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Supplementary Methods 1. Multiple Imputation

We used multiple imputation for variables with incomplete data (i.e. missing values for haemoglobin A1c, BMI and smoking) in all analyses.[1 2] This method is more efficient than a complete case analysis.[3] To impute missing data, an ordinal regression model was used with explanatory variables and cumulative hazard,[3] use of DPP-4 inhibitors and GLP-1 receptor agonists at cohort entry and all confounders listed in the manuscript. Using Rubin's rules, we combined the results of five imputations to estimate the value of missing variables.[4]

Supplementary Methods 2. Marginal Structural Modelling

To address the possibility of residual time-dependent confounding associated with time-varying exposures, we repeated the analysis using a marginal structural Cox proportional hazards model.[5] [6] Using two pooled logistic regression models (numerator and denominator of the stabilized inverse-probability-of-treatment weights [IPTWs]), we estimated the conditional probability of being exposed to DPP-4 inhibitors and GLP-1 receptor agonists given previous treatment history in the 30-days prior. The numerator model included baseline covariates (listed in the manuscript) and follow-up time, and the denominator model included covariates (listed in the manuscript) measured at each 30-day interval and follow-up time. Follow-up was modelled using a restricted cubic spline with five knots to avoid biases from the linearity assumption.[7] We used similar methods to estimate inverse probability of censoring weights (IPCWs). Thus, using predicted probabilities from treatment and censoring models, we calculated stabilized IPTW and IPCW for each patient. The product of these weights was used to reweigh the cohort, in which we estimated the hazard ratios of cholangiocarcinoma associated with the use of DPP-4 inhibitors and GLP-1 receptor agonists, with 95% confidence intervals calculated using robust variance estimators.[6]

Supplementary Methods 3. Negative Control Exposure

To address the potential impact of confounding by diabetes severity, we used insulin as a negative control exposure[8], a drug typically reserved to patients with advanced disease that has not been associated with the incidence of cholangiocarcinoma. For this analysis, we excluded patients who had previously used insulin at any time before cohort entry and modelled new use of insulin as a time-varying variable lagged by one year. Specifically, each person-day of follow-up was categorised into one of four mutually-exclusive categories: 1) use of insulin (alone or in combination with other antidiabetic drugs, excluding incretin-based drugs); 2) use of insulin in but with current or previous use of incretin-based drugs; 3) use of second or third line drugs (drugs (defined as initiation of treatment with either thiazolidinediones, prandial glucose regulators, acarbose, sodium-glucose cotransporter-2 inhibitors, insulin, or combination of oral antidiabetic drugs; or switch to or add-on of an antidiabetic drug, including insulin, after failure with metformin or sulfonylurea in monotherapy); and 4) use of first line drugs (defined as use of metformin or sulfonylurea in monotherapy). For this analysis, we compared use of insulin without incretin-based drugs to use of other second or third line antidiabetic drugs.

Supplementary Methods 4. Propensity Score Matched Analysis

To investigate the potential impact of confounding by diabetes severity, we conducted an ancillary analysis using a propensity score-matched design. This analysis was an extension of the *sequence of non-randomized trials approach* proposed by Hernan et al.[9] Using the study cohort defined in the manuscript, we identified all new users of incretin-based drugs and other second or third line drugs at each calendar month of the study accrual period (January 1, 2007 to March 31, 2017). Each calendar month generated a separate cohort. We applied the same exclusion criteria detailed in the manuscript at the time of entry into each of these 123 sequential cohorts. Patients in the comparator group who eventually added-on or switched to an incretin-based drug were allowed to contribute to the exposed group after the time of the switch. Within each cohort, we estimate the predicted probability (propensity score) of receiving an incretin-based drug versus another second or third line drug using conditional logistic regression, stratified on calendar month and conditional on the variables listed in the manuscript. Age and duration of diabetes were modelled as continuous variables using restricted cubic splines to avoid linearity assumptions. We then matched each incretin-based drug user chronologically to one patient (without replacement) initiating a second-to third-line antidiabetic drug in the same calendar month and propensity score using a calliper of 0.01 using a greedy matching algorithm, with the nearest neighbour chosen as the match. The matched sets were followed until an incident diagnosis of cholangiocarcinoma, death from any cause, end of registration with the practice, or end of the study period (March 31, 2018), whichever occurred first. We used a Cox proportional hazards model to estimate the hazard ratio and 95% confidence interval of cholangiocarcinoma, comparing use of incretin-based drugs with use of other second or third line drugs.

Supplementary Methods 5. Pharmacovigilance Analysis using the World Health Organization Vigibase

Using the World Health Organization global individual case safety report database, Vigibase, we conducted a case/non-case study.[10] This database includes information on over 16 million individual case safety reports forwarded to the World Health Organization Uppsala Monitoring Center by national pharmacovigilance systems from over 150 countries around the world since 1967.[11] Individual case safety reports register information about patients, prescription drugs (classified as suspected or concomitant), suspected adverse drug reactions, and the country reporting. The likelihood that the drug has caused the reported event varies from case to case. We included all individual case safety reports from January 1, 2008 to April 1, 2018 in adults over the age of 18 and excluded all duplicate reports.

We defined cases of cholangiocarcinoma as an individual case report containing any of the following terms: bile duct adenocarcinoma, bile duct adenosquamous carcinoma, bile duct cancer/recurrent/stage 0 to IV, bile duct squamous cell carcinoma, biliary cancer metastasis, cholangiocarcinoma or biliary malignant tumours. Non-cases were all other reports in Vigibase during the same period, with known age and sex. We defined exposure among cases and non-cases as the use of dipeptidyl peptidase-4 inhibitors or glucagon-like peptide-1 receptor agonists, compared to the use of sulfonylureas or thiazolidinediones. To investigate the impact of confounding by diabetes severity, we repeated the analysis using long-acting insulin analogues as a negative control exposure.

