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Journal:	*BMJ*
Manuscript ID	BMJ.2015.029703
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	02-Oct-2015
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Keywords:	

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Manuscripts

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Incretin-based drugs and the risk of pancreatic cancer: An international multi-centre cohort study

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Word Count: 2945
Running head: Incretin-based drugs and pancreatic cancer

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October 2, 2015

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ABSTRACT

Objective: To determine whether the use of incretin-based drugs, when compared with the use of sulfonylureas, is associated with an increased risk of incident pancreatic cancer in patients with type 2 diabetes.

Design: Population-based cohort.

Setting: Large, international, multi-centre study combining the health records from six participating sites in Canada, the United States, and the United Kingdom.

Participants: A cohort of 972,384 patients initiating antidiabetic drugs between January 1, 2007 and June 30, 2013, with follow-up until June 30, 2014.

Main outcome measures: Within each cohort, we conducted nested case-control analyses, where incident cases of pancreatic cancer were matched with up to 20 controls on sex, age, cohort entry date, duration of treated diabetes, and follow-up duration. Hazard ratios (HRs) and 95% confidence intervals (CIs) for incident pancreatic cancer were estimated, comparing use of incretin-based drugs with use of sulfonylureas, which were lagged by one year for latency purposes. Secondary analyses assessed whether the risk varied by class (DPP-4 inhibitors and GLP-1 analogues) or by duration of use (cumulative duration of use and time since treatment initiation). Site-specific HRs were pooled using random-effects models.

Results: During 2,024,441 person-years of follow-up, 1221 patients were newly-diagnosed with pancreatic cancer (incidence rate: 0.60 per 1,000 person-years). Compared with sulfonylureas, incretin-based drugs were not associated with an increased risk of pancreatic cancer (pooled adjusted HR: 1.02, 95% CI: 0.84 to 1.23). Similarly, the risk did not vary by class and there was no evidence of a duration-response relationship.

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Conclusions: In this large, population-based study that followed patients for up to eight years, incretin-based drugs were not associated with an increased risk of pancreatic cancer compared with sulfonylureas.

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INTRODUCTION

Incretin-based drugs, which include dipeptidylpeptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) analogues, are a relatively new class of drugs used in the treatment of type 2 diabetes. While these drugs have been associated with a lower risk of hypoglycaemia and with favourable effects on body weight,[1] concern has arisen that their use may be associated with the development of pancreatic cancer.[2 3] This concern has been heightened by an analysis of the United States (US) Food and Drug Administration Adverse (FDA) Events database, where the spontaneous reporting rate of pancreatic cancer was 2.9 and 2.7 times higher with exenatide and sitagliptin, respectively, compared to other oral antidiabetic drugs.[4] In contrast, randomized controlled trials (RCTs) have not demonstrated this signal,[5-10] although most of these RCTs were of short duration and none were designed or powered to assess the risk of pancreatic cancer.

To date, four observational studies have assessed the association between incretin–based drugs and the risk of pancreatic cancer.[11-14] None of these was sufficiently powered to detect a modest increase in the risk of pancreatic cancer.[15] Consequently, regulatory agencies have called for additional studies of this potential association.[16] To this end, the Canadian Network for Observational Drug Effect Studies (CNODES)[17] designed a large, international, multi-centre study to determine whether the use of incretin-based drugs is associated with an increased risk of pancreatic cancer in patients with type 2 diabetes.

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METHODS

Data sources

This study used a common analytical protocol to conduct cohort studies using the administrative and electronic medical record databases from six participating sites across three countries – four Canadian provinces: Alberta, Manitoba, Ontario and Quebec; the United States [US]: MarketScan; the United Kingdom [UK]: Clinical Practice Research Datalink [CPRD]. The Canadian databases include patient-level information on physician billings, hospitalization data, and prescription drug claims, and the Ontario data were restricted to patients aged 65 years or older. The US MarketScan database includes medical information of individuals and their dependents insured by private health insurance plans. Finally, the UK CPRD contains the complete primary care medical records for more than 13 million individuals enrolled in more than 680 general practices, and has been shown to be representative of the UK population.[18]

The study protocol was approved by the institutional review boards at all participating sites, and by the Independent Scientific Advisory Committee (ISAC) of the CPRD (protocol number 14_119R). The ISAC protocol was made available to the journal reviewers. The study protocol is registered at www.clinicaltrials.gov (NCT02475499).

Study population

Base-cohort

In each participating site, a base-cohort was assembled consisting of all patients who commenced treatment with a first-ever prescription for a non-insulin antidiabetic drug (metformin, sulfonylureas, thiazolidinediones (TZDs), DPP-4 inhibitors, GLP-1

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analogues, alpha-glucosidase inhibitors, and meglitinides) from the earliest date of data availability in each participating site up to June 30, 2013 (or the latest date of data availability in each participating site). The date of each patient's first prescription defined base-cohort entry. We then sequentially excluded patients with the following characteristics at base-cohort entry: age less than 18 years (or the minimum age for which prescription data are available plus 365 days), less than 365 days of medical history in the database prior to base-cohort entry, previous insulin prescription (as this may indicate more advanced disease), and women with a history of polycystic ovarian syndrome or a diagnosis of gestational diabetes in the 365 days prior to base-cohort entry, as these conditions are other possible indications for metformin.

Study cohort

Within the base-cohort defined above, we identified a study cohort consisting of all patients who initiated a new antidiabetic drug class any time after incretin-based drugs entered the market in each participating site up until June 30, 2013 (or the latest date of data availability in each participating site). These new users included those who commenced treatment with an antidiabetic drug (i.e., first-ever prescription of a non-insulin antidiabetic drug), as well as those who added on or switched to an antidiabetic drug class not previously identified in their medication history. The date of this new prescription defined study cohort entry. We then sequentially excluded patients with any previous diagnosis of any cancer (other than non-melanoma skin cancer), those who had undergone pancreatectomy, and those with a history of congenital defects of the pancreas at any time prior to study cohort entry. Finally, we excluded patients with less than 365

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days of follow-up after study cohort entry to ensure a minimum exposure duration and to minimize protopathic bias from the inclusion of patients whose therapies might reflect type 2 diabetes secondary to pancreatic cancer.[19]

Thus, for all patients meeting the study inclusion criteria, the start of follow-up was set to 365 days after study cohort entry (i.e., the start of the person-time at risk), and they were followed until a diagnosis of incident pancreatic cancer (defined below), or censoring upon death from any cause, end of coverage in the database, or end of the study period (June 30, 2014, or the latest date of data availability in each participating site), whichever occurred first.

Case-control selection

We conducted nested-case control analyses within the study cohort in each participating site. This approach was chosen because of the time-varying nature of exposure, the size of the cohorts, and the relatively long duration of follow-up.[20] We used risk-set sampling for the matching of controls to cases, a method that produces odds ratios that are unbiased estimators of hazard ratios (HRs).[20-22]

Cases consisted of all patients with a hospital admission (lasting at least one day) for pancreatic cancer during follow-up (International Classification of Diseases version 9 [ICD-9] codes: 157.0-157.9; ICD-10 codes: C25.x, in either the primary or secondary position). This outcome definition has excellent positive and negative predictive values (88.2% and 99.9%, respectively; unpublished data) when compared to the Ontario Cancer Registry[23]. For each case, the index date was defined by the date of hospital admission.

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We randomly selected up to 20 controls for each case, matched on age (± 365 days), sex, date of study cohort entry (± 180 days), duration of treated diabetes prior to study cohort entry (defined as the time between base-cohort entry and study cohort entry ± 90 days), and duration of follow-up. Matched controls were assigned the index date of their respective cases.

Exposure assessment

Cases and matched controls were classified into one of three mutually-exclusive exposure groups, defined hierarchically by use of 1) incretin-based drugs (DPP-4 inhibitors [sitagliptin, vildagliptin, and saxagliptin] or GLP-1 analogues [exenatide, liraglutide]), 2) sulfonylureas, and 3) other antidiabetic drugs. The use of these antidiabetic drug classes was defined as receiving at least one prescription at any time before the year immediately preceding the index date (i.e., prescriptions received during a one-year lag period were ignored for latency purposes and to minimize reverse causality). The reference category for all analyses was use of sulfonylureas, a drug class sharing a similar indication as incretin-based drugs.[24]

Statistical analysis

We calculated the crude incidence rate of pancreatic cancer with 95% confidence intervals (CIs) based on the Poisson distribution. Conditional logistic regression was used to estimate HRs and corresponding 95% CIs of incident pancreatic cancer, comparing use of incretin-based drugs with use of sulfonylureas. This was considered the pre-specified primary analysis.

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All models were adjusted for potential confounders measured at study cohort entry, including haemoglobin A1c level (where available), alcohol-related disorders, body mass index (where available), smoking status (where available), history of acute or chronic pancreatitis, and use of statins at any time before study cohort entry. We also adjusted for the presence of microvascular complications of diabetes (neuropathy, renal disease, retinopathy, and peripheral arteriopathy; measured at any time before study cohort entry), and the number of unique antidiabetic drugs received in the 365 days before study cohort entry, both as proxies for diabetes severity. Finally, the models were adjusted for two general measures of comorbidity (total number of hospitalizations and total number of unique non-diabetic drugs prescribed, both measured in the 365 days before study cohort entry).[25]

Secondary analyses

We conducted four pre-specified secondary analyses. In the first, incretin-based drugs were stratified as DPP-4 inhibitors (linagliptin, saxagliptin, sitagliptin, vildagliptin) and GLP-1 analogues (exenatide, liraglutide). In the remaining three analyses, we tested for a duration-response relationship between use of incretin-based drugs and pancreatic cancer. In the first of these analyses, we assessed whether the risk of pancreatic cancer varied with cumulative duration of use. For this analysis, cumulative duration was calculated as the total duration of all prescriptions received from study cohort entry to the index date (classified as <1 year, 1-1.9 years, and ≥2 years). Similarly, we modelled the time since initiation of treatment, defined as the time between the first-ever prescription of an incretin-based drug and the index date (classified as 1-1.9 years and ≥2 years). Finally, we

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repeated the cumulative duration of use and time since initiation analyses for DPP-4 inhibitors and GLP-1 analogues, separately.

Sensitivity analyses

We conducted four sensitivity analyses to assess the robustness of our findings. First, to account for uncertainty in the length of the possible latency period, and to assess the impact of protopathic bias, we varied the lag period prior to the index date to 6 months and 2 years. Second, we replicated the primary analysis using a stricter exposure definition, requiring at least four prescriptions within any 12-month period between study cohort entry and the year immediately prior to index date. Third, we repeated the primary analysis comparing use of incretin-based drugs with use of sulfonylureas among those who initiated sulfonylureas on or after study cohort entry, since some sulfonylurea users may have initiated treatment prior to study cohort entry. Finally, we repeated the primary analysis with a reduced set of covariates to facilitate model convergence at all participating sites.

We used DerSimonian and Laird random-effects models[26] with inverse variance weighting to pool site-specific estimates. The estimates were also pooled using fixed-effects modelling in sensitivity analyses. Between-site heterogeneity was estimated using the I^2 statistic.

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RESULTS

The study cohort included a total of 972,384 patients initiating antidiabetic drugs (Figure 1). The mean age at study cohort entry was 56.9 years, and 50.9% were males. Additional baseline characteristics of the study cohort can be found in Supplementary Table 1. Overall, the study cohort generated a total of 2,024,441 person-years of follow-up. During this time, 1,221 patients were newly-diagnosed with pancreatic cancer, generating a crude incidence rate of 0.60 (95% CI: 0.57 to 0.64) per 1,000 person-years.

The baseline characteristics of the cases and 22,298 matched controls are shown in Table 1. Compared with controls, cases were less likely to be obese, but were more likely to have uncontrolled diabetes, alcohol-related disorders, to have ever smoked, and to have a history of acute or chronic pancreatitis. The cases and matched controls were otherwise similar on the other characteristics.

Overall, compared with users of sulfonylureas, users of incretin-based drugs were younger, had longer durations of treated diabetes, were more likely to be obese, and had higher haemoglobin A1c levels. In contrast, users of incretin-based drugs were less likely to have been diagnosed with microvascular complications of diabetes. Both exposure groups had similar histories of pancreatitis (Supplementary Table 2).

Table 2 presents the results of the primary and secondary analyses. Compared with use of sulfonylureas, use of incretin-based drugs was not associated with an increased risk of incident pancreatic cancer (pooled adjusted HR: 1.02, 95% CI: 0.84 to 1.23; Figure 2). Similarly, there was no association in the secondary analysis that categorized the use of incretin-based drugs by class (DPP-4 inhibitors, pooled adjusted HR: 1.02, 95% CI: 0.84 to 1.24; GLP-1 analogues, pooled adjusted HR: 1.13, 95% CI: 0.38 to 3.38). In other secondary

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analyses, a cumulative duration of less than one year yielded an elevated but non-significant HR (pooled adjusted HR: 1.53, 95% CI: 0.93 to 2.51), while longer durations of use generated HRs close to or below unity (1-1.9 years, pooled adjusted HR: 1.07, 95% CI: 0.82 to 1.39; ≥2 years, pooled adjusted HR: 0.62, 95% CI: 0.36 to 1.07). The time since initiation analysis yielded HRs close to the null (1-1.9 years, pooled adjusted HR: 1.06, 95% CI: 0.86 to 1.31; ≥2 years, pooled adjusted HR: 0.93, 95% CI: 0.60 to 1.45). Similar findings were observed with each class of incretin-based drug (Supplementary Figures 1-17).

Sensitivity analyses

The results of the sensitivity analyses are presented in Table 3. Overall, these analyses yielded findings that were consistent with those of the primary analysis (Supplementary Figures 18-23). The HR in the fixed-effects model was identical to that generated with the random-effects model for the primary analysis (pooled adjusted HR: 1.02, 95% CI: 0.80 to 1.23).

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DISCUSSION

To our knowledge, this is the largest population-based study to have investigated the association between the use of incretin-based drugs and the risk of pancreatic cancer. With a combined cohort of almost one million patients with type 2 diabetes, our findings suggest that use of incretin-based drugs is not associated with an increased risk of pancreatic cancer compared to use of sulfonylureas. These results remained consistent in several secondary and sensitivity analyses, which considered type of incretin-based drugs and duration of use.

Comparison with other studies

To our knowledge, only four observational studies have been conducted to assess the association between the use of incretin-based drugs and the incidence of pancreatic cancer.[11-14] Overall, none of these studies reported statistically significant associations.[11-14] However, these studies had some methodological shortcomings, including the potential inclusion of prevalent (rather than new) users,[12 13] lack of an appropriate comparator group,[12] small sample sizes,[11-14] and limited follow-up.[11-14] Moreover, three studies examined drugs from only one class of incretin-based drugs, the GLP-1 analogues exenatide[11 12] and liraglutide.[13]

Our null findings are also consistent with those of recent large RCTs of three DPP-4 inhibitors; saxagliptin, alogliptin, and sitagliptin.[8-10] However, these RCTs generated a total of only 39 pancreatic cancer events, and were thus not statistically powered to detect a moderate increased risk of this rare outcome.[8-10] Indeed, in the SAVOR-TIMI 53 trial, there were a total of 16 pancreatic cancer events (5 in the saxagliptin group versus 11 in the

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placebo group) after a median follow-up of 2.1 years.[8] In the EXAMINE trial, there were no pancreatic cancer events in either the alogliptin group or placebo group after a median follow-up of 18 months.[9] Finally, in the TECOS trial, there were a total of 23 pancreatic cancer events (9 in the sitagliptin group versus 14 in the placebo group) after a median follow-up of 3.0 years.[10]

Strengths and limitations of this study

Our study was specifically designed to circumvent the methodological limitations of the aforementioned observational studies[11-14] and RCTs.[8-10] First, the use of population-based cohorts from six participating sites across three countries strengthens the generalizability of our findings. Second, with an overall sample size of close to one million patients followed for up to eight years, the study was well powered to detect modest but clinically important associations. Third, all patients entering the base and study cohorts were new users of antidiabetic drugs, thus avoiding biases related to the inclusion of prevalent users.[27] Fourth, confounding by indication was minimized through matching, statistical adjustment, and by comparing users of incretin-based drugs to users of sulfonylureas, a drug class sharing similar indications.[24] Finally, latency and protopathic bias were addressed by excluding all exposures initiated in the year prior to the index date, with generally consistent findings in sensitivity analyses in which the duration of the lag period was varied.

