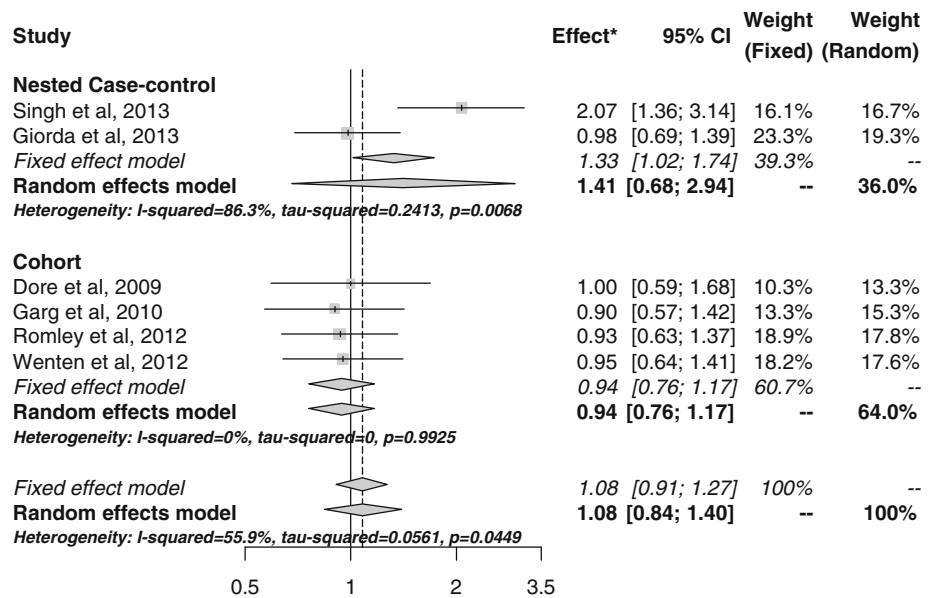| Study	Effect*	95% CI	Weight (Fixed)	Weight (Random)
Nested Case-control				
Singh et al, 2013	2.07	[1.36; 3.14]	16.1%	16.7%
Giorda et al, 2013	0.98	[0.69; 1.39]	23.3%	19.3%
Fixed effect model	*1.33*	*[1.02; 1.74]*	*39.3%*	--
Random effects model	**1.41**	**[0.68; 2.94]**	--	**36.0%**
Heterogeneity: I-squared=86.3%, tau-squared=0.2413, p=0.0068				
Cohort				
Dore et al, 2009	1.00	[0.59; 1.68]	10.3%	13.3%
Garg et al, 2010	0.90	[0.57; 1.42]	13.3%	15.3%
Romley et al, 2012	0.93	[0.63; 1.37]	18.9%	17.8%
Wenten et al, 2012	0.95	[0.64; 1.41]	18.2%	17.6%
Fixed effect model	*0.94*	*[0.76; 1.17]*	*60.7%*	--
Random effects model	**0.94**	**[0.76; 1.17]**	--	**64.0%**
Heterogeneity: I-squared=0%, tau-squared=0, p=0.9925				
Fixed effect model	*1.08*	*[0.91; 1.27]*	*100%*	--
Random effects model	**1.08**	**[0.84; 1.40]**	--	**100%**
Heterogeneity: I-squared=55.9%, tau-squared=0.0561, p=0.0449				

Fig. 3 Power functions of two-sided tests of no population effect (RR = 1) against the alternative hypotheses on the x *axis*

In conclusion, the major strength of this study is that the systematic review and meta-analysis of available studies is robust enough to reassure the practitioner that the claims for a 25-fold excess of risk are unfounded, even though a risk increase lower than 35 % cannot be completely excluded. The safety profile of type 2 diabetes drugs has come under increased scrutiny as the prevalence of diabetes continues to rise and ever more patients receive treatment for the condition. More research is needed, especially large cohort studies that could account for covariates in drug- and patient-related characteristics. A further area of focus is research into potential harmful effects on the exocrine pancreas beyond AP.

Finally, genetically predisposed persons may be at increased risk of developing AP, a condition similar to the recent demonstration that certain genotypes and epitopes predispose to autoimmune AP [37], which might explain the severe pancreatitis some case reports have described [7–9]. Likewise, our findings cannot rule out the silent destruction of pancreatic cells, as revealed by increased serum amylase and lipase levels [38]. This issue will need to be addressed with a prospective analysis of the outcome of patients found to have abnormal levels of pancreatic enzymes.

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