Descriptive statistics were used to summarize the baseline characteristics of the cholangiocarcinoma cases. We performed a disproportionality analysis to estimate reporting odds ratios (RORs) of cholangiocarcinoma with 95% confidence intervals (CIs) compared to all other adverse drug reactions in Vigibase.[12] The ROR is the exposure odds among reported cases of cholangiocarcinoma compared with the exposure odds among reported non-cases. The ROR was calculated among users of the incretin-based drugs compared to users of sulfonylureas and/or thiazolidinediones. RORs were adjusted for age, sex, notifier type (physician, consumer or other), country of report (Americas, Asia or other) and year of report. This frequentist approach (ROR and 95% CIs) based the concept of disproportionality has been largely used in pharmacovigilance databases to detect signals of disproportionate reporting, and the performance, accuracy and reliability are usually similar to other frequentist approaches (Proportional Reporting Ratio and Relative Reporting Ratio) or Bayesian approaches.[13,14]

Supplementary Table 1. British National Formulary Codes for Antidiabetic Drugs

BNF Code	BNF Header
06010100	Insulins
06010101	Short-acting Insulins
06010102	Intermediate- And Long-acting Insulins
06010151	Biphasic Insulins
06010200	Antidiabetic Drugs
06010201	Sulphonylureas
06010202	Biguanides
06010203	Other Antidiabetic Drugs
06010101/06010300	Short-acting Insulins/Diabetic Ketoacidosis
06010103/59010400	Diabetes Hypodermic Equipment/-
06010200/06010203	Antidiabetic Drugs/Other Antidiabetic Drugs
06010201/06010203	Sulphonylureas/Other Antidiabetic Drugs
06010202/06010203	Biguanides/Other Antidiabetic Drugs

BNF=British national formulary

Supplementary Table 2. Read Codes and Associated Terms for Cholangiocarcinoma

Read code	Read term
B151.00	Malignant neoplasm of intrahepatic bile ducts
B151000	Malignant neoplasm of interlobular bile ducts
B151100	Malignant neoplasm of interlobular biliary canals
B151200	Malignant neoplasm of intrahepatic biliary passages
B151400	Malignant neoplasm of intrahepatic gall duct
B151z00	Malignant neoplasm of intrahepatic bile ducts NOS
B16..00	Malignant neoplasm gallbladder and extrahepatic bile ducts
B160.00	Malignant neoplasm of gallbladder
B161.00	Malignant neoplasm of extrahepatic bile ducts
B161.11	Carcinoma gallbladder
B161000	Malignant neoplasm of cystic duct
B161100	Malignant neoplasm of hepatic duct
B161200	Malignant neoplasm of common bile duct
B161z00	Malignant neoplasm of extrahepatic bile ducts NOS
B163.00	Malignant neoplasm, overlapping lesion of biliary tract
B16y.00	Malignant neoplasm other gallbladder/extrahepatic bile duct
B16z.00	Malignant neoplasm gallbladder/extrahepatic bile ducts NOS
BB5D100	[M]Cholangiocarcinoma
BB5D300	[M]Bile duct cystadenocarcinoma
BB5D700	[M]Combined hepatocellular carcinoma and cholangiocarcinoma
B162.00	Malignant neoplasm of ampulla of Vater
B15..00	Malignant neoplasm of liver and intrahepatic bile ducts
BB5D.00	[M]Hepatobiliary tract adenomas and carcinomas
B15z.00	Malignant neoplasm of liver and intrahepatic bile ducts NOS
BB5D711	[M]Hepatocholangiocarcinoma

NOS=not otherwise specified

Supplementary Table 3. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors According to Cumulative Duration of Use, Time since Initiation and Drug Type

Exposure [a]	Events	Person-years	Incidence rate (95% CI) [b]	Crude HR	Adjusted HR (95% CI) [c]
Cumulative duration of use, years					
≤ 1 year of use					
Other second or third line antidiabetic drugs [d]	5	13,252	37.7 (12.3 to 88.1)	1.00	1.00 (reference)
DPP-4 inhibitors	9	25,023	36.0 (16.4 to 68.3)	0.93	0.90 (0.29 to 2.78)
1.1-2 years of use					
Other second or third line antidiabetic drugs [d]	5	49,447	10.1 (3.3 to 23.6)	1.00	1.00 (reference)
DPP-4 inhibitors	9	32,848	27.4 (12.5 to 52.0)	2.59	2.51 (0.82 to 7.70)
> 2 years of use					
Other second or third line antidiabetic drugs [d]	23	160,832	14.3 (9.1 to 21.5)	1.00	1.00 (reference)
DPP-4 inhibitors	9	45,491	19.8 (9.0 to 37.6)	1.28	1.39 (0.63 to 3.05)
Time since first use, years					
≤ 2 years					
Other second or third line antidiabetic drugs [d]	9	44,756	20.1 (9.2 to 38.2)	1.00	1.00 (reference)
DPP-4 inhibitors use	10	32,456	30.8 (14.8 to 56.7)	1.51	1.43 (0.56 to 3.61)
> 2 years					
Other second or third line antidiabetic drugs [d]	24	178,775	13.4 (8.6 to 20.0)	1.00	1.00 (reference)
DPP-4 inhibitors use	17	70,907	24.0 (14.0 to 38.4)	1.67	1.76 (0.93 to 3.33)
Type of DPP-4 inhibitor [e]					
Other second or third line antidiabetic drugs [d]	33	223,531	14.8 (10.2 to 20.7)	1.00	1.00 (reference)
Sitagliptin/saxagliptin/alogliptin	20	87,296	22.9 (14.0 to 35.4)	1.50	1.64 (0.92 to 2.90)
Linagliptin/vildagliptin	S*	S*	41.8 (13.6 to 97.7)	2.69	2.25 (0.86 to 5.90)
Other DPP-4 combinations	S*	S*	48.6 (5.9 to 175.4)	2.96	2.61 (0.62 to 11.1)

DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; HR=hazard ratio; CI=confidence interval.