Our study has some limitations. Given the observational nature of the study, residual confounding by disease severity remains possible. We addressed this by matching cases and controls on duration of treated diabetes, a proxy for disease severity,[28] as well as

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adjusting the models for the presence of microvascular complications of type 2 diabetes and number of antidiabetic drugs received before study cohort entry. It was not possible to adjust for certain pancreatic cancer risk factors such as physical activity, occupational exposures, diet, and family history. However, as achieving glycaemic control is the main motivation for prescribing incretin-based drugs or sulfonylureas, we do believe these unmeasured variables are differentially distributed across the exposure groups. In the secondary analysis of cumulative duration of use, we observed an elevated HR for <1 year (pooled adjusted HR: 1.53, 95% CI: 0.93 to 2.51). This association is of questionable plausibility given the limited duration of exposure, and may point to some residual protopathic bias. Specifically, it is possible that some patients were prescribed incretin-based drugs because of worsening glycaemic control due to early signs of pancreatic cancer, but were switched to step-up therapy (such as insulin) after failing to achieve glycaemic control in the first months of use. Finally, incretin-based drugs are relatively new therapies, limiting the potential duration of follow-up. It is important to note, however, that the previous signal was based on spontaneous reports that occurred relatively soon after the availability of incretin-based drugs.[4] Thus, our null findings are important and argue against a tumour promoter effect. Nonetheless, given the latency of pancreatic cancer, this association will need to be re-assessed once these drugs have been on the market for a longer period of time.

Conclusions and implications

In summary, in this large, population-based study, we found that the use of incretin-based drugs is not associated with an overall increased risk of pancreatic cancer when

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compared with the use of sulfonylureas in patients followed for up to eight years. These findings remained consistent by class and by duration of use. Based on the upper limit of the CI, our study had sufficient statistical power to exclude a 24% increased risk of pancreatic cancer and should thus provide considerable reassurance to patients and clinicians with concerns of an association between these drugs and pancreatic cancer.

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What is already known on this subject

- The safety of incretin-based drugs is controversial, with some studies reporting an association with pancreatic cancer incidence
- Additional observational studies are needed to assess whether these drugs are associated with this outcome

What this study adds

- In the largest study conducted to date, the use incretin-based drugs was not associated with an increased risk of pancreatic cancer, when compared with sulfonylureas
- The risk did not vary by duration of use or by type
- These null findings remained consistent in several sensitivity analyses, and should provide reassurance to patients treated with incretin-based drugs

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ACKNOWLEDGEMENTS

We are grateful for the programming support of Zhihai Ma, MSc and Jianguo Zhang, MSc (Alberta), Gregory A. Carney BSc (US MarketScan), Hui Yin MSc (UK CPRD), Caixia Fangyun Wu MSc MA and Simon Hollands MSc (Ontario), and Menglan Pang MSc (Quebec). We also thank Corine Mizrahi, Melissa Dahan, and Laura Sang MPH at the Coordinating Center. In addition, we acknowledge Héloïse Cardinal MD PhD for her contribution to the development of the study design. We would like to acknowledge the important contributions of the CNODES collaborators and assistants at each site.

This study was made possible through data sharing agreements between CNODES member research centres and the respective provincial governments of Alberta, Manitoba (HIPC #: 2014/2015 – 08; HREB #: H2014:236), Ontario, and Quebec. The opinions, results, and conclusions reported in this paper are those of the authors. No endorsement by the provinces is intended or should be inferred.

Dr Filion holds a Canadian Institutes of Health Research New Investigator Award. Dr Platt is supported by a *Chercheur-National* Award of the *Fonds de Recherche du Quebec - Santé* (FRQS; Quebec Foundation for Health Research). Dr Durand is supported by a Clinical investigator award of the FRQS. Dr Juurlink is supported by the Eaton Scholar program, Department of Medicine, University of Toronto

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COMPETING INTEREST STATEMENT

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: Dr Targownik is on the Speaker's Panel for Janssen Canada, Takeda Canada, Pfizer Canada, and Shire Canada, has received grant support from Pfizer Canada and Abbvie Canada, and is on advisory boards for Takeda Canada, Abbvie Canada, and Janssen Canada. Dr. Platt received consulting fees for work unrelated to this project from Pfizer, Amgen, Abbvie, and Novartis. All other authors have no conflicts to disclose.

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Study concept and design: LA, KBF, RWP, MD, CRD, KKC, MD, DNJ, LET, TCT, JMP, and PE.

Acquisition of data: LA, KBF, CRD, MD, LT, TCT, JMP, and PE.

Analysis and interpretation of data: LA, KBF, RWP, MD, CRD, KKC, MD, DNJ, LT, TCT, JMP, and PE.

Drafting of the manuscript: LA.

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Critical revision of the manuscript for important intellectual content: LA, KBF, RWP, MD, CRD, KKC, MD, DNJ, LET, TCT, JMP, and PE.

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Obtained funding: Canadian Network for Observational Drug Effect Studies Investigators.

Study supervision: LA, KBF, RWP, PE.

LA is the guarantor.

DETAILS OF ETHICAL APPROVAL

The study protocol was approved by the institutional review boards at all participating sites, and by the Independent Scientific Advisory Committee (ISAC) of the CPRD (protocol number 14_119R).

DETAILS OF FUNDING

Canadian Network for Observational Drug Effect Studies, a collaborating centre of the Drug Safety and Effectiveness Network, is funded by the Canadian Institutes of Health Research (Grant Number DSE-111845). The sponsor had no influence on design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. This study was made possible through data sharing agreements between CNODES member research centres and the respective provincial governments of Alberta, Manitoba, Ontario, and Quebec. The opinions, results, and conclusions reported in this paper are those of the authors. No endorsement by the provinces is intended or should be inferred.

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DATA SHARING: No additional data available.

TRANSPARENCY DECLARATION

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

*The manuscript's guarantor.

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FIGURE LEGENDS

Figure 1 Study flow diagram describing the construction of the base and study cohorts.

Figure 2 Forest plot of the association between the use of incretin-based drugs and the risk of pancreatic cancer among patients with type 2 diabetes. The reference category was use of sulfonylureas. The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.

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Figure 1

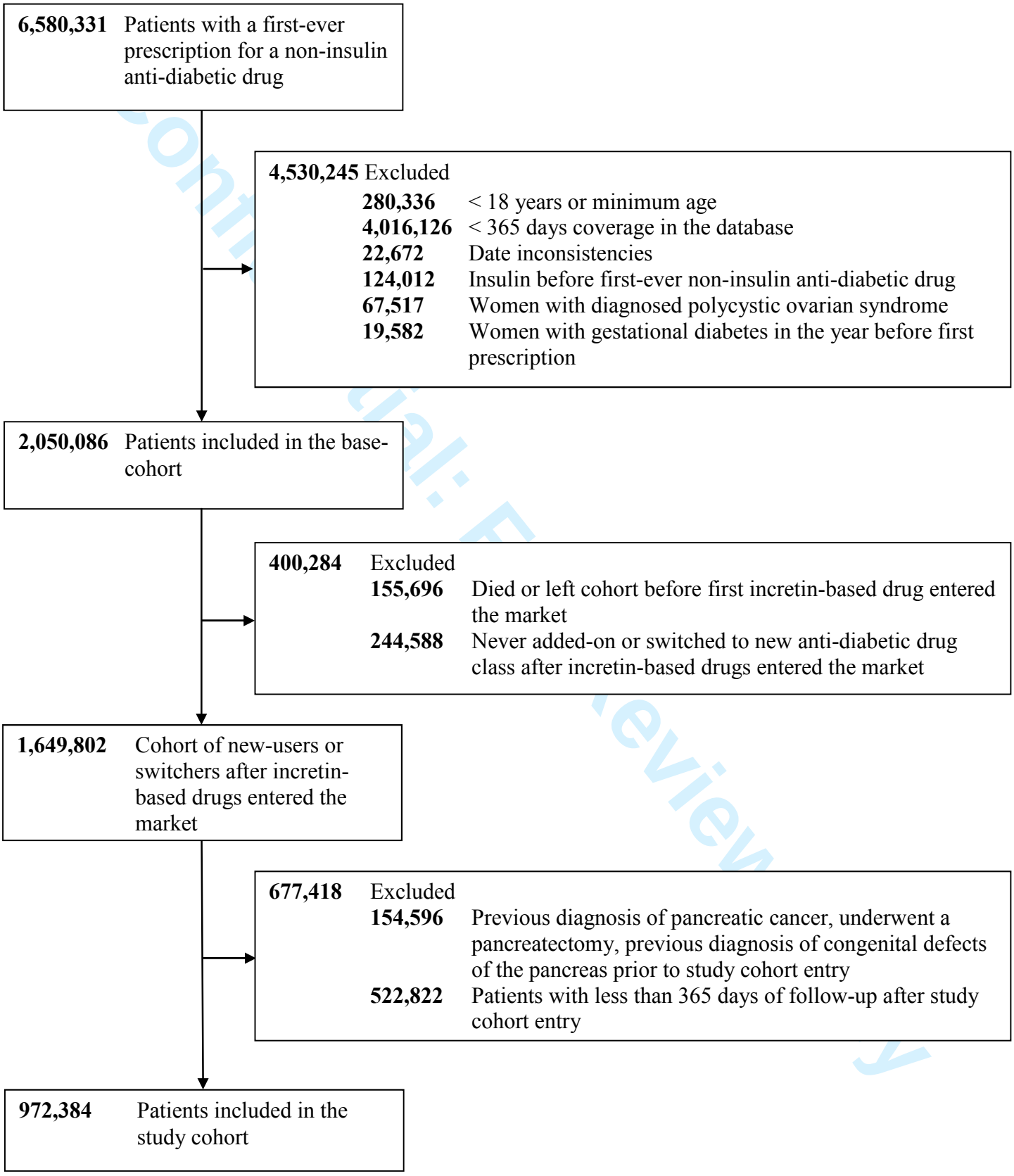
6,580,331 Patients with a first-ever prescription for a non-insulin anti-diabetic drug
4,530,245 Excluded
280,336 < 18 years or minimum age
4,016,126 < 365 days coverage in the database
22,672 Date inconsistencies
124,012 Insulin before first-ever non-insulin anti-diabetic drug
67,517 Women with diagnosed polycystic ovarian syndrome
19,582 Women with gestational diabetes in the year before first prescription
2,050,086 Patients included in the base-cohort
400,284 Excluded
155,696 Died or left cohort before first incretin-based drug entered the market
244,588 Never added-on or switched to new anti-diabetic drug class after incretin-based drugs entered the market
1,649,802 Cohort of new-users or switchers after incretin-based drugs entered the market
677,418 Excluded
154,596 Previous diagnosis of pancreatic cancer, underwent a pancreatectomy, previous diagnosis of congenital defects of the pancreas prior to study cohort entry
522,822 Patients with less than 365 days of follow-up after study cohort entry
972,384 Patients included in the study cohort

Figure 2

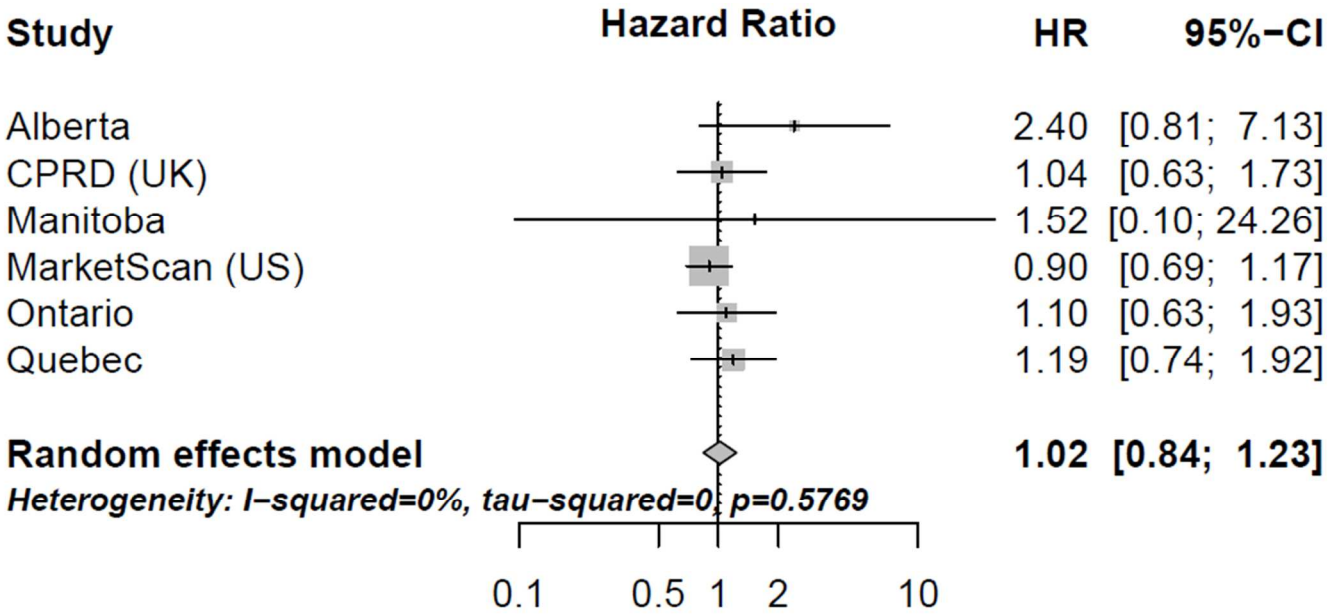

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Table 1. Characteristics of pancreatic cancer cases and matched controls among patients with type 2 diabetes*

Baseline characteristics	Cases	Controls †
Number of patients	1,221	22,298
CNODES Site, No. (%)		
US MarketScan	568 (46.5)	11,349 (50.9)
Quebec	251 (20.6)	4,135 (18.5)
UK Clinical Practice Research Datalink	209 (17.1)	3,473 (15.6)
Ontario	95 (7.8)	1,725 (7.7)
Alberta	59 (4.8)	1,180 (5.3)
Manitoba	39 (3.2)	436 (2.0)
Age (years), mean ‡	68.2	68.1
18-25, n (%)	S*	9 (0.0)
26-35, n (%)	S*	31 (0.1)
36-45, n (%)	18 (1.5)	344 (1.5)
46-55, n (%)	147 (12)	2,904 (12.5)
56-65, n (%)	315 (25.8)	5,730 (25.5)
66-75, n (%)	418 (34.2)	7,769 (34.6)
≥76, n (%)	320 (26.2)	5,511 (25.8)
Male, n (%) ‡	671 (55.0)	12,379 (55.0)
Calendar year of study cohort entry, No. (%) ‡		
2007	204 (16.7)	3,827 (16.5)
2008	200 (16.4)	3,613 (16.9)
2009	280 (22.9)	5,134 (22.8)
2010	260 (21.3)	4,703 (21.0)
2011	194 (15.9)	3,784 (17.0)
2012	S*	1,227 (5.9)
2013	S*	12 (0.1)
Duration of treated diabetes (years), mean ‡	1.5	1.5
Body mass index, No. (%) §		
<25 kg/m^2	32 (15.3)	394 (12.0)
25-29 kg/m^2	73 (34.9)	1,186 (35.5)
≥30 kg/m^2	96 (45.9)	1,830 (50.9)
Missing	8 (3.8)	63 (1.5)
Haemoglobin A1c, No. (%) §		
≤7 % [53 mmol/mol]	24 (11.5)	504 (14.4)
7.1-8.0 % [54-64 mmol/mol]	54 (25.8)	1,044 (29.3)
>8 [64 mmol/mol]	104 (49.8)	1,353 (42.5)
Missing	27 (12.9)	572 (13.8)

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Baseline characteristics	Cases	Controls †
Alcohol-related disorders, No. (%)	37 (3.0)	541 (2.6)
Smoking status, No. (%) §		
Ever	134 (64.1)	2,108 (40.1)
Never	S*	1,350 (59.5)
Missing	S*	15 (0.4)
Statins, No. (%)	764 (62.6)	13,761 (63.6)
Acute or chronic pancreatitis, No. (%)	43 (3.5)	224 (1.2)
Neuropathy, No. (%)	36 (2.9)	488 (2.9)
Renal disease, No. (%)	120 (9.8)	1,885 (10.1)
Retinopathy, No. (%)	140 (11.5)	2,486 (12.6)
Peripheral arteriopathy, No. (%)	87 (7.1)	1,310 (6.0)
Number of hospitalizations, mean	0.2	0.2
0, No. (%)	1,023 (83.8)	19,365 (86.2)
1, No. (%)	151 (12.4)	2,317 (10.7)
2, No. (%)	33 (2.7)	463 (2.2)
3, No. (%)	12 (1.0)	94 (0.5)
≥4, No. (%)	7 (0.6)	58 (0.4)
Number of unique non-antidiabetic drugs, mean	8.8	8.3
0, No. (%)	72 (5.9)	1,802 (7.4)
1, No. (%)	52 (4.3)	979 (4.1)
2, No. (%)	61 (5.0)	1,177 (5.1)
3, No. (%)	61 (5.0)	1,374 (5.9)
≥4, No. (%)	976 (79.9)	19,966 (77.4)
Pre-study cohort entry antidiabetic drugs, mean	0.3	0.3
0, No. (%)	994 (81.4)	19,829 (81.5)
1, No. (%)	117(9.6)	1,470 (10.7)
2, No. (%)	66 (5.4)	615 (4.5)
3, No. (%)	34 (2.8)	252 (2.2)
≥4, No. (%)	8 (0.7)	132 (1.1)
Study cohort entry drugs, No. (%) £		
Metformin	853 (69.9)	16,824 (70.5)
Sulfonylureas	278(22.8)	4,024 (20.0)
Thiazolidinediones	72 (5.9)	1,235 (6.0)
DPP-4 inhibitors	85 (7.0)	1,521 (7.3)
GLP-1 analogues	6 (0.5)	125 (1.4)
Alpha-glucosidase inhibitors	S*	59 (0.4)
Meglitinides	17 (1.4)	188 (1.2)
Insulins	43 (3.5)	223 (2.1)
Others	S*	43 (0.2)

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Abbreviations: CNODES, Canadian Network for Observational Drug Effect Studies; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; PC, pancreatic cancer; UK, United Kingdom; US, United States.

