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