[a] Use of other anti-diabetic drugs was considered in the models, but not presented in the table.

[b] Per 100,000 Person-Years.

[c] Adjusted for age, sex, year of cohort entry, obesity, smoking status, alcohol-related disorders, Charlson comorbidity index score, inflammatory bowel disease, gallbladder disease, haemoglobin A1c, and duration of diabetes.

[d] Including initiating on combination therapy or switching to or adding-on a new antidiabetic drug class.

e Renal excretion: sitagliptin, saxagliptin and alogliptin. Biliary excretion: linagliptin and vildagliptin.

S* Numbers less than 5 are not displayed, as per the confidentiality policies of the Clinical Practice Research Datalink.

Supplementary Table 4. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors and GLP-1 Receptor Agonists and the Risk of Cholangiocarcinoma (Lag 2 Years)

Exposure [a]	Events	Person-years	Incidence rate (95% CI) [b]	Crude HR	Adjusted HR (95% CI) [c]
Other second or third line antidiabetic drugs [d]	25	177,523	14.1 (9.1 to 20.8)	1.00	1.00 (reference)
DPP-4 inhibitors	17	74,007	23.0 (13.4 to 36.8)	1.52	1.62 (0.85 to 3.07)
GLP-1 receptor agonists	6	27,507	21.8 (8.0 to 47.5)	1.37	2.01 (0.79 to 5.16)

DPP-4=dipeptidyl peptidase-4; HR=hazard ratio; CI=confidence interval.

[a] Use of other anti-diabetic drugs was considered in the models, but not presented in the table.

[b] Per 100,000 Person-Years.

[c] Adjusted for age, sex, year of cohort entry, obesity, smoking status, alcohol-related disorders, Charlson comorbidity index score, inflammatory bowel disease, gallbladder disease, haemoglobin A1c, and duration of diabetes.

[d] Including initiating on combination therapy or switching to or adding-on a new antidiabetic drug class.

Supplementary Table 5. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors and GLP-1 Receptor Agonists and the Risk of Cholangiocarcinoma (Lag 3 Years)

Exposure [a]	Events	Person-years	Incidence rate (95% CI) [b]	Crude HR	Adjusted HR (95% CI) [c]
Other second or third line antidiabetic drugs [d]	25	137,376	18.2 (11.8 to 26.9)	1.00	1.00 (reference)
DPP-4 inhibitors	12	50,795	18.5 (8.0 to 36.4)	1.23	1.31 (0.64 to 2.68)
GLP-1 receptor agonists	6	19,533	23.6 (12.2 to 41.3)	1.54	2.38 (0.92 to 6.20)

DPP-4=dipeptidyl peptidase-4; HR=hazard ratio; CI=confidence interval.

[a] Use of other anti-diabetic drugs was considered in the models, but not presented in the table.

[b] Per 100,000 Person-Years.

[c] Adjusted for age, sex, year of cohort entry, obesity, smoking status, alcohol-related disorders, Charlson comorbidity index score, inflammatory bowel disease, gallbladder disease, haemoglobin A1c, and duration of diabetes.

[d] Including initiating on combination therapy or switching to or adding-on a new antidiabetic drug class.

Supplementary Table 6. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors and GLP-1 Receptor Agonists and the Risk of Cholangiocarcinoma (No Lag)

Exposure [a]	Events	Person-years	Incidence rate (95% CI) [b]	Crude HR	Adjusted HR (95% CI) [c]
Other second or third line antidiabetic drugs [d]	43	276,167	15.6 (11.3 to 21.0)	1.00	1.00 (reference)
DPP-4 inhibitors	33	139,792	23.6 (16.2 to 33.2)	1.49	1.48 (0.92 to 2.37)
GLP-1 receptor agonists	7	48,214	14.5 (5.8 to 29.9)	0.90	1.42 (0.62 to 3.27)

DPP-4=dipeptidyl peptidase-4; HR=hazard ratio; CI=confidence interval.

[a] Use of other anti-diabetic drugs was considered in the models, but not presented in the table.

[b] Per 100,000 Person-Years.

[c] Adjusted for age, sex, year of cohort entry, obesity, smoking status, alcohol-related disorders, Charlson comorbidity index score, inflammatory bowel disease, gallbladder disease, haemoglobin A1c, and duration of diabetes.

[d] Including initiating on combination therapy or switching to or adding-on a new antidiabetic drug class.

Supplementary Table 7. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors and GLP-1 Receptor Agonists and the Risk of Cholangiocarcinoma (Competing Risk)

Exposure [a]	Events	Person-years	Incidence rate (95% CI) [b]	Crude HR	Adjusted HR (95% CI) [c]
Other second or third line antidiabetic drugs [d]	33	223,531	14.8 (10.2 to 20.7)	1.00	1.00 (reference)
DPP-4 inhibitors	27	103,362	26.1 (17.2 to 38.0)	1.75	1.86 (1.08 to 3.19)
GLP-1 receptor agonists	7	37,041	18.9 (7.6 to 38.9)	1.27	2.07 (0.87 to 4.95)

DPP-4=dipeptidyl peptidase-4; HR=hazard ratio; CI=confidence interval.

[a] Use of other anti-diabetic drugs was considered in the models, but not presented in the table.

[b] Per 100,000 Person-Years.

[c] Adjusted for age, sex, year of cohort entry, obesity, smoking status, alcohol-related disorders, Charlson comorbidity index score, inflammatory bowel disease, gallbladder disease, haemoglobin A1c, and duration of diabetes.