* When the total across participating sites was less than 6, data were suppressed (denoted by an S) due to privacy restrictions. When summing data across sites, we assigned a value of 3 to small cells (≤5). As such, the sum of count data may differ from the presented total.

† The means and proportions among controls were weighted by the number of controls per case and then weighted by the number of cases per site.

‡ Matching variable.

§ Data from the UK Clinical Practice Research Datalink; percentages based on 209 cases and 3,473 matched controls.

£ Non-mutually exclusive categories.

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Table 2. The association between use of incretin-based drugs and the incidence of pancreatic cancer*

Exposure†	Cases (n=1,221)	Controls (n=22,298)	Adjusted HR (95% CI) ‡	I^2 (%)
Primary analysis				
Sulfonylureas, No. (%)	439 (36.0)	5,851 (26.2)	1.00 [Reference]	0
Incretin-based drugs, No. (%)	200 (16.4)	2,800 (12.6)	1.02 (0.84 to 1.23)	
Class of incretin-based drug, No. (%)				
DPP-4 inhibitors	183 (15.0)	2,543 (11.4)	1.02 (0.84 to 1.24)	0
GLP-1 analogues §	17 (1.4)	257 (1.2)	1.13 (0.38 to 3.38)	72.0
Cumulative duration of use, No. (%)				
< 1 year	80 (6.6)	1,012 (4.5)	1.53 (0.93 to 2.51)	61.5
1-1.9 years	86 (7.0)	1,183 (5.3)	1.07 (0.82 to 1.39)	0
≥2 years	34 (2.8)	605 (2.7)	0.62 (0.36 to 1.07)	34.9
Time since initiation, No. (%)				
1-1.9 years	149 (12.2)	2,126 (9.5)	1.06 (0.86 to 1.31)	0
≥2 years	51 (4.2)	674 (3.0)	0.93 (0.60 to 1.45)	27.3

Abbreviations: HR, hazard ratio; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.
* Cases and controls were matched on the sex, age, year of cohort entry, duration of treated diabetes, and duration of follow-up.
† Users of other antidiabetic drugs (corresponding to 582 cases and 13,647 controls) are not displayed in the table, but were considered in the regression model for proper estimation of treatment effects.
‡ Adjusted for alcohol-related disorders, history of acute or chronic pancreatitis, microvascular complications of diabetes (neuropathy, renal disease, retinopathy, and peripheral arteriopathy), number of hospitalizations (0,1,2,3,4+), number of unique non-diabetic drugs in the prior year (0,1,2,3,4+), number of antidiabetic drugs received prior to study cohort entry (0,1,2,3,4+), ever-use of statins. In the CPRD, the models were further adjusted for body mass index, smoking status, and glycated haemoglobin A1c level (≤7.0% [53 mmol/mol], 7.1-8.0% [54-64 mmol/mol], >8.0% [64 mmol/mol]).
§ This analysis was limited to the United Kingdom Clinical Practice Research Datalink and the United States MarketScan, the two sites where GLP-1 analogues were available during the study period.

Table 3. Sensitivity analyses for the association between the use of incretin-based drugs and the incidence of pancreatic cancer

Sensitivity Analyses	Adjusted HR (95% CI)	I^2 (%)
6-month lag period *ǂ	1.14 (0.95 to 1.35)	0
2-year lag period *ǂ	1.07 (0.60 to 1.89)	54.2
Stricter exposure definition †*	0.87 (0.69 to 1.10)	0
Sulfonylurea initiation after study cohort entry as reference category *	1.14 (0.86 to 1.51)	22.8
Reduced model 1 §	1.03 (0.85 to 1.25)	0
Reduced model 2 £	1.03 (0.86 to 1.25)	0

Abbreviations: HR, hazard ratio; CI, confidence interval.
* Adjusted for alcohol-related disorders, history of acute or chronic pancreatitis, microvascular complications of diabetes (neuropathy, renal disease, retinopathy, and peripheral arteriopathy), number of hospitalizations (0,1,2,3,4+), number of unique non-diabetic drugs in the prior year (0,1,2,3,4+), number of antidiabetic drugs received prior to study cohort entry (0,1,2,3,4+), ever-use of statins. In the CPRD, we further adjusted for body mass index, smoking status, and glycated haemoglobin A1c level (≤7.0% [53 mmol/mol], 7.1-8.0% [54-64 mmol/mol], >8.0% [64 mmol/mol]).
† Defined as receiving at least 4 prescriptions within any 12-month period.
§ Adjusted for alcohol-related disorders, history of acute or chronic pancreatitis, a composite variable of microvascular complications of diabetes, number of hospitalizations (continuous), number of unique non-diabetic drugs in the prior year (continuous), number of antidiabetic drugs received prior to study cohort entry (continuous), ever-use of statins. In the CPRD, we further adjusted for body mass index, smoking status, and glycated haemoglobin A1c level (≤7.0% [53 mmol/mol], 7.1-8.0% [54-64 mmol/mol], >8.0% [64 mmol/mol]).
£ Adjusted for the Deyo version of the Charlson comorbidity index and history of acute or chronic pancreatitis.

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SUPPLEMENTARY MATERIAL

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Supplemental Figure 2. Forest plot for the secondary analysis comparing use of GLP-1 analogues with use of sulfonylureas on the incidence of pancreatic cancer 4

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Supplemental Figure 15. Forest plot for the secondary analysis assessing the association between cumulative durations of GLP-1 analogue use of ≥2 years and pancreatic cancer* 17

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Supplementary Table 1. The baseline characteristics of patients included in study cohort* 26

Supplementary Table 2. The baseline characteristics of users of incretin-based drugs and sulfonylureas among controls* 28

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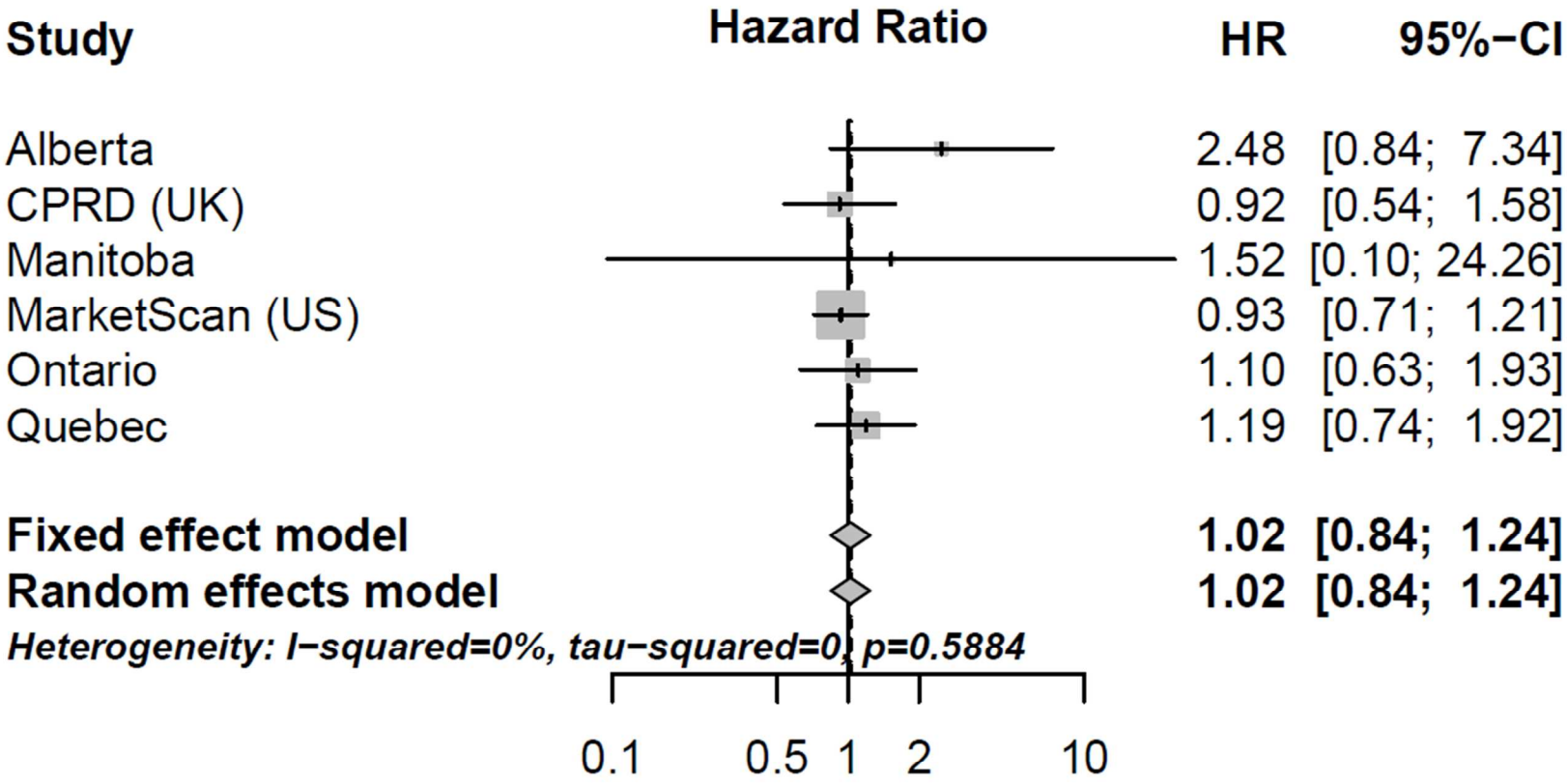
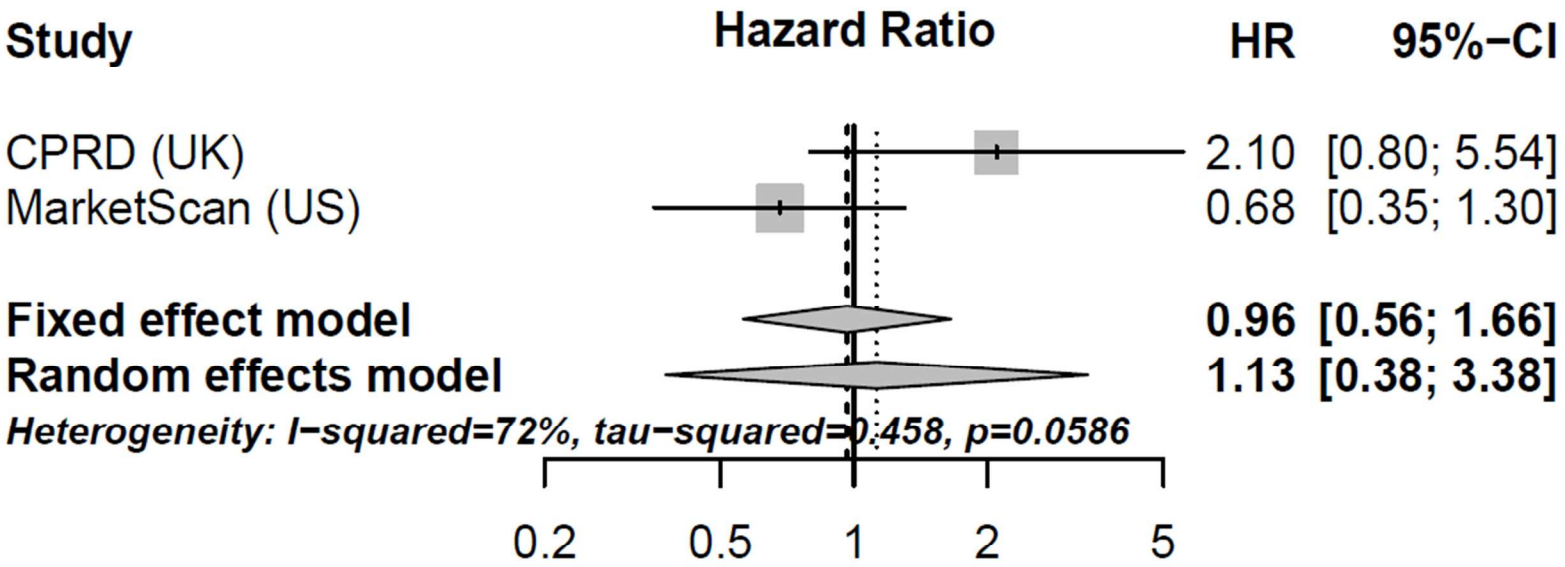
Supplemental Figure 1. Forest plot for the secondary analysis comparing use of DPP-4 inhibitors with use of sulfonylureas on the incidence of pancreatic cancer



Abbreviations: DPP-4, dipeptidyl peptidase-4; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States. The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.

Supplemental Figure 2. Forest plot for the secondary analysis comparing use of GLP-1 analogues with use of sulfonylureas on the incidence of pancreatic cancer



Abbreviations: GLP-1, glucagon-like peptide-1; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.
The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.
Note: This analysis was limited to the United Kingdom Clinical Practice Research Datalink and the United States MarketScan, the two sites where GLP-1 analogues were available during the study period.

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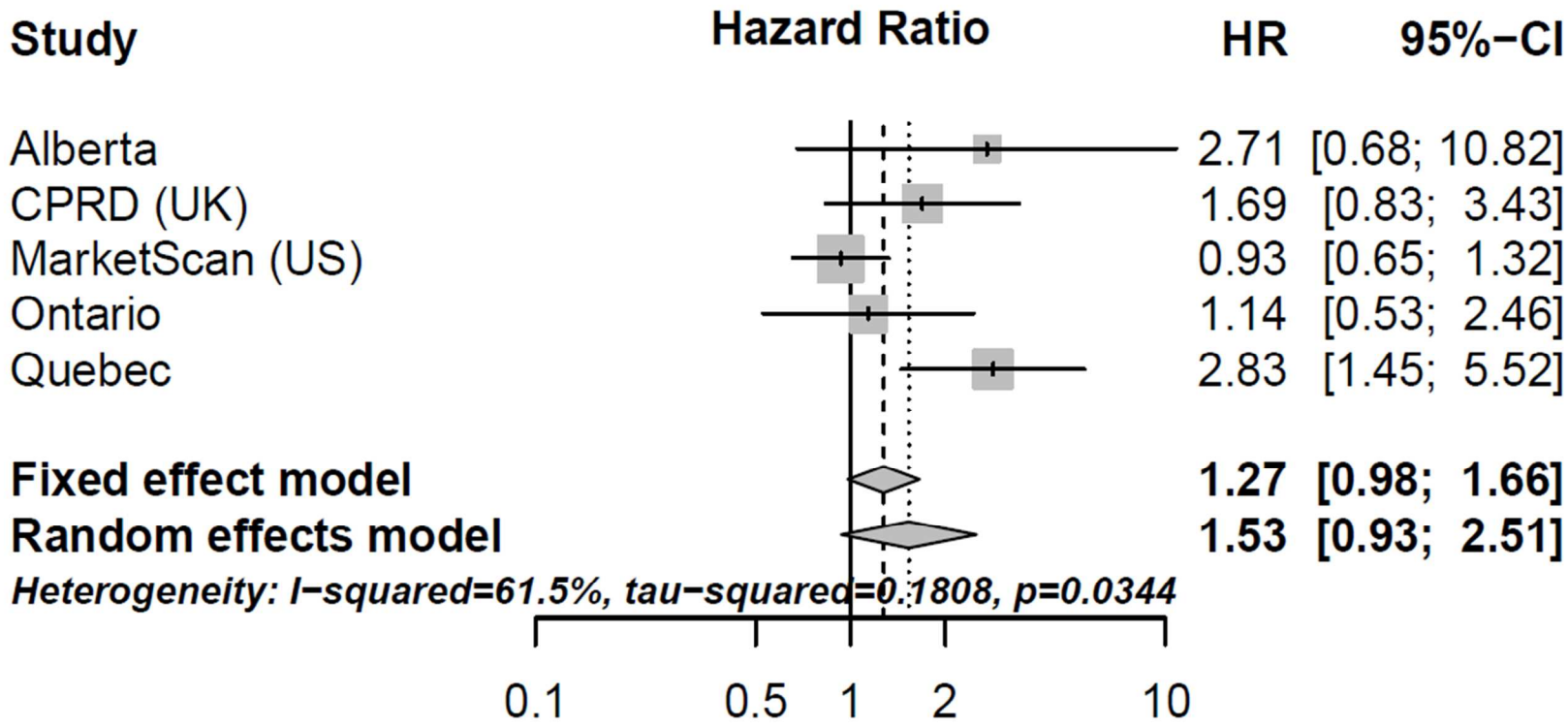
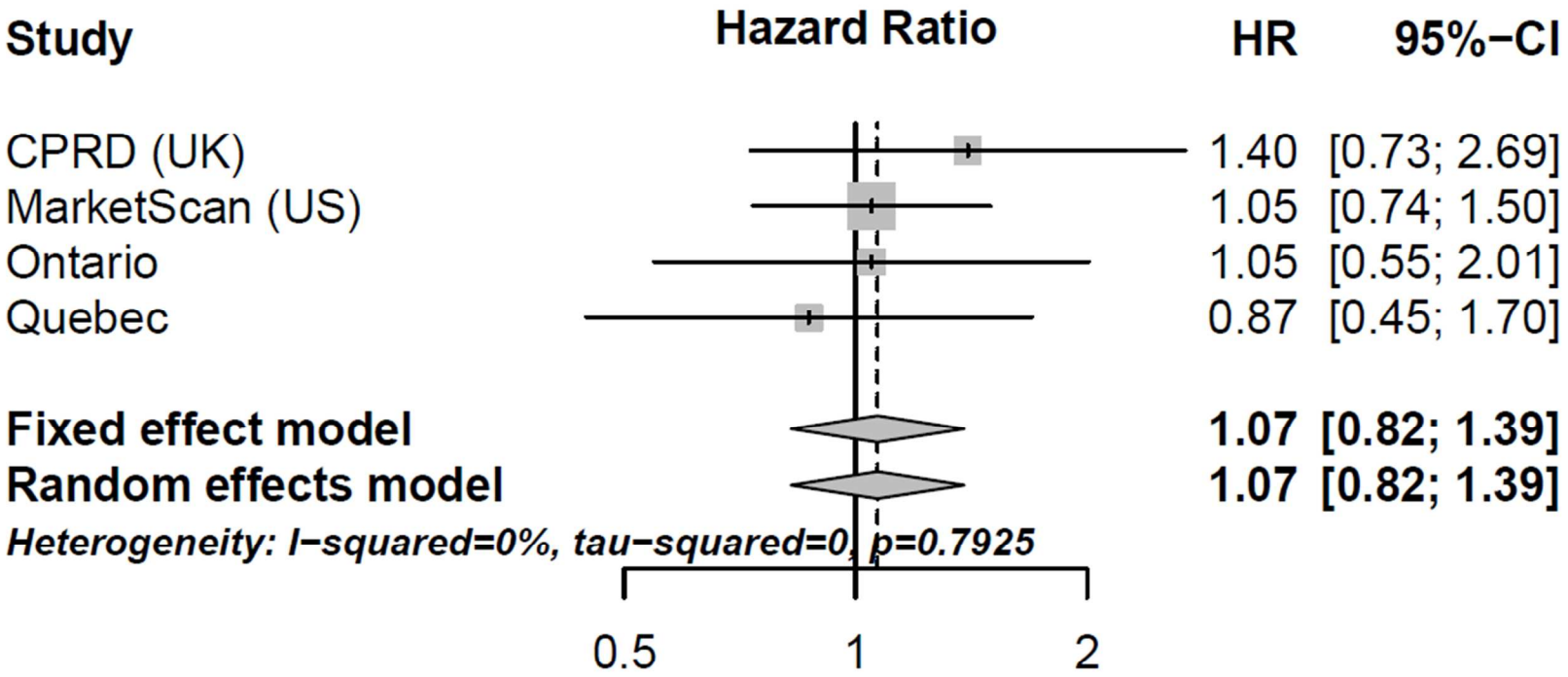
Supplemental Figure 3. Forest plot for the secondary analysis assessing the association between cumulative durations of incretin-based drug use < 1 year and pancreatic cancer*



Abbreviations: CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.
*The reference category is use of sulfonylureas.
The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.
Note: This analysis was limited to participating sites generating stable estimates (Alberta, Ontario, Quebec, CPRD, and MarketScan).

Supplemental Figure 4. Forest plot for the secondary analysis assessing the association between cumulative durations of incretin-based drug use of 1-1.9 years and pancreatic cancer*



Abbreviations: CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.
*The reference category is use of sulfonylureas. The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.
Note: This analysis was limited to participating sites generating stable estimates (Ontario, Quebec, CPRD, and MarketScan).

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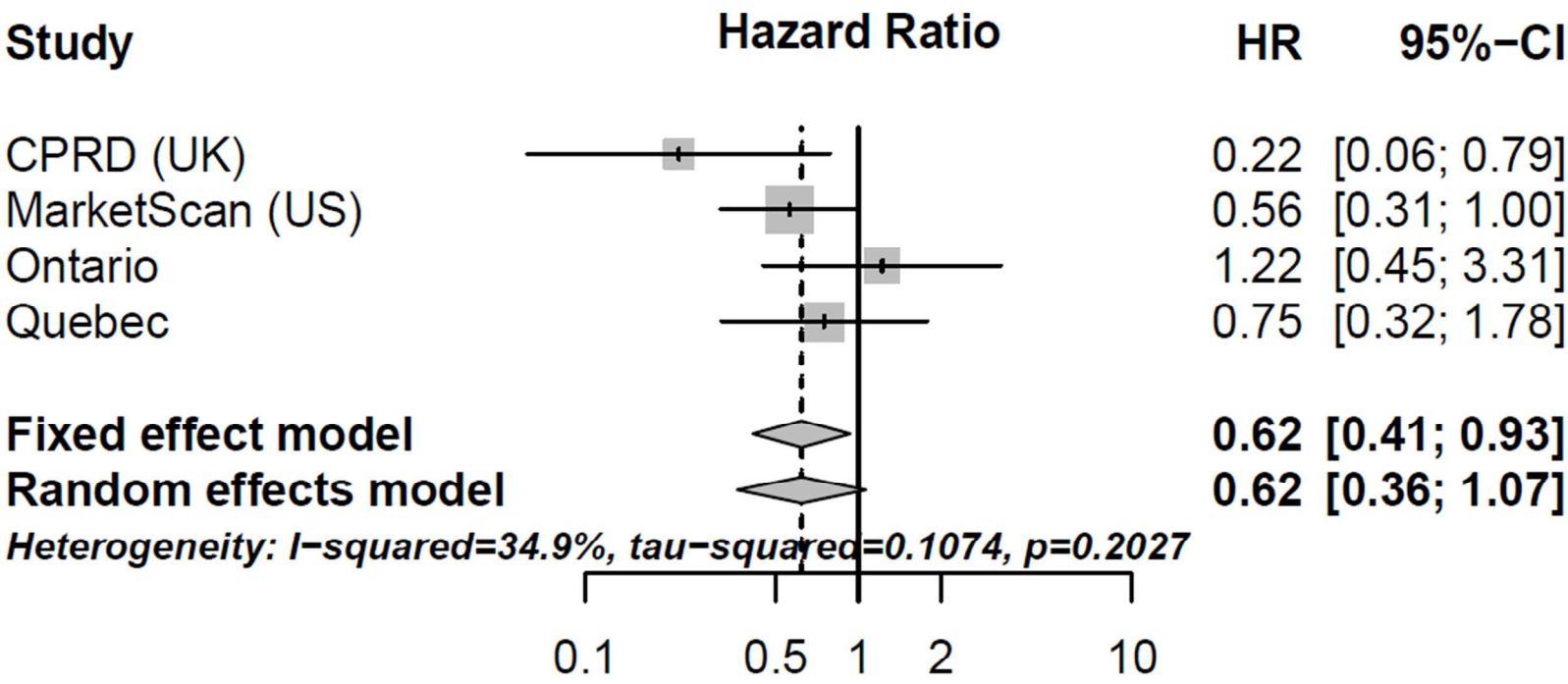
Supplemental Figure 5. Forest plot for the secondary analysis assessing the association between cumulative durations of incretin-based drug use of ≥2 years and pancreatic cancer*



Abbreviations: CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.
*The reference category is use of sulfonylureas. The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.
Note: This analysis was limited to participating sites generating stable estimates (Ontario, Quebec, CPRD, and MarketScan).

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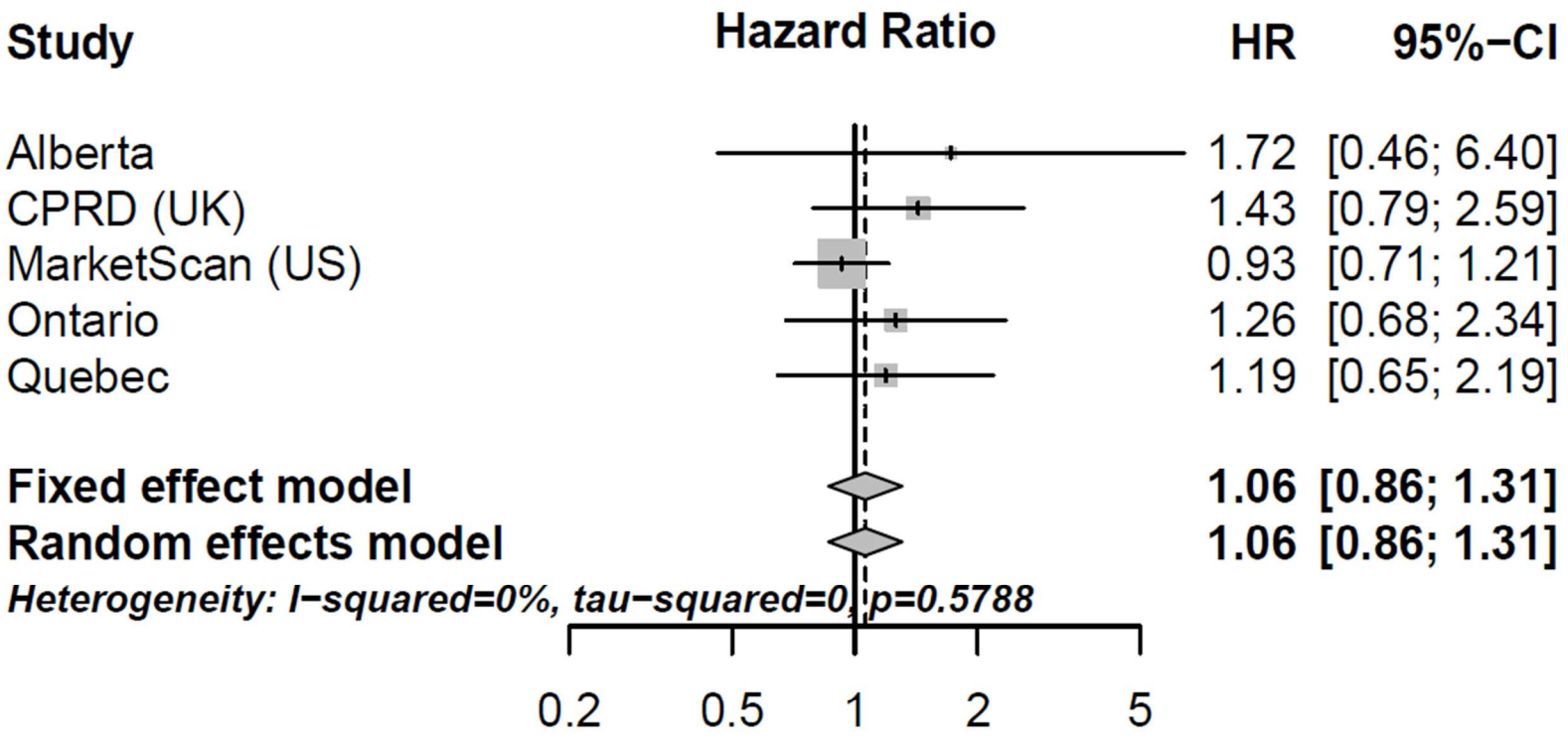
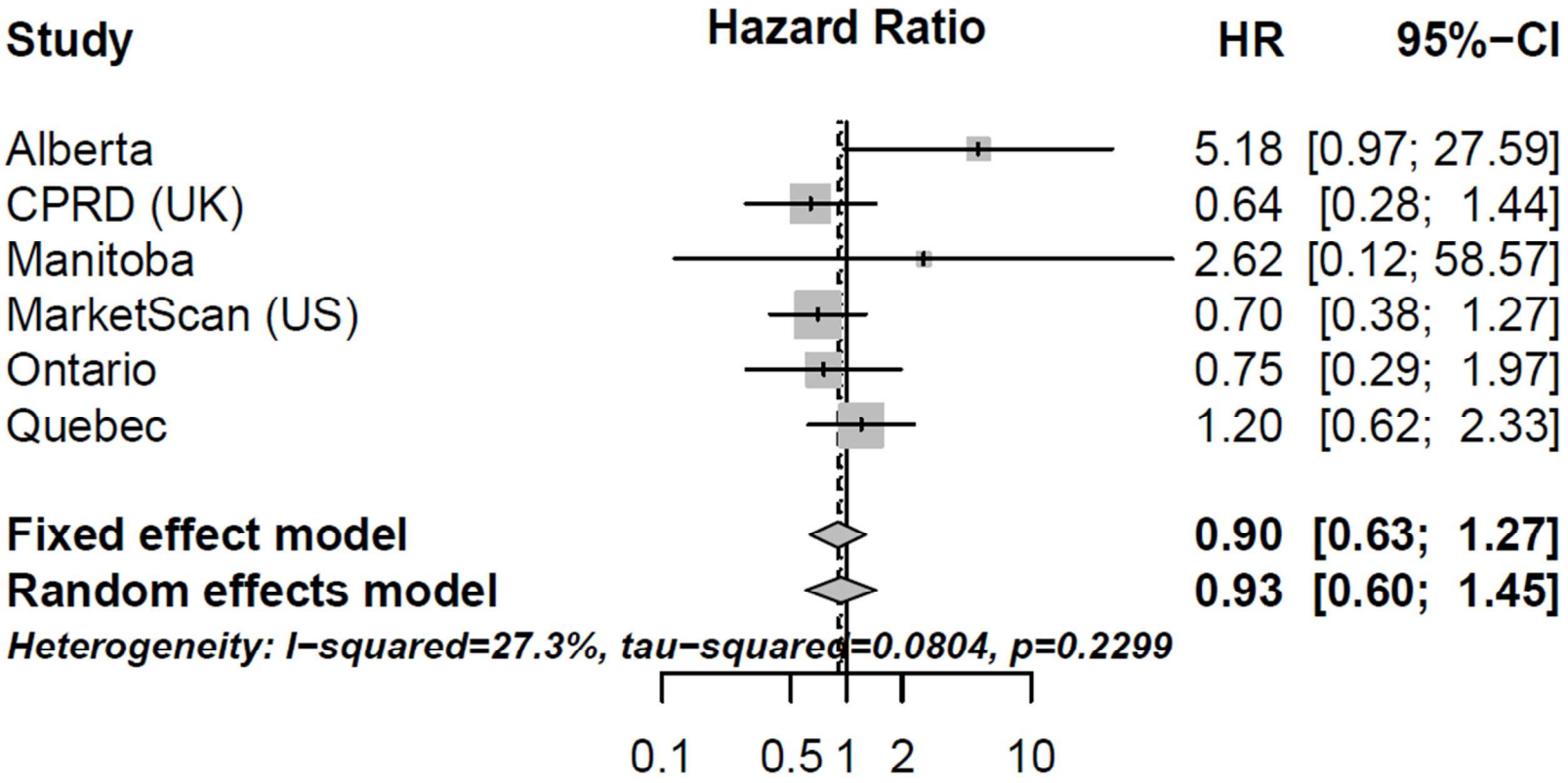
Supplemental Figure 6. Forest plot for the secondary analysis assessing the association between initiation of incretin-based drugs between 1 and 1.9 years before index date and pancreatic cancer*



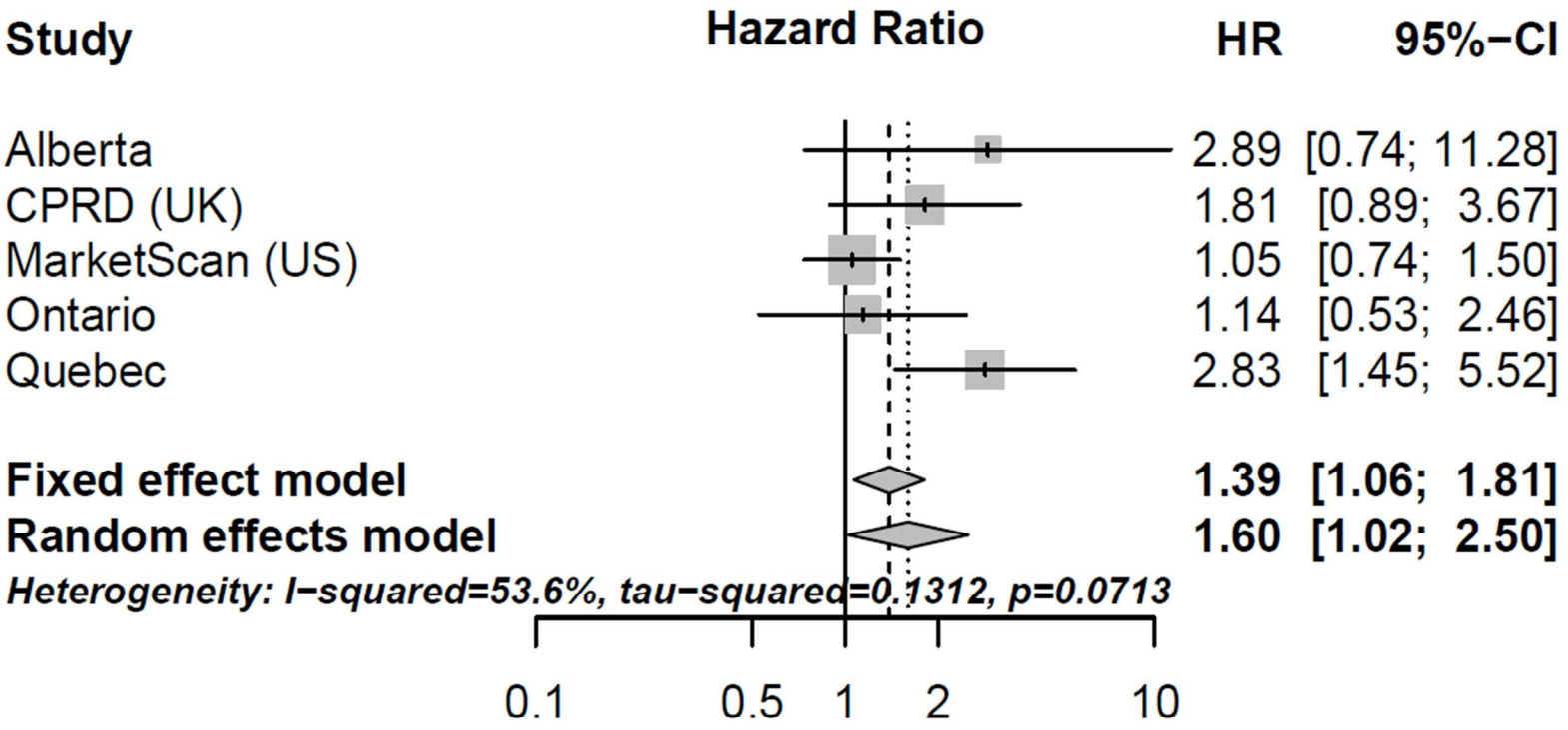
Abbreviations: CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.
*The reference category is use of sulfonylureas. The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.
Note: This analysis was limited to participating sites generating stable estimates (Alberta, Ontario, Quebec, CPRD, and MarketScan).