[d] Including initiating on combination therapy or switching to or adding-on a new antidiabetic drug class.

Supplementary Table 8. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors and GLP-1 Receptor Agonists and the Risk of Cholangiocarcinoma (Four Prescriptions within a 12-Month Period)

Exposure [a]	Events	Person-years	Incidence rate (95% CI) [b]	Crude HR	Adjusted HR (95% CI) [c]
Other second or third line antidiabetic drugs [d]	33	223,531	14.8 (10.2 to 20.7)	1.00	1.00 (reference)
DPP-4 inhibitors	22	85,922	25.6 (16.0 to 38.8)	1.69	1.77 (1.01 to 3.11)
GLP-1 receptor agonists	7	30,475	23.0 (9.2 to 47.3)	1.46	2.46 (1.04 to 5.85)

DPP-4=dipeptidyl peptidase-4; HR=hazard ratio; CI=confidence interval.

[a] Use of other anti-diabetic drugs was considered in the models, but not presented in the table.

[b] Per 100,000 Person-Years.

[c] Adjusted for age, sex, year of cohort entry, obesity, smoking status, alcohol-related disorders, Charlson comorbidity index score, inflammatory bowel disease, gallbladder disease, haemoglobin A1c, and duration of diabetes.

[d] Including initiating on combination therapy or switching to or adding-on a new antidiabetic drug class.

Supplementary Table 9. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors and GLP-1 Receptor Agonists and the Risk of Cholangiocarcinoma (Marginal Structural Model)

Exposure [a]	Events	Person-months	Incidence rate (95% CI) [b]	Crude HR in weighted model	Adjusted HR in weighted model (95% CI) [c]
Other second or third line antidiabetic drugs [d]	33	2,750,036	1.2 (0.8 to 1.7)	1.00	1.00 (reference)
DPP-4 inhibitors	27	1,283,048	2.1 (1.4 to 3.1)	1.65	1.72 (0.95 to 3.11)
GLP-1 receptor agonists	7	459,201	1.5 (0.6 to 3.1)	1.10	1.80 (0.73 to 4.43)

DPP-4=dipeptidyl peptidase-4; HR=hazard ratio; CI=confidence interval.

[a] Use of other anti-diabetic drugs was considered in the models, but not presented in the table.

[b] Per 100,000 Person-Years.

[c] Adjusted for age, sex, year of cohort entry, obesity, smoking status, alcohol-related disorders, Charlson comorbidity index score, inflammatory bowel disease, gallbladder disease, haemoglobin A1c, and duration of diabetes.

[d] Including initiating on combination therapy or switching to or adding-on a new antidiabetic drug class.

Supplementary Table 10. Crude and Adjusted Hazard Ratios for the Association between the Use of Insulin and the Risk of Cholangiocarcinoma (Negative Control Exposure)

Exposure [a]	Events	Person-years	Incidence rate (95% CI) [b]	Crude HR	Adjusted HR (95% CI) [c]
Other second or third line antidiabetic drugs [d]	25	171,359	14.6 (9.4 to 21.5)	1.00	1.00 (reference)
Insulin	6	43,108	13.9 (5.1 to 30.3)	0.93	0.89 (0.36 to 2.19)

DPP-4=dipeptidyl peptidase-4; HR=hazard ratio; CI=confidence interval.

[a] Use of other anti-diabetic drugs was considered in the models, but not presented in the table.

[b] Per 100,000 Person-Years.

[c] Adjusted for age, sex, year of cohort entry, obesity, smoking status, alcohol-related disorders, Charlson comorbidity index score, inflammatory bowel disease, gallbladder disease, haemoglobin A1c, and duration of diabetes.

[d] Including initiating on combination therapy or switching to or adding-on a new antidiabetic drug class.

Supplementary Table 11. Baseline Characteristics of the Propensity Score-Matched Analysis. Values are numbers (percentages) unless stated otherwise

Characteristics	DPP-4 inhibitors (n=30,408)	Other second or third line drugs (n=30,408)	Standardized difference
Mean (SD) age (years)	64.9 (11.0)	65.0 (11.0)	0.01
Men	17,804 (58.6)	17,778 (58.5)	0.00
Year of cohort entry			
2007	275 (0.9)	275 (0.9)	0.00
2008	1291 (4.3)	1291 (4.3)	0.00
2009	3318 (10.9)	3318 (10.9)	0.00
2010	5482 (18.0)	5482 (18.0)	0.00
2011	4777 (15.7)	4777 (15.7)	0.00
2012	4204 (13.8)	4204 (13.8)	0.00
2013	3425 (11.3)	3425 (11.3)	0.00
2014	2865 (9.4)	2865 (9.4)	0.00
2015	2466 (8.1)	2466 (8.1)	0.00
2016	1966 (6.5)	1966 (6.5)	0.00
2017	339 (1.1)	339 (1.1)	0.00
Body mass index, kg/m^2:			
< 30	12,426 (40.9)	12,457 (41.0)	0.00
≥30.0	17,907 (58.9)	17,876 (58.8)	0.00
Unknown	75 (0.3)	75 (0.3)	0.00
Smoking status:			
Ever	19,417 (63.9)	19,345 (63.6)	0.00
Never	10,968 (36.1)	11,037 (36.3)	0.00
Unknown	23 (0.1)	26 (0.1)	0.00
Alcohol related disorders	5613 (18.5)	5606 (18.4)	0.00
Mean (SD) Charlson comorbidity index score score	2.7 (1.8)	2.7 (1.9)	0.01
Inflammatory bowel disease	455 (1.5)	452 (1.5)	0.00
Gallbladder disease, n (%)	1031 (3.4)	1024 (3.4)	0.00
Glycated haemoglobin (HbA1c) (%):			
≤7.0%	2386 (7.9)	2437 (8.0)	0.01
>7.0%	27,839 (91.5)	27,812 (91.5)	0.00
Unknown	183 (0.6)	159 (0.5)	0.01
Mean (SD) duration of diabetes (years)	7.5 (5.6)	7.4 (5.7)	0.02