Supplemental Figure 7. Forest plot for the secondary analysis assessing the association between initiation of incretin-based drugs ≥2 years before index date and pancreatic cancer*



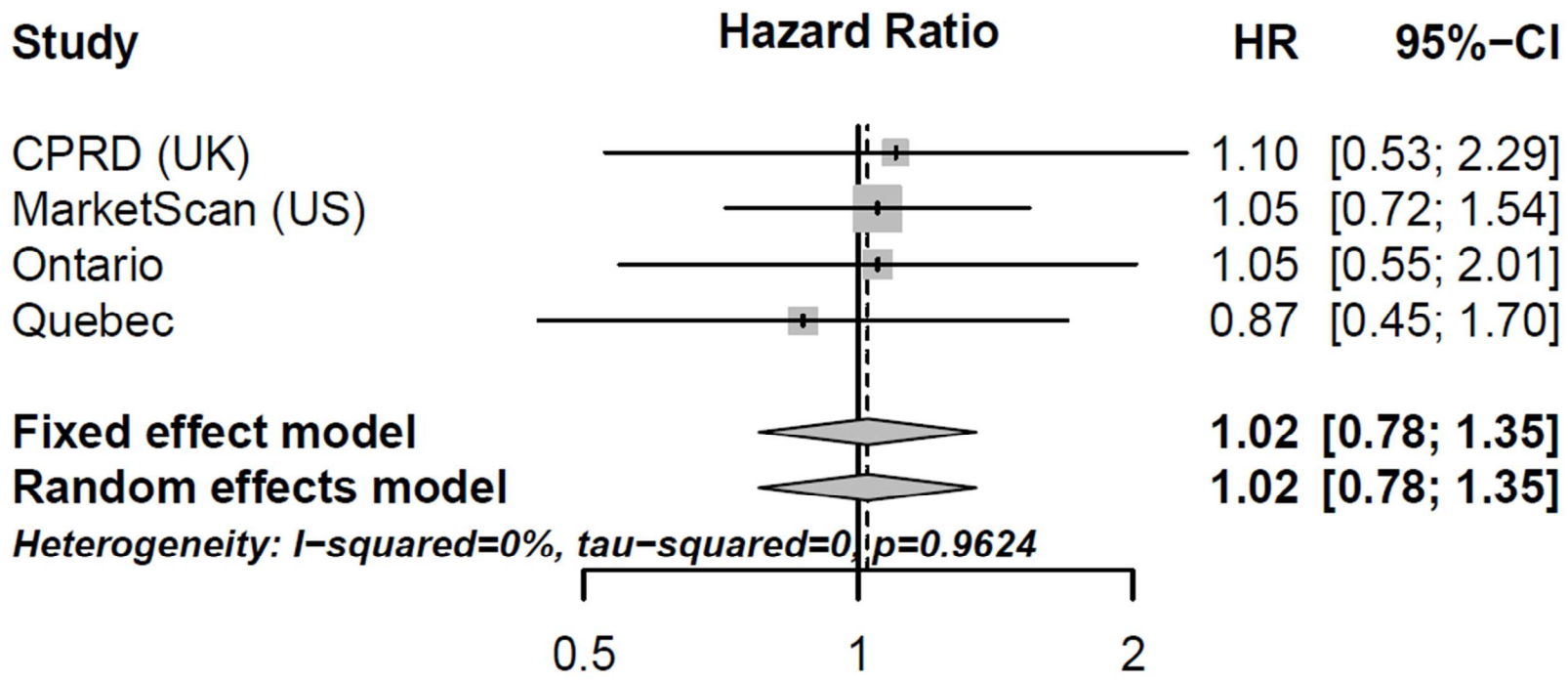
Abbreviations: CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.
*The reference category is use of sulfonylureas.
The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.

Supplemental Figure 8. Forest plot for the secondary analysis assessing the association between cumulative duration of DPP-4 inhibitor use of < 1 year and pancreatic cancer*



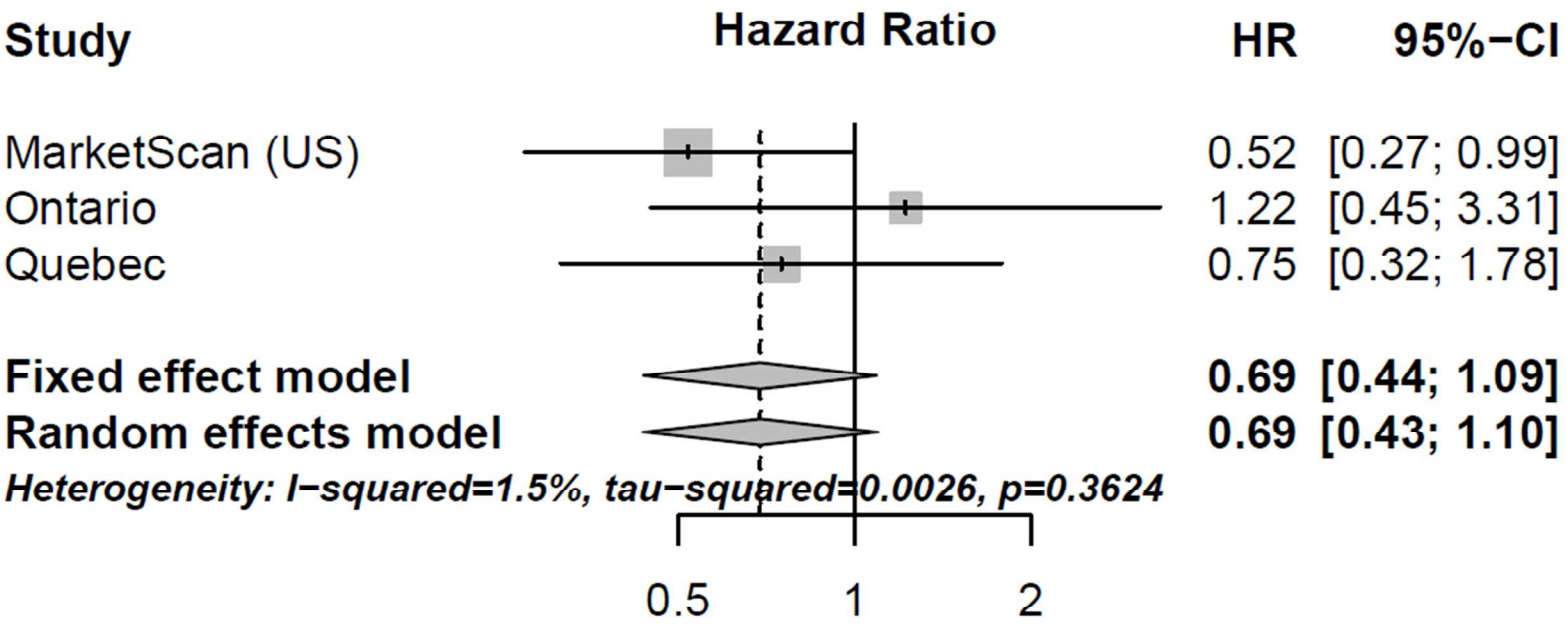
Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; UK, United Kingdom; US, United States.
*The reference category is use of sulfonylureas. The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.
Note: This analysis was limited to participating sites generating stable estimates (Alberta, Ontario, Quebec, CPRD, and MarketScan).

Supplemental Figure 9. Forest plot for the secondary analysis assessing the association between cumulative duration of DPP-4 inhibitor use of 1-1.9 years and pancreatic cancer*



Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; UK, United Kingdom; US, United States.
*The reference category is use of sulfonylureas. The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.
Note: This analysis was limited to participating sites generating stable estimates (Ontario, Quebec, CPRD, and MarketScan).

Supplemental Figure 10. Forest plot for the secondary analysis assessing the association between cumulative duration of DPP-4 inhibitor use of ≥2 years and pancreatic cancer*



Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; US, United States.
*The reference category is use of sulfonylureas. The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.
Note: This analysis was limited to participating sites generating stable estimates (Ontario, Quebec, MarketScan).

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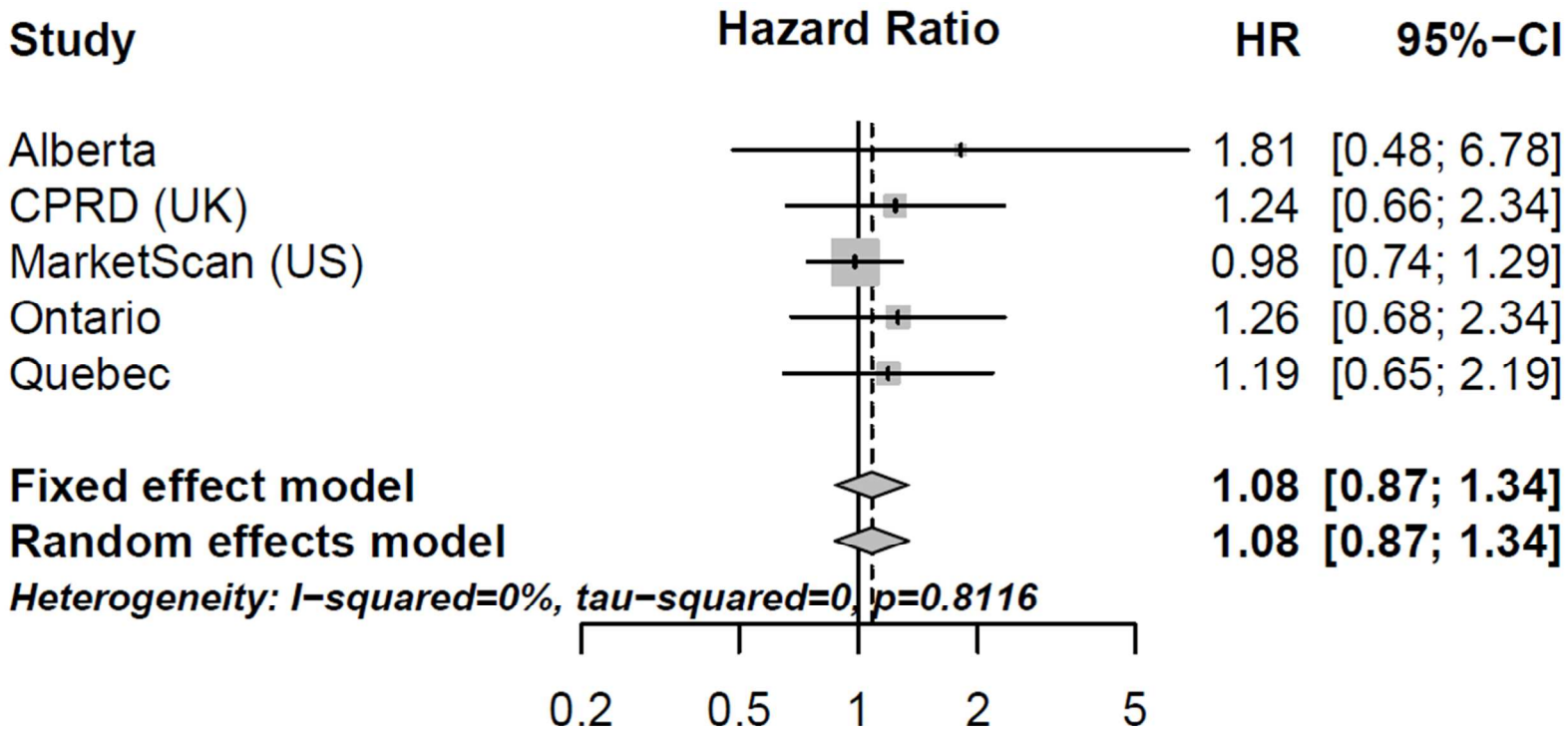
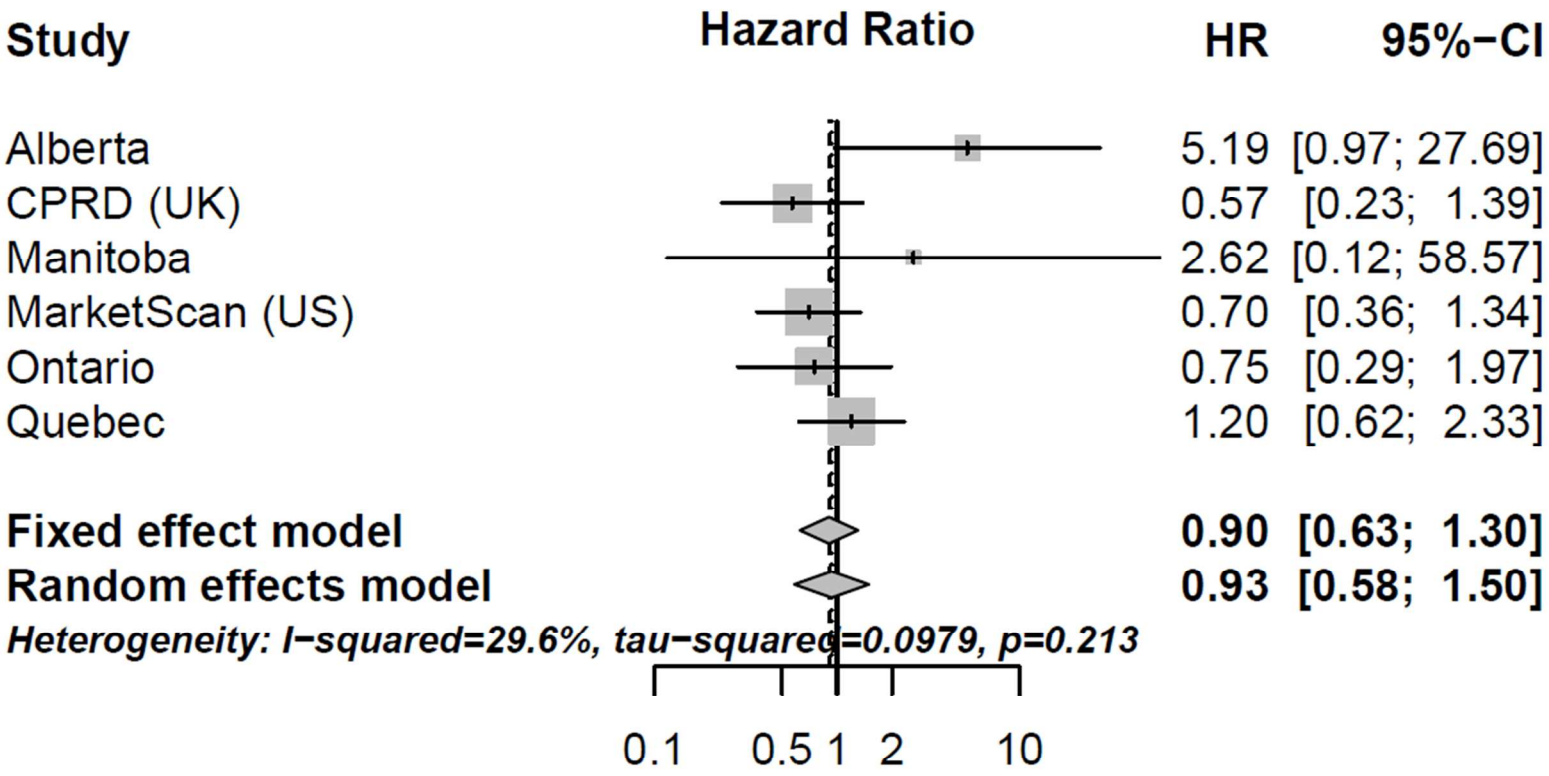
Supplemental Figure 11. Forest plot for the secondary analysis assessing the association between initiation of DPP-4 inhibitors between 1 and 1.9 years before index date and pancreatic cancer*



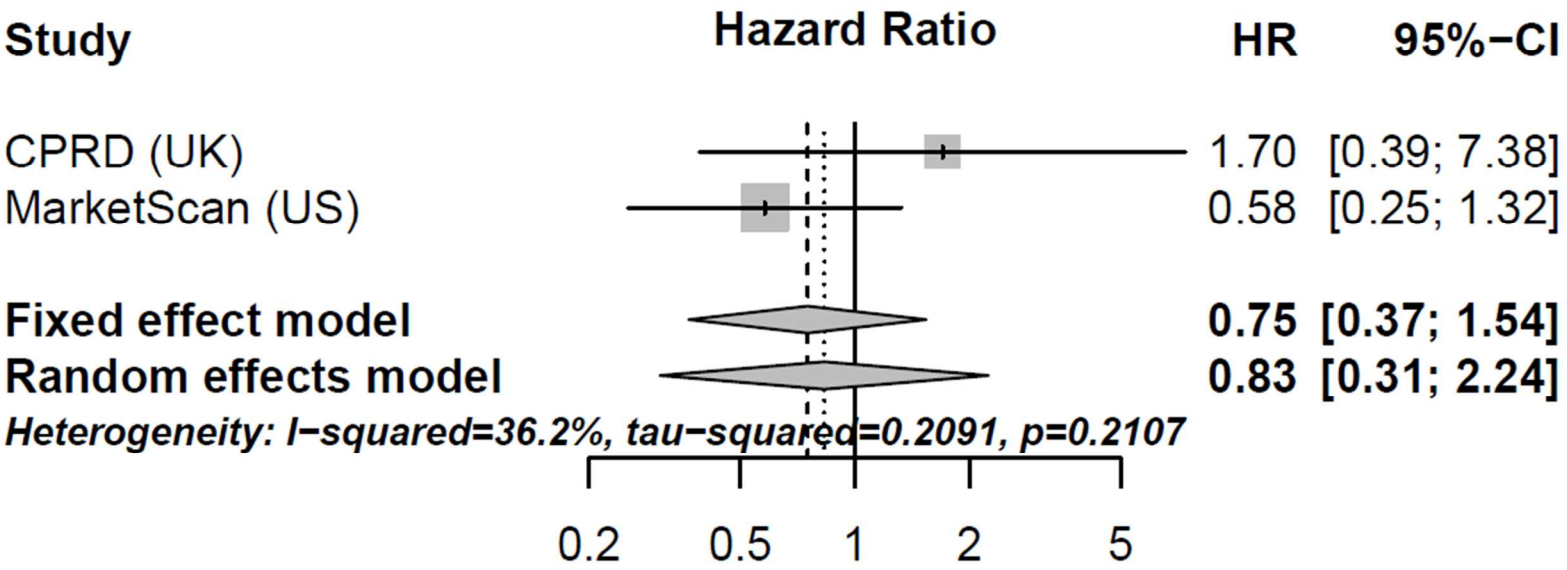
Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; UK, United Kingdom; US, United States.
*The reference category is use of sulfonylureas. The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.
Note: This analysis was limited to participating sites generating stable estimates (Alberta, Ontario, Quebec, CPRD, and MarketScan).

Supplemental Figure 12. Forest plot for the secondary analysis assessing the association between initiation of DPP-4 inhibitors ≥2 years before index date and pancreatic cancer*



Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; UK, United Kingdom; US, United States.
*The reference category is use of sulfonylureas. The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.

Supplemental Figure 13. Forest plot for the secondary analysis assessing the association between cumulative durations of GLP-1 analogue use of < 1 year and pancreatic cancer*



Abbreviations: GLP-1, glucagon-like peptide-1; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

*The reference category is use of sulfonylureas. The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.

Note: This analysis was limited to the United Kingdom Clinical Practice Research Datalink and the United States MarketScan, the two sites where GLP-1 analogues were available during the study period.

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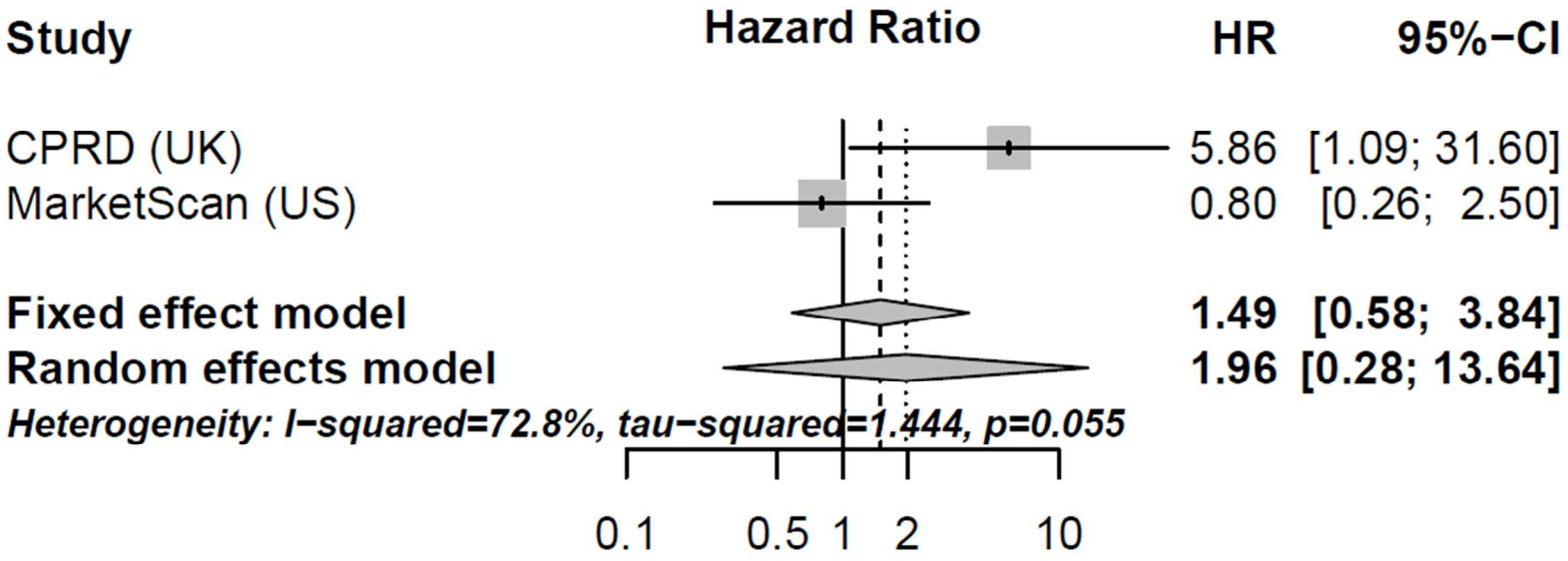
Supplemental Figure 14. Forest plot for the secondary analysis assessing the association between cumulative durations of GLP-1 analogue use of 1-1.9 years and pancreatic cancer*



Abbreviations: GLP-1, glucagon-like peptide-1; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.
*The reference category is use of sulfonylureas. The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.
Note: This analysis was limited to the United Kingdom Clinical Practice Research Datalink and the United States MarketScan, the two sites where GLP-1 analogues were available during the study period.

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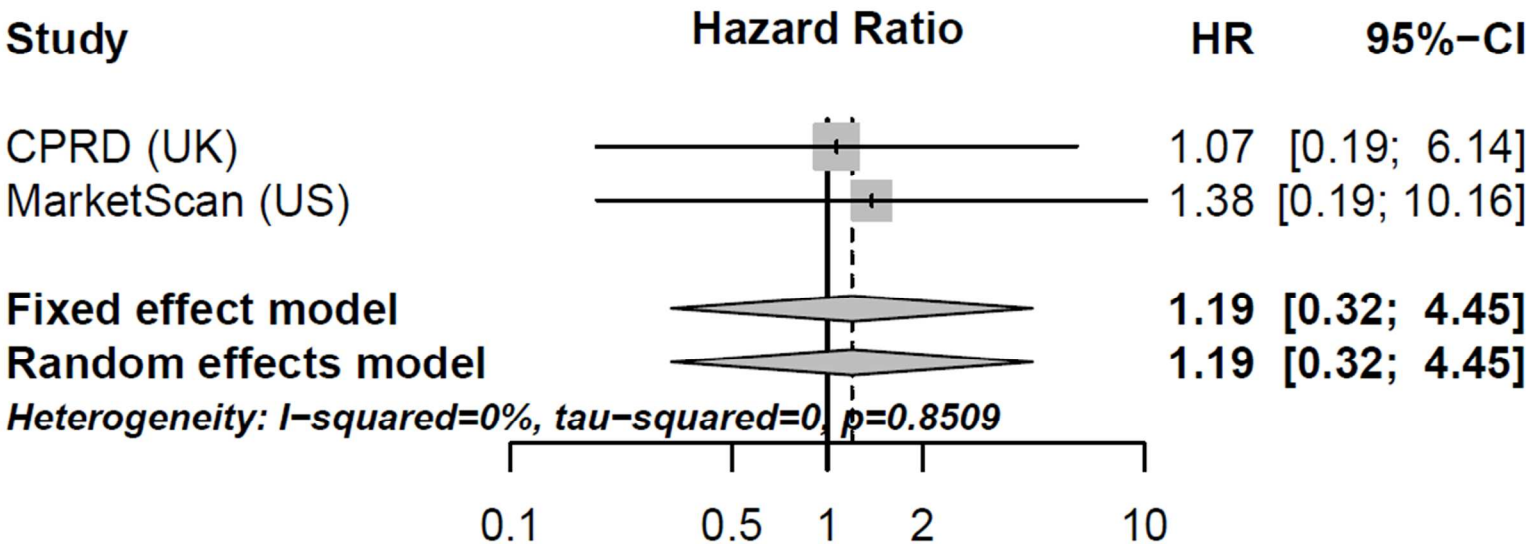
Supplemental Figure 15. Forest plot for the secondary analysis assessing the association between cumulative durations of GLP-1 analogue use of ≥2 years and pancreatic cancer*



Abbreviations: GLP-1, glucagon-like peptide-1; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

*The reference category is use of sulfonylureas. The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.

Note: This analysis was limited to the United Kingdom Clinical Practice Research Datalink and the United States MarketScan, the two sites where GLP-1 analogues were available during the study period.

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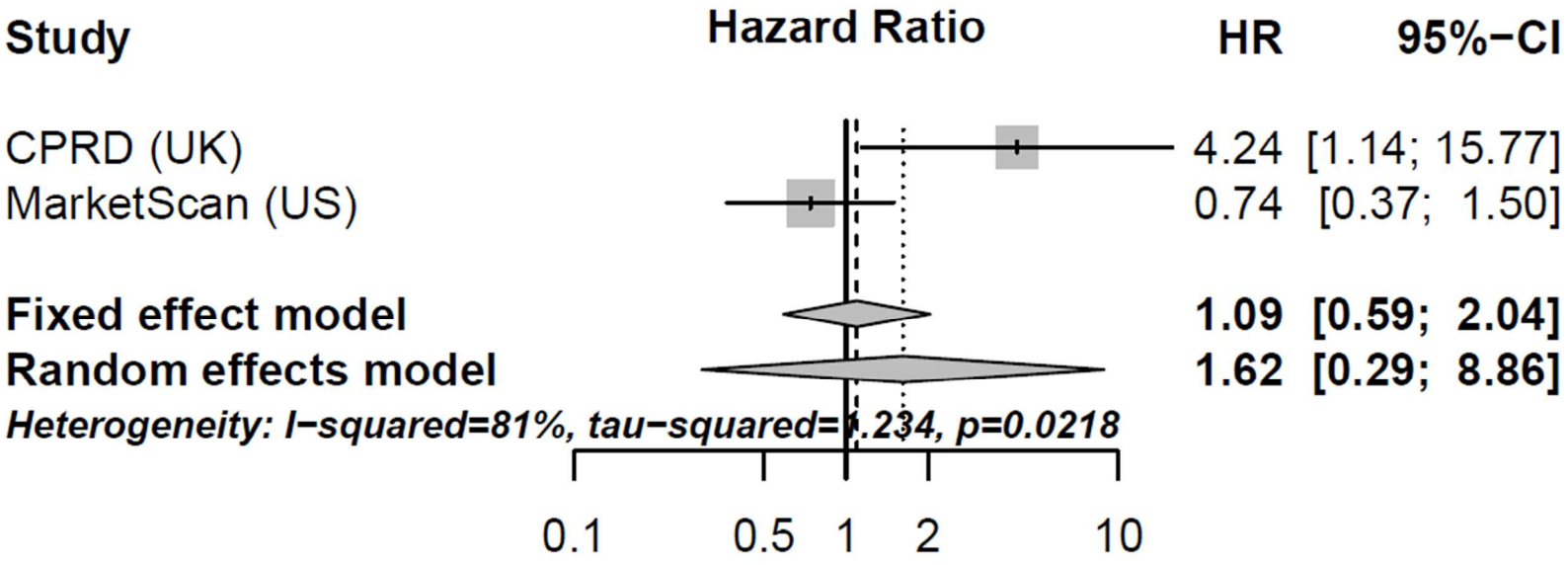
Supplemental Figure 16. Forest plot for the secondary analysis assessing the association between initiation of GLP-1 analogues between 1 and 1.9 years before index date and pancreatic cancer*



Abbreviations: GLP-1, glucagon-like peptide-1; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.
*The reference category is use of sulfonylureas. The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.
Note: This analysis was limited to the United Kingdom Clinical Practice Research Datalink and the United States MarketScan, the two sites where GLP-1 analogues were available during the study period.

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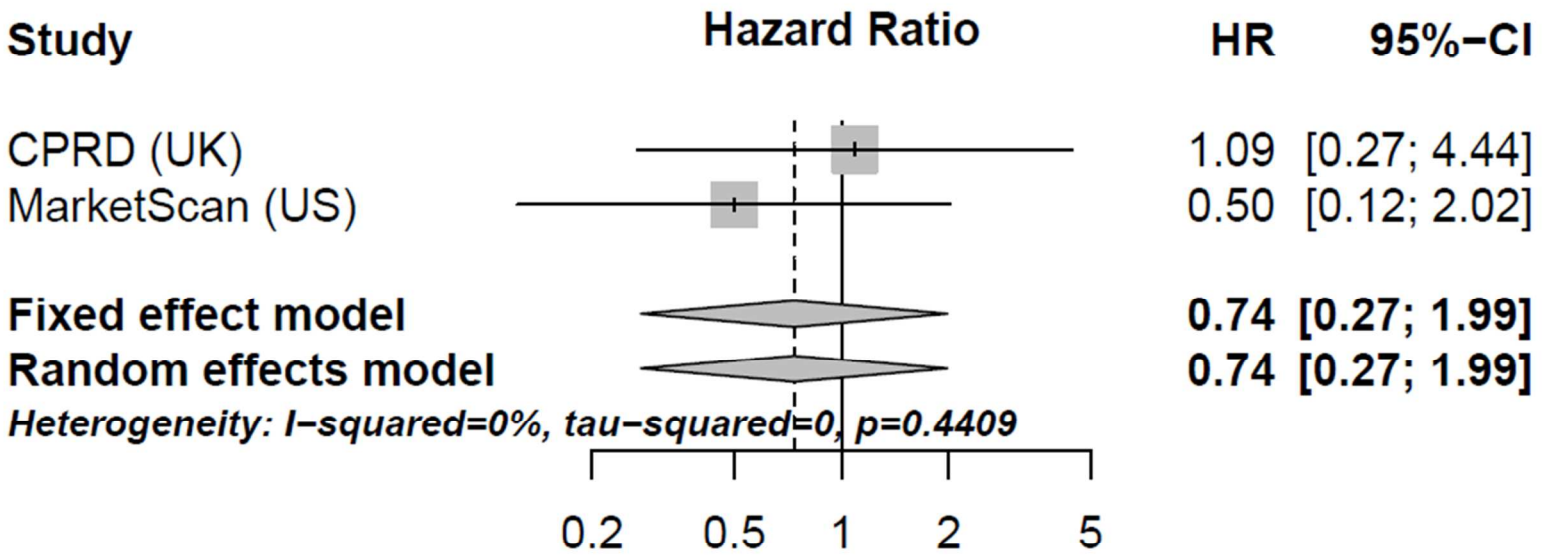
Supplemental Figure 17. Forest plot for the secondary analysis assessing the association between initiation of GLP-1 analogues ≥2 years before index date and pancreatic cancer*



Abbreviations: GLP-1, glucagon-like peptide-1; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

*The reference category is use of sulfonylureas. The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.