SD=standard deviation; DPP-4=dipeptidyl peptidase-4

Supplementary Table 12. Propensity Score-Matched Analysis Comparing New Users of DPP-4 Inhibitors Versus New Users of Other Second or third Line Antidiabetic Drugs and the Risk of Cholangiocarcinoma

Exposure	Number of patients	Events	Person-years	Incidence rate (95% CI) [a]	HR
Other second or third line antidiabetic drugs [b]	30,408	12	76,216	15.7 (8.1 to 27.5)	1.00 (reference)
DPP-4 inhibitors	30,408	24	89,691	26.8 (17.1 to 39.8)	1.71 (0.86 to 3.43)

DPP-4=dipeptidyl peptidase-4; HR=hazard ratio; CI=confidence interval.

[a] Per 100,000 Person-Years.

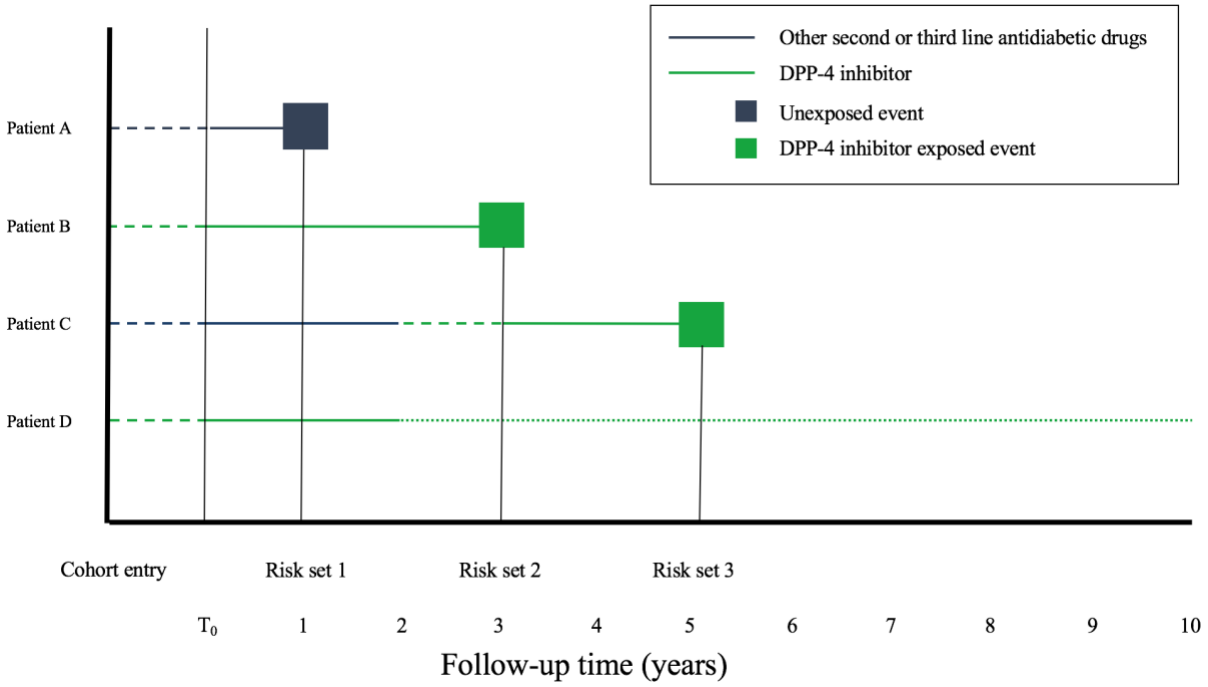
[b] Including initiating on combination therapy or switching to or adding-on a new antidiabetic drug class.

Supplementary Table 13. Impact of Imperfect Sensitivity and Specificity on the Association between the Use of DPP-4 Inhibitors and the Risk of Cholangiocarcinoma

Rate Ratios*	**Sensitivity (Se)**					
Specificity (Sp)	**0.50**	**0.60**	**0.70**	**0.80**	**0.90**	**1.00**
0.5	1.00	1.57	1.66	1.69	1.71	1.72
0.6	1.61	1.68	1.71	1.72	1.73	1.74
0.7	1.70	1.72	1.73	1.74	1.74	1.75
0.8	1.74	1.74	1.75	1.75	1.75	1.76
0.9	1.76	1.76	1.76	1.76	1.76	1.76
1.00	1.77	1.77	1.77	1.77	1.77	1.77

$$* \; Rate\ Ratio = \frac{P(Y=1|X=1)*Se(Y)+\left(1-P(Y=1|X=1)\right)*(1-Sp(Y))}{P(Y=1|X=0)*Se(Y)+\left(1-P(Y=1|X=0)\right)*(1-Sp(Y))}$$