Note: This analysis was limited to the United Kingdom Clinical Practice Research Datalink and the United States MarketScan, the two sites where GLP-1 analogues were available during the study period.

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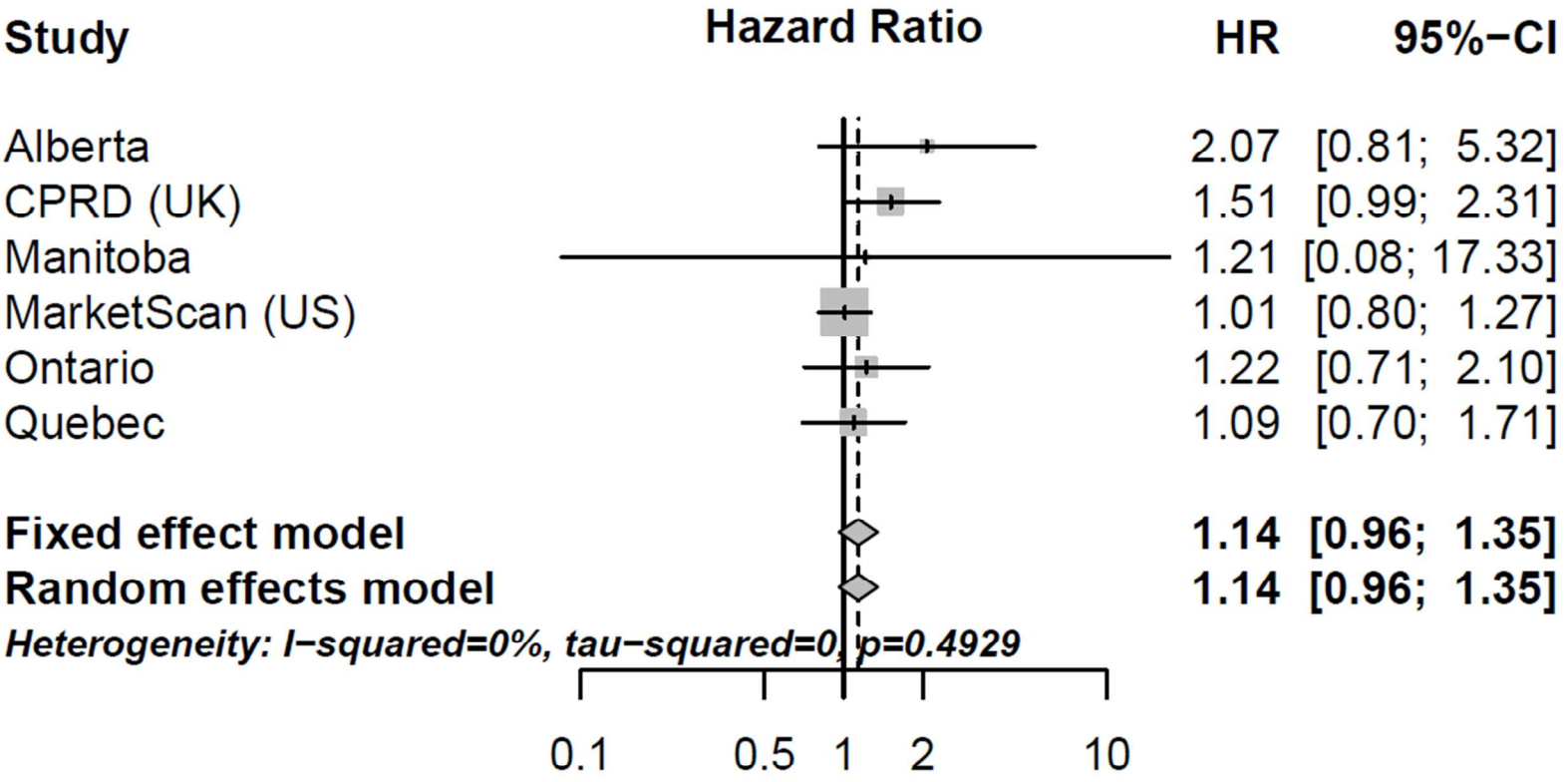
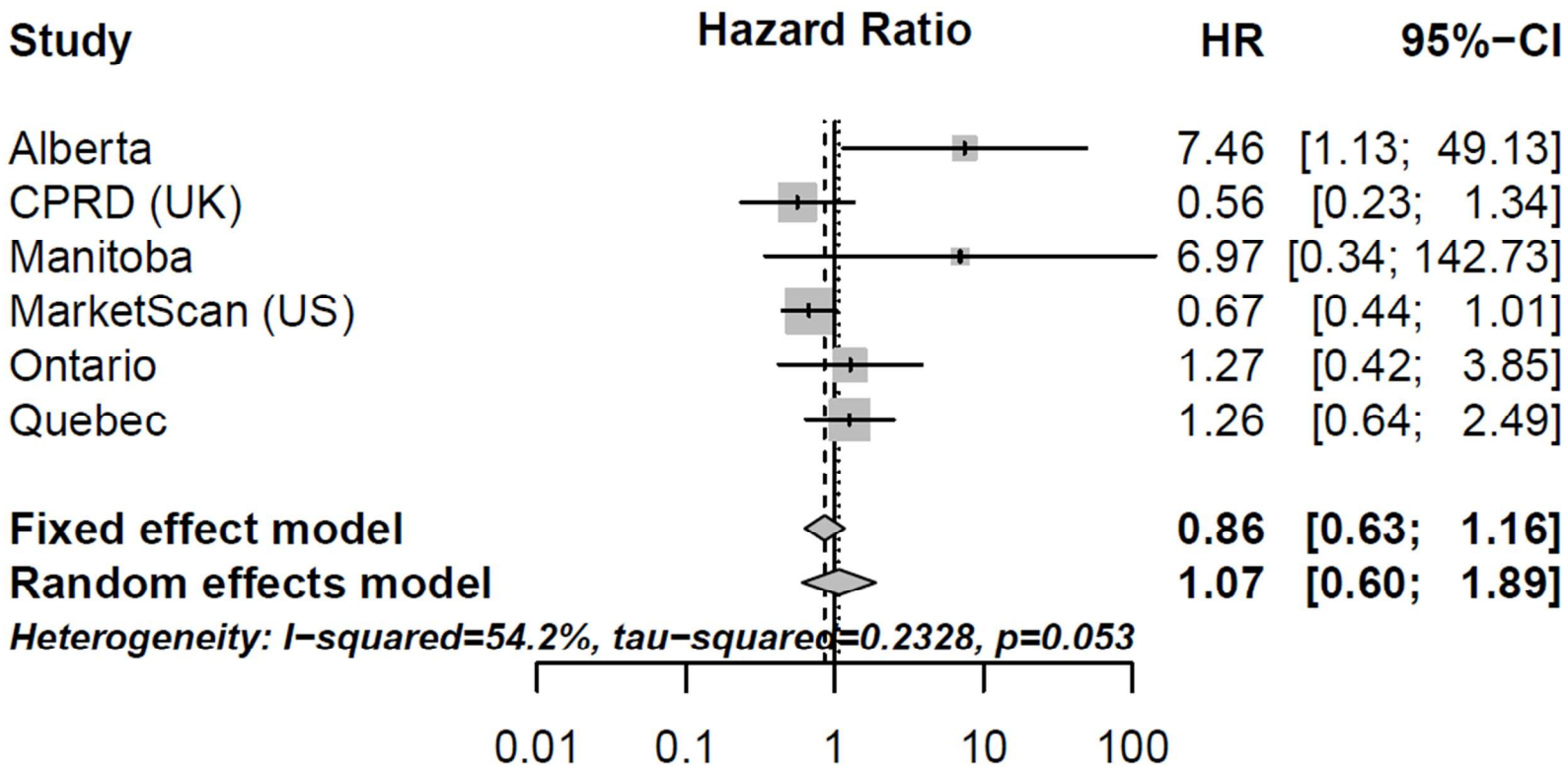
Supplemental Figure 18. Forest plot for the sensitivity analysis comparing use of incretin-based drugs with use of sulfonylureas varying the lag period to 6 months*



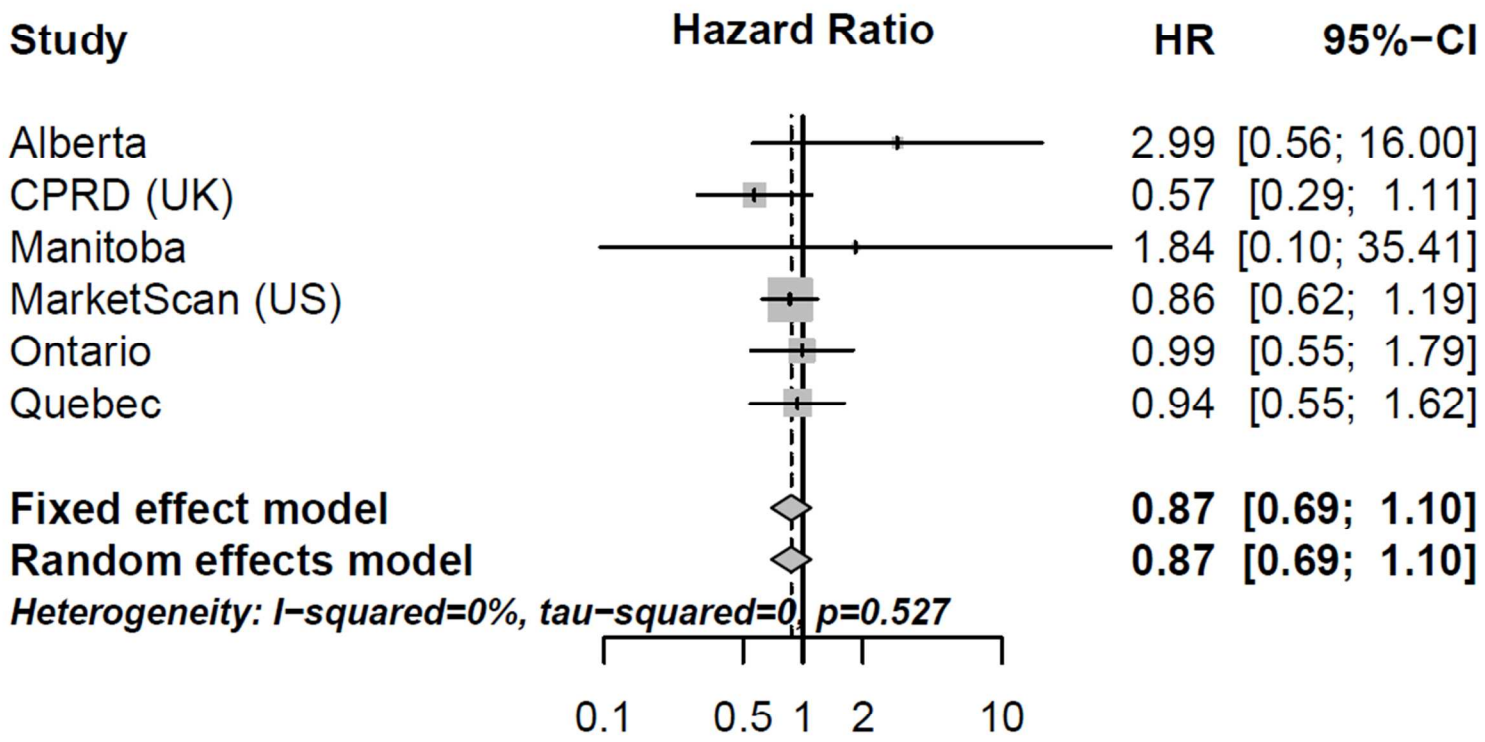
Abbreviations: CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.
*The reference category is use of sulfonylureas.
The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.

Supplemental Figure 19. Forest plot for the sensitivity analysis comparing use of incretin-based drugs with use of sulfonylureas varying the lag period to 2 years*



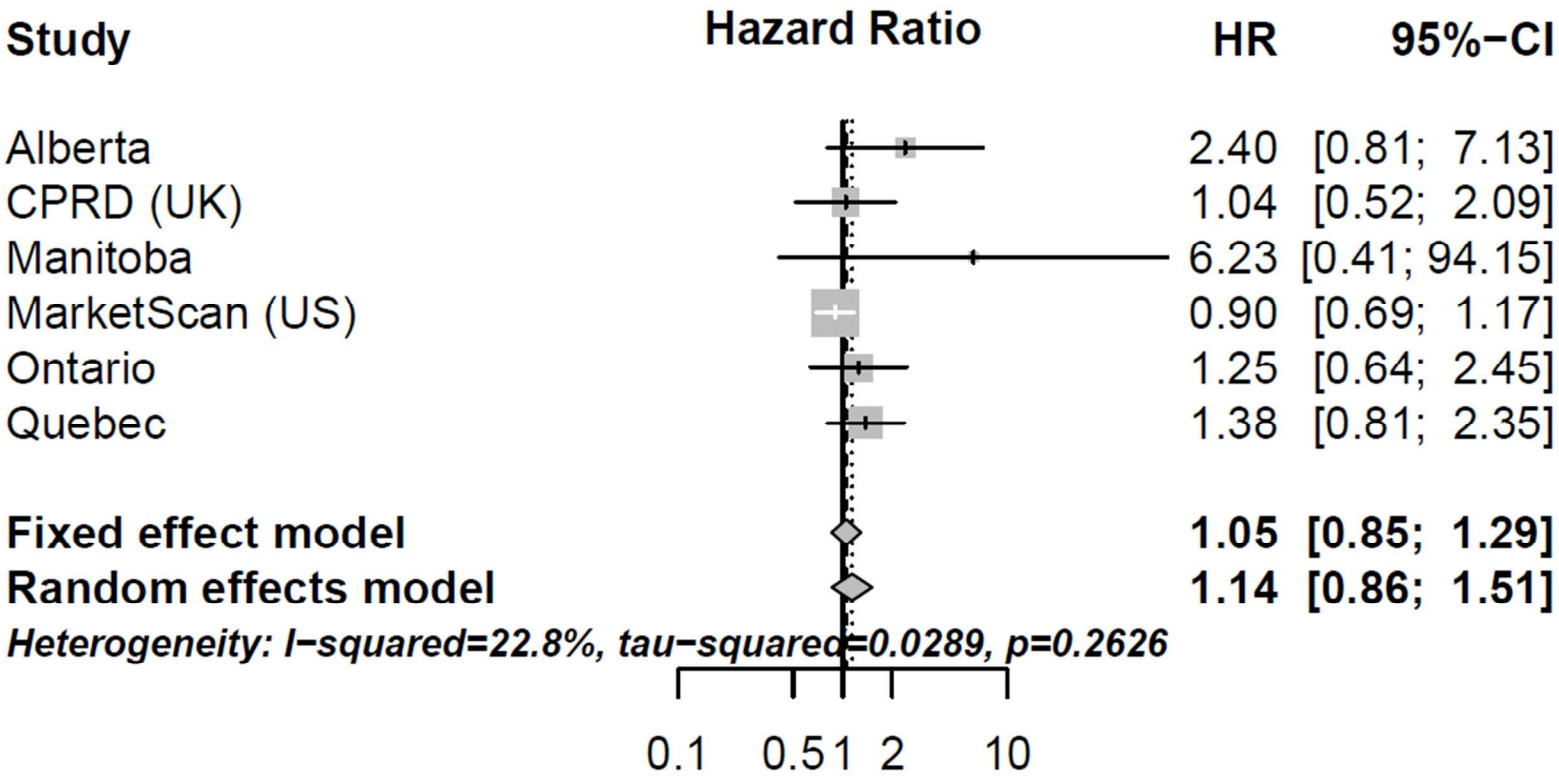
Abbreviations: CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.
*The reference category is use of sulfonylureas.
The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.

Supplemental Figure 20. Forest plot for the sensitivity analysis using a stricter exposure definition for incretin-based drugs (at least 4 prescriptions within a 12-month window)*



Abbreviations: CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.
*The reference category is use of sulfonylureas.
The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.

Supplemental Figure 21. Forest plot for the sensitivity analysis comparing use of incretin-based drugs with use of sulfonylureas initiated after study cohort entry*



Abbreviations: CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.
*The reference category is use of sulfonylureas.
The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.