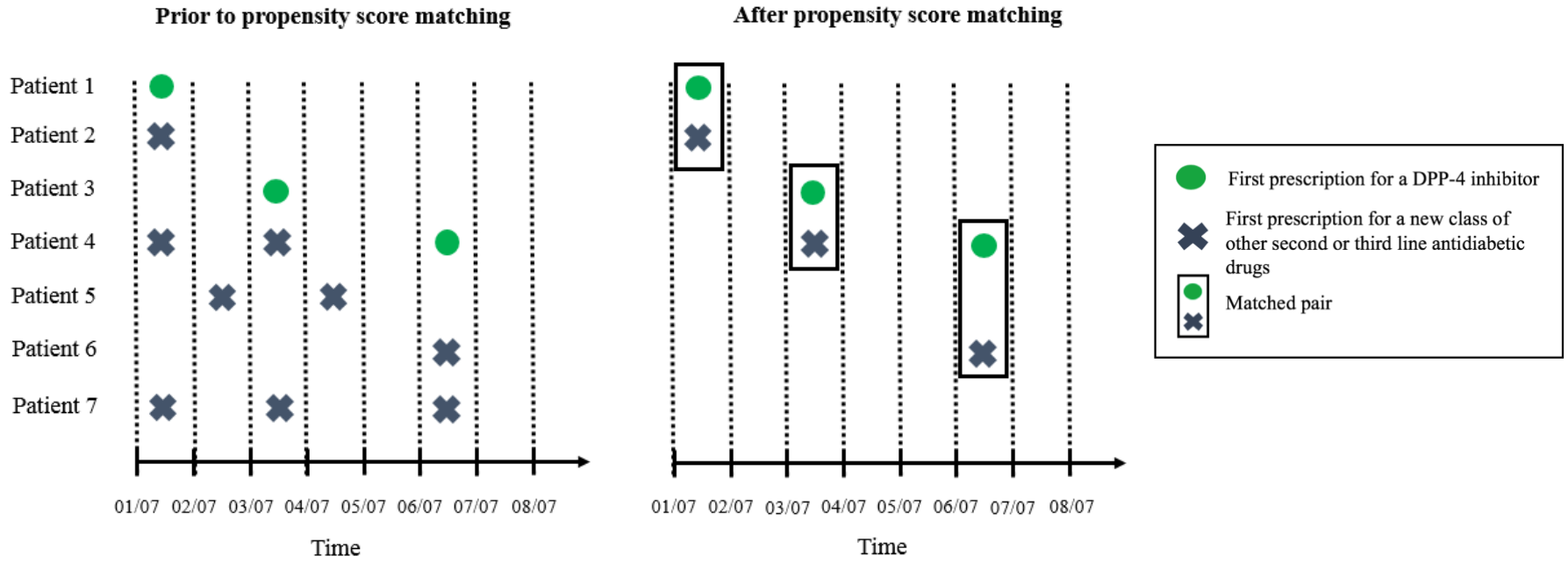
Supplementary Figure 1. Exposure Definition



Supplementary Figure 1 summarizes the exposure definition. The dashed lines represent the one-year lag period applied after each new antidiabetic prescription; patients were considered exposed to each new antidiabetic drug starting one year after their initial prescription. The solid lines represent the exposure periods. The dotted line (in green) represents the period after discontinuation of an incretin-based drug, whereby patients remain exposed until the end of the follow-up period. Finally, each event date forms a risk set, where exposure to the different antidiabetic drugs is assessed at these time points.

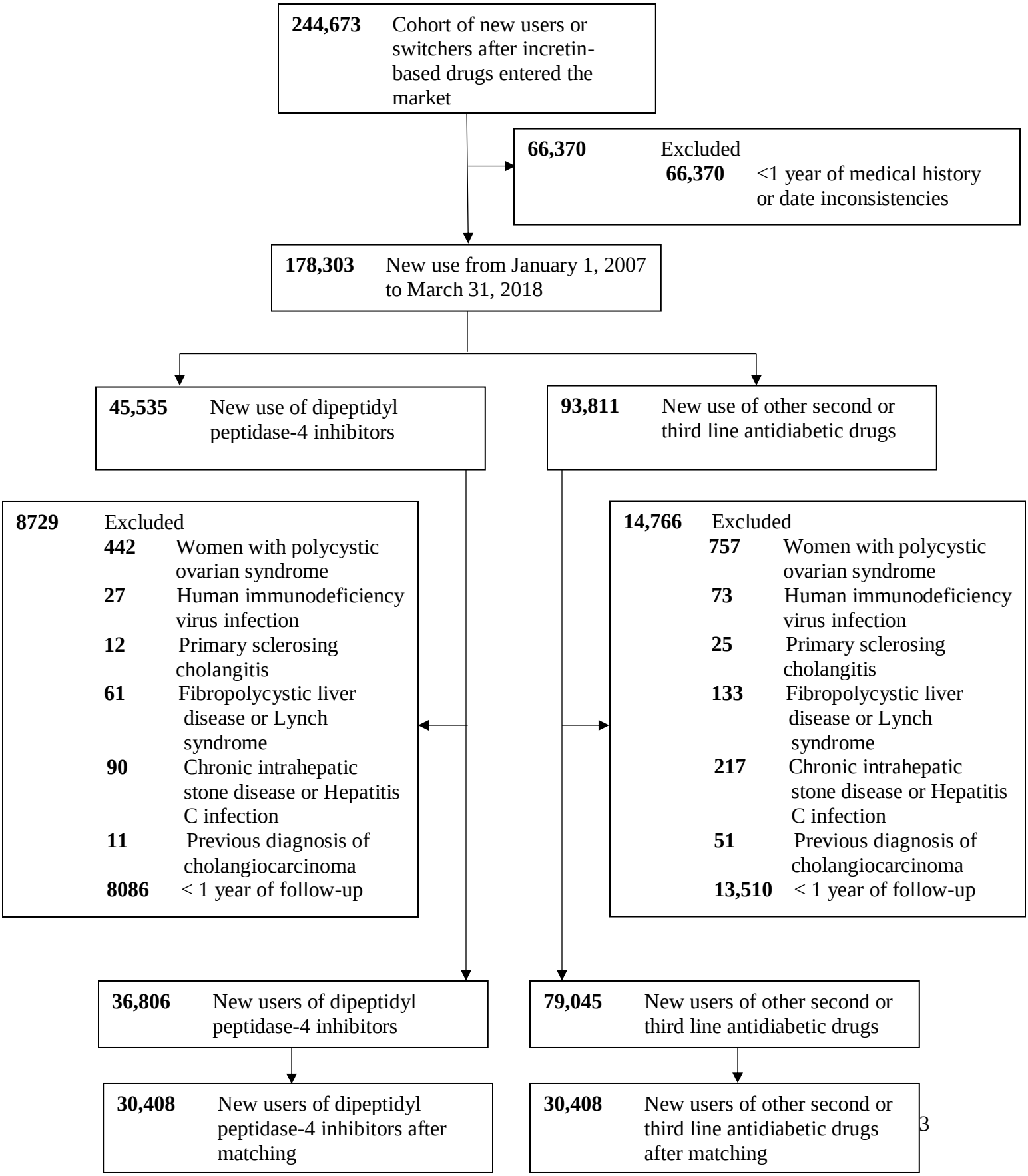
In the scenario above, Patient A is exposed to a second or third line antidiabetic drug (other than an incretin-based drug) and contributes an unexposed event (risk set 1) after one year of follow up. At this point, this patient's exposure is compared with the exposure of Patient B (DPP-4 inhibitors), Patient C (use of other second or third line antidiabetic drugs) and Patient D (DPP-4 inhibitors). Patient C contributes both unexposed and exposed person time to the analysis. When this patient experiences the event (risk set 3), they contribute an exposed event to the DPP-4 inhibitor analysis. At this time, the exposure of Patient C is compared with the exposure of Patient D (DPP-4 inhibitor). While Patient D had discontinued use of DPP-4 inhibitors at year 2 of follow-up, they are considered exposed until the end of follow-up. We used a similar exposure definition for the GLP-1 receptor agonist analysis.

Supplementary Figure 2: Illustration of the Propensity Score-Matched Analysis

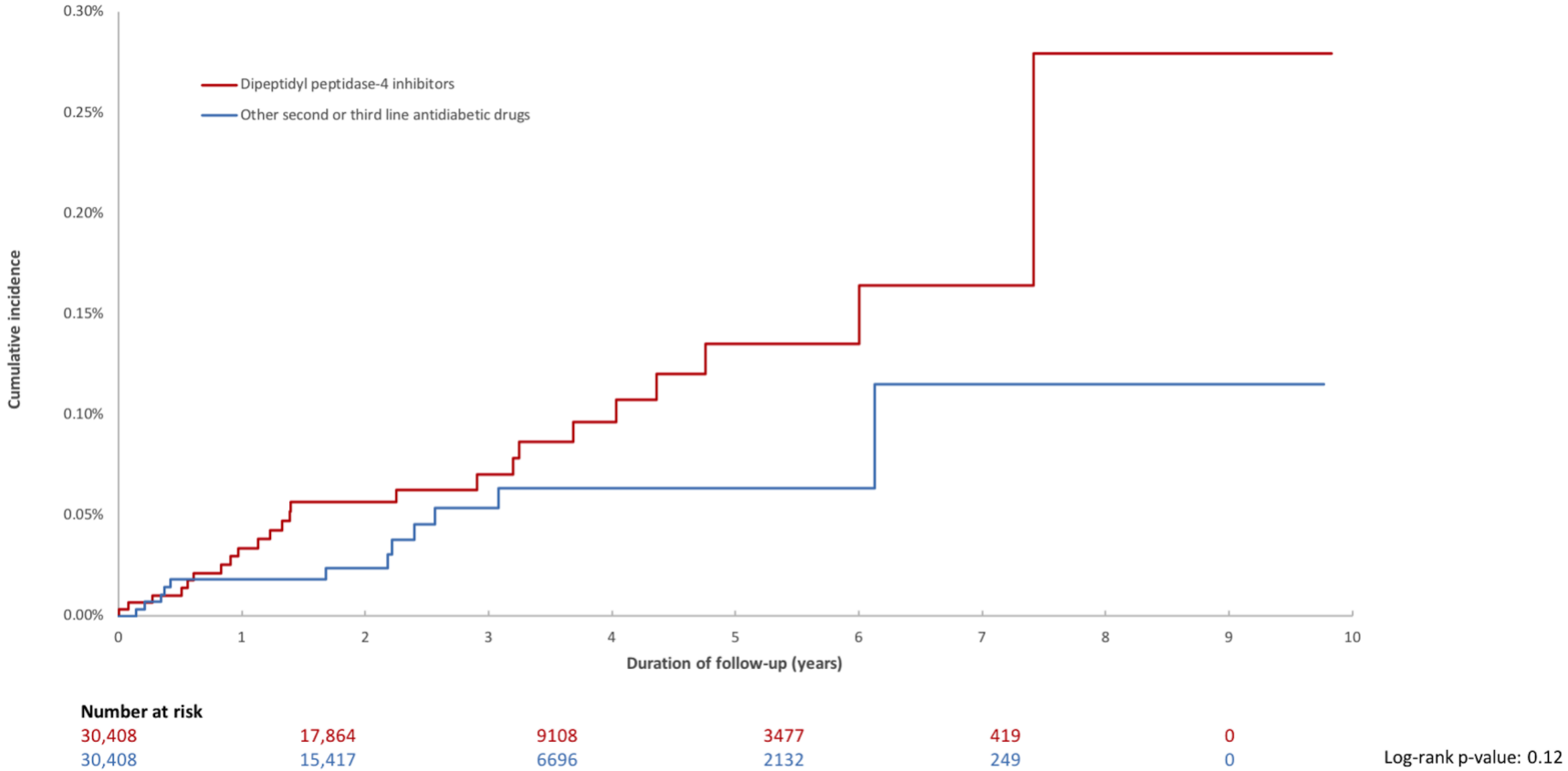


In each of the 123 months of the patient accrual period (January 1, 2007 to March 31, 2017), new users of DPP-4 inhibitors (exposed group) were matched 1:1 to new users of other second- to third-line antidiabetic drugs (comparator group) on propensity scores. For example, in January 2007 patient 1 could be matched to patient 2, 4 or 7; the patient with the closest propensity score with a maximum calliper of 0.01 could become a match. Patients in the comparator group eventually adding on or switching to a DPP-4 inhibitor could contribute to the DPP-4 inhibitor group, but only after the time of switch. For example, patient 4 stopped contributing to the comparator group and started contributing to the DPP-4 inhibitor group after June 2007 (and was matched on propensity score to patient 6 from the comparator group in the same month).