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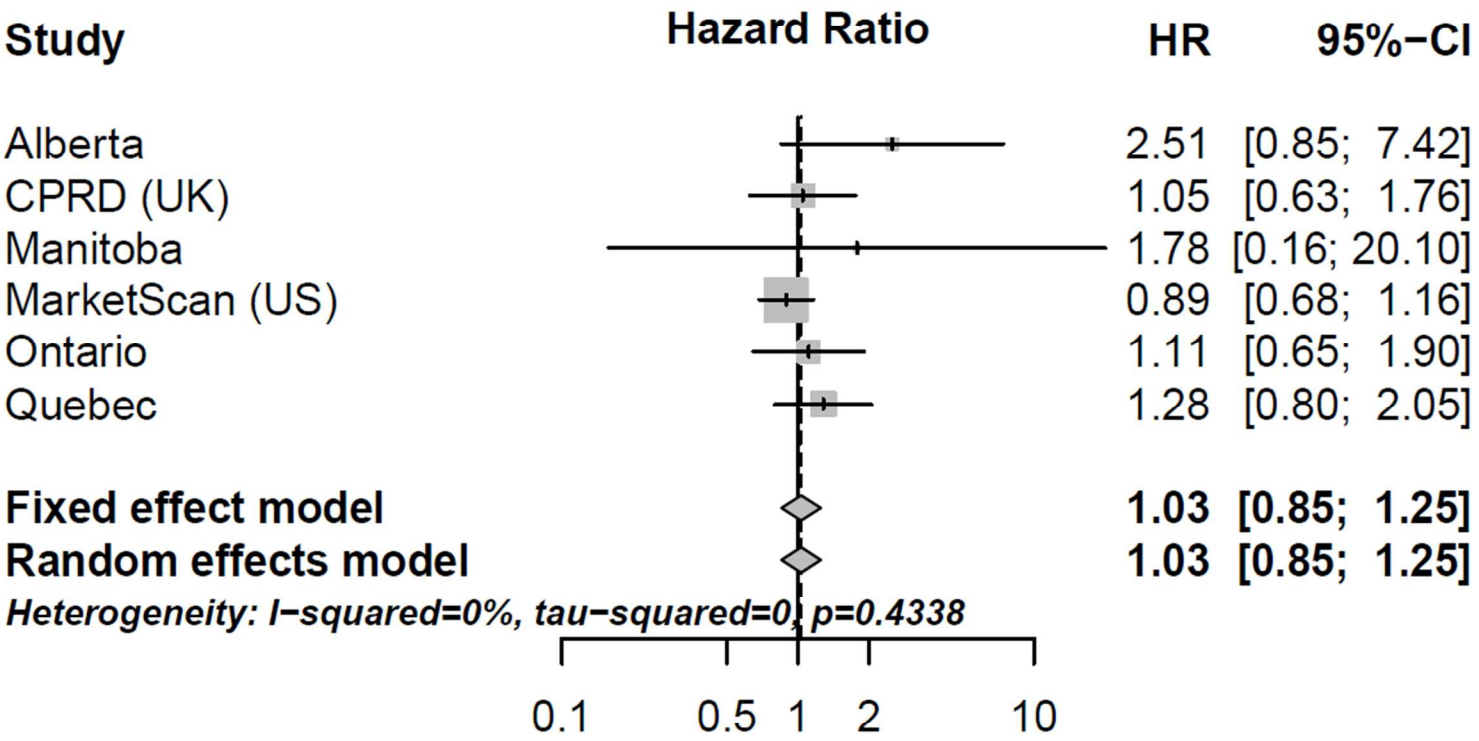
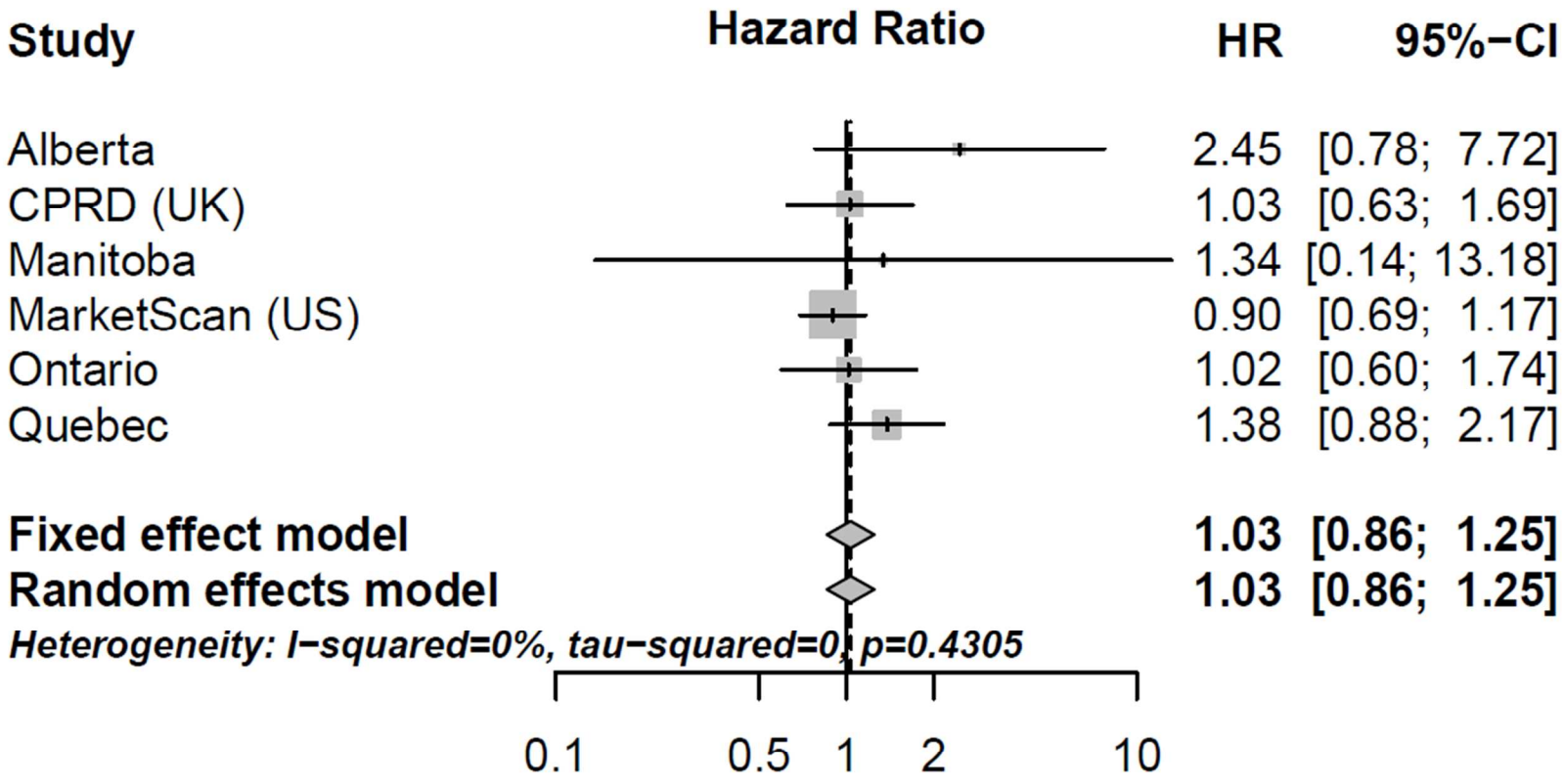
Supplemental Figure 22. Forest plot for the sensitivity analysis comparing use of incretin-based drugs with use of sulfonylureas adjusted for a reduced set of covariates*



Abbreviations: CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.
The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.
*Adjusted for alcohol-related disorders, history of acute or chronic pancreatitis, a composite variable of microvascular complications of diabetes, number of hospitalizations (continuous), number of unique non-diabetic drugs in the prior year (continuous), number of anti-diabetic drugs received prior to study cohort entry (continuous), use of statins. In the CPRD, we further adjusted for body mass index, smoking status, and glycated haemoglobin A1c level (≤7.0% [53 mmol/mol], 7.1-8.0% [54-64 mmol/mol], >8.0% [64 mmol/mol]).

Supplemental Figure 23. Forest plot for the sensitivity analysis comparing use of incretin-based drugs with use of sulfonylureas adjusted for a reduced set of covariates*



Abbreviations: CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States
The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis.
*Adjusted for the Deyo version of the Charlson comorbidity index and history of acute or chronic pancreatitis.

Supplementary Table 1. The baseline characteristics of patients included in study cohort*

Baseline characteristics †	
Number of patients	972,384
CNODES Site, No. (%)	
US MarketScan	649,052 (66.7)
UK Clinical Practice Research Datalink	93,032 (9.6)
Quebec	86,212 (8.9)
Alberta	56,280 (5.8)
Ontario	54,949 (5.7)
Manitoba	32,859 (3.4)
Age (years), mean	56.9
18-25, n (%)	12,368 (1.3)
26-35, n (%)	53,209 (5.5)
36-45, n (%)	130,647 (13.4)
46-55, n (%)	256,296 (26.4)
56-65, n (%)	263,606 (27.1)
66-75, n (%)	158,874 (16.3)
≥76, n (%)	97,384 (10.0)
Male, n (%)	495,098 (50.9)
Calendar year of study cohort entry, No. (%)	
2007	122,646 (12.6)
2008	157,816 (16.2)
2009	189,185 (19.5)
2010	173,528 (17.8)
2011	179,525 (18.5)
2012	137,121 (14.1)
2013	12,563 (1.3)
Duration of treated diabetes (years), mean	1.2
Body mass index, kg/m^2, No. (%) ‡	
<25	9,404 (10.1)
25-29	27,606 (29.7)
≥30	54,145 (58.2)
Missing	1,877 (2.0)
Haemoglobin A1c, No. (%) ‡	
≤7 % [53 mmol/mol]	12,854 (13.8)
7.1-8.0 % [54-64 mmol/mol]	25,058 (26.9)
>8 [64 mmol/mol]	40,174 (43.2)
Missing	14,946 (16.1)
Alcohol-related disorders, No. (%)	17,926 (1.8)
Smoking status, No. (%)	
Ever	57,204 (61.5)

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Baseline characteristics †	
Never	35,527 (38.2)
Missing	301 (0.3)
Statins, No. (%)	469,634 (48.3)
Acute or chronic pancreatitis, No. (%)	9,527 (1.0)
Neuropathy, No. (%)	16,342 (1.7)
Renal disease, No. (%)	55,657 (5.7)
Retinopathy, No. (%)	82,131 (8.4)
Peripheral arteriopathy, No. (%)	38,590 (4.0)
Number of hospitalizations, mean	0.1
0, No. (%)	867,023 (89.2)
1, No. (%)	82,975 (8.5)
2, No. (%)	16,105 (1.7)
3, No. (%)	3,990 (0.4)
≥4, No. (%)	2,291 (0.2)
Number of unique non-antidiabetic drugs, mean	7.4
0, No. (%)	111,992 (11.5)
1, No. (%)	58,450 (6.0)
2, No. (%)	65,530 (6.7)
3, No. (%)	69,996 (7.2)
≥4, No. (%)	666,416 (68.5)
Pre-study cohort entry antidiabetic drugs, mean	0.2
0, No. (%)	884,903 (91.0)
1, No. (%)	42,675 (4.4)
2, No. (%)	25,322 (2.6)
3, No. (%)	12,524 (1.3)
≥4, No. (%)	6,960 (0.7)
Study cohort entry drugs, No. (%)‡	
Metformin	762,971 (78.5)
Sulfonylureas	156,480 (16.1)
Thiazolidinediones	57,490 (5.9)
DPP-4 inhibitors	66,186 (6.8)
GLP-1 analogues	12,129 (1.2)
Alpha-glucosidase inhibitors	3,153 (0.3)
Meglitinides	7,211 (0.7)
Insulins	11,880 (1.2)
Others	1,896 (0.2)

* Due to privacy restrictions in some of the participating sites, we assigned a value of 3 to small cells (≤5). As such, the sum of count data may differ from the presented total.
† Data from the UK Clinical Practice Research Datalink.
‡ Non-mutually exclusive categories.

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Supplementary Table 2. The baseline characteristics of users of incretin-based drugs and sulfonylureas among controls*

Baseline characteristics †	Use of incretin-based drugs	Use of sulfonylureas
Number of patients	2,828	5,942
CNODES Site, No. (%)		
US MarketScan	1,562 (55.2)	2,891 (48.7)
Ontario	661 (23.4)	414 (7.0)
UK Clinical Practice Research Datalink	292 (10.3)	1,189 (20.0)
Quebec	280 (9.9)	1,108 (18.6)
Alberta	27 (1.0)	198 (3.3)
Manitoba	6 (0.2)	142 (2.4)
Age (years), mean ‡	66.9	68.7
18-25, n (%)	S†	S†
26-35, n (%)	S†	S†
36-45, n (%)	49 (1.7)	73 (1.2)
46-55, n (%)	409 (14.5)	649 (10.9)
56-65, n (%)	743 (26.3)	1,432 (24.1)
66-75, n (%)	1,050 (37.2)	2,202 (37.1)
≥76, n (%)	572 (20.3)	1,578 (26.6)
Male, n (%) ‡	1,563 (55.3)	3,445 (58.0)
Calendar year of study cohort entry, No. (%)		
2007	474 (16.8)	1,277 (21.5)
2008	421 (14.9)	1,212 (20.4)
2009	500 (17.7)	1,395 (23.5)
2010	571 (20.2)	1,043 (17.6)
2011	578 (20.4)	779 (13.1)
2012	287 (10.1)	236 (4.0)
2013	474 (16.8)	1,277 (21.5)
Duration of treated diabetes (years), mean ‡	2.4	1.6
Body mass index, kg/m^2, No. (%) §		
<25	S**	176 (14.8)
25-29	67 (22.9)	432 (36.3)
≥30	199 (68.2)	556 (46.8)
Missing	S**	25 (2.1)
Haemoglobin A1c, No. (%) §		
≤7 % [53 mmol/mol]	23 (7.9)	137 (11.5)
7.1-8.0 % [54-64 mmol/mol]	70 (24.0)	308 (25.9)
>8 [64 mmol/mol]	164 (56.2)	584 (49.1)
Missing	35 (12.0)	160 (13.5)
Alcohol-related disorders, No. (%)	44 (1.6)	178 (3.0)
Smoking status, No. (%) §		

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Baseline characteristics †	Use of incretin-based drugs	Use of sulfonylureas
Ever	180 (61.6)	762 (64.1)
Never	S**	419 (35.2)
Missing	S**	8 (0.7)
Statins, No. (%)	1,897 (67.1)	3,641 (61.3)
Acute or chronic pancreatitis, No. (%)	35 (1.2)	73 (1.2)
Neuropathy, No. (%)	74 (2.6)	184 (3.1)
Renal disease, No. (%)	281 (9.9)	763 (12.8)
Retinopathy, No. (%)	341 (12.1)	826 (13.9)
Peripheral arteriopathy, No. (%)	172 (6.1)	461 (7.8)
Number of hospitalizations, mean	0.2	0.2
0, No. (%)	2516 (89.0)	4,858 (81.8)
1, No. (%)	263 (9.3)	828 (13.9)
2, No. (%)	35 (1.2)	188 (3.2)
3, No. (%)	S†	44 (0.7)
≥4, No. (%)	S†	28 (0.5)
Number of unique non-antidiabetic drugs, mean	8.8	8.1
0, No. (%)	247 (8.7)	684 (11.5)
1, No. (%)	108 (3.8)	277 (4. 7)
2, No. (%)	139 (4.9)	297 (5.0)
3, No. (%)	146 (5.2)	348 (5.9)
≥4, No. (%)	2,189 (77.4)	4,336 (73.0)
Pre-study cohort entry antidiabetic drugs, mean	0.7	0.3
0, No. (%)	1,888 (66.8)	4,506 (75.8)
1, No. (%)	335 (11.8)	1,024 (17.2)
2, No. (%)	327 (11.6)	298 (5.0)
3, No. (%)	176 (6.2)	86 (1.4)
≥4, No. (%)	108 (3.8)	28 (0.5)
Study cohort entry drugs, No. (%) ‡		
Metformin	1,171 (41.4)	2,699 (45.4)
Sulfonylureas	341 (12.1)	3,730 (62.8)
Thiazolidinediones	162 (5.7)	386 (6.5)
DPP-4 inhibitors	1,527 (54.0)	0 (0)
GLP-1 analogues	128 (4.5)	0 (0)
Alpha-glucosidase inhibitors	S†	19 (0.3)
Meglitinides	18 (0.6)	40 (0.7)
Insulins	13 (0.5)	181 (3.0)
Others	S†	6 (0.1)

* Due to privacy restrictions in some of the participating sites, we assigned a value of 3 to small cells (≤5). As such, the sum of count data may differ from the presented total.

† When the total across participating sites was less than 6, data were suppressed (denoted by an S) due to privacy restrictions. When summing data across sites, we assigned a value of 3 to small cells (≤5). As such, the sum of count data may differ from the presented total.

‡ Data from the UK Clinical Practice Research Datalink.

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§ Non-mutually exclusive categories.
** Suppressed because cell value is less than 5.

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