Supplementary Figure 3: Flow Chart of Patients Included in the Propensity Score-Matched Analysis

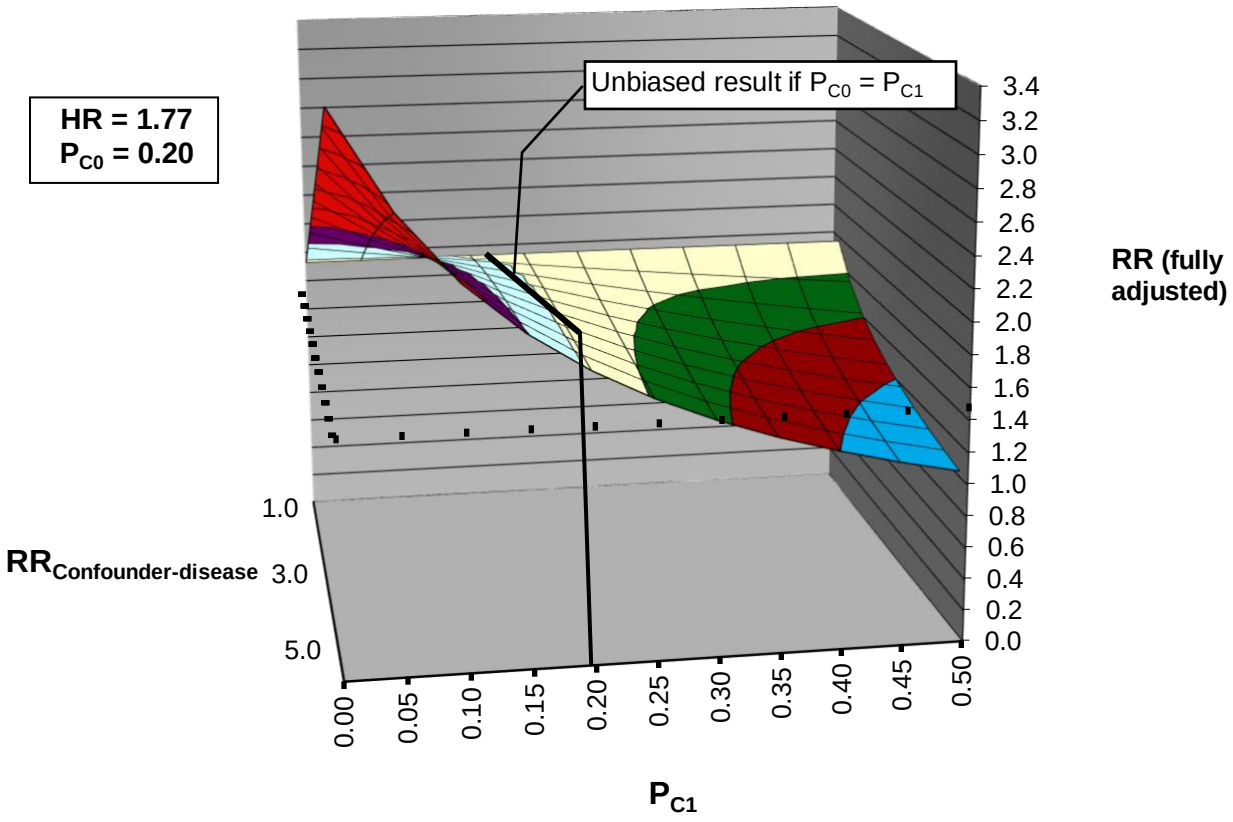


Supplementary Figure 4: Cumulative Incidence of Incident Cholangiocarcinoma Among Users of Dipeptidyl Peptidase-4 Inhibitors and Other Second- to Third-Line Antidiabetic Drugs (Propensity Score- Matched Analysis)



Cumulative incidence curves of cholangiocarcinoma among users of dipeptidyl peptidase-4 inhibitors and other second or third line antidiabetic drugs. Duration of follow-up is in addition to the one-year lag imposed at cohort entry. Thus, the curves begin to diverge after two years of follow-up.

Supplementary Figure 5: Array Approach to Quantify the Effect of Unmeasured Confounding



We used the Array approach to estimate the effect of an unknown or unmeasured confounder on our observed estimate.[15] We fixed the prevalence of a hypothetical confounder in the reference group (use of at least two antidiabetic drug classes) to 0.2 and varied the strength of the confounder-disease association (1.0 to 5.5) and the prevalence of the confounder in the group exposed to DPP-4 inhibitors (0.0 to 0.5). The relationship between these three factors is plotted in the three-dimensional graph above.

If the hypothetical confounder is equally distributed among the group exposed to DPP-4 inhibitors and the reference group, there is no bias. If the confounder is imbalanced between the two groups, the estimate will change from the observed HR. Thus, if the prevalence of the confounder in the DPP-4 inhibitor group is less than the prevalence of the confounder in the reference group, the "true" HR would be higher than the observed HR. However, if the prevalence of the confounder in the DPP-4 inhibitor group is higher than the prevalence of the confounder in the reference group, the "true" HR would be lower than the observed HR. This would require the confounder to be strongly associated with the outcome, with RR estimates ranging from 3.0 to 5.5. It is unlikely that such a confounder exists beyond what was adjusted for in the analyses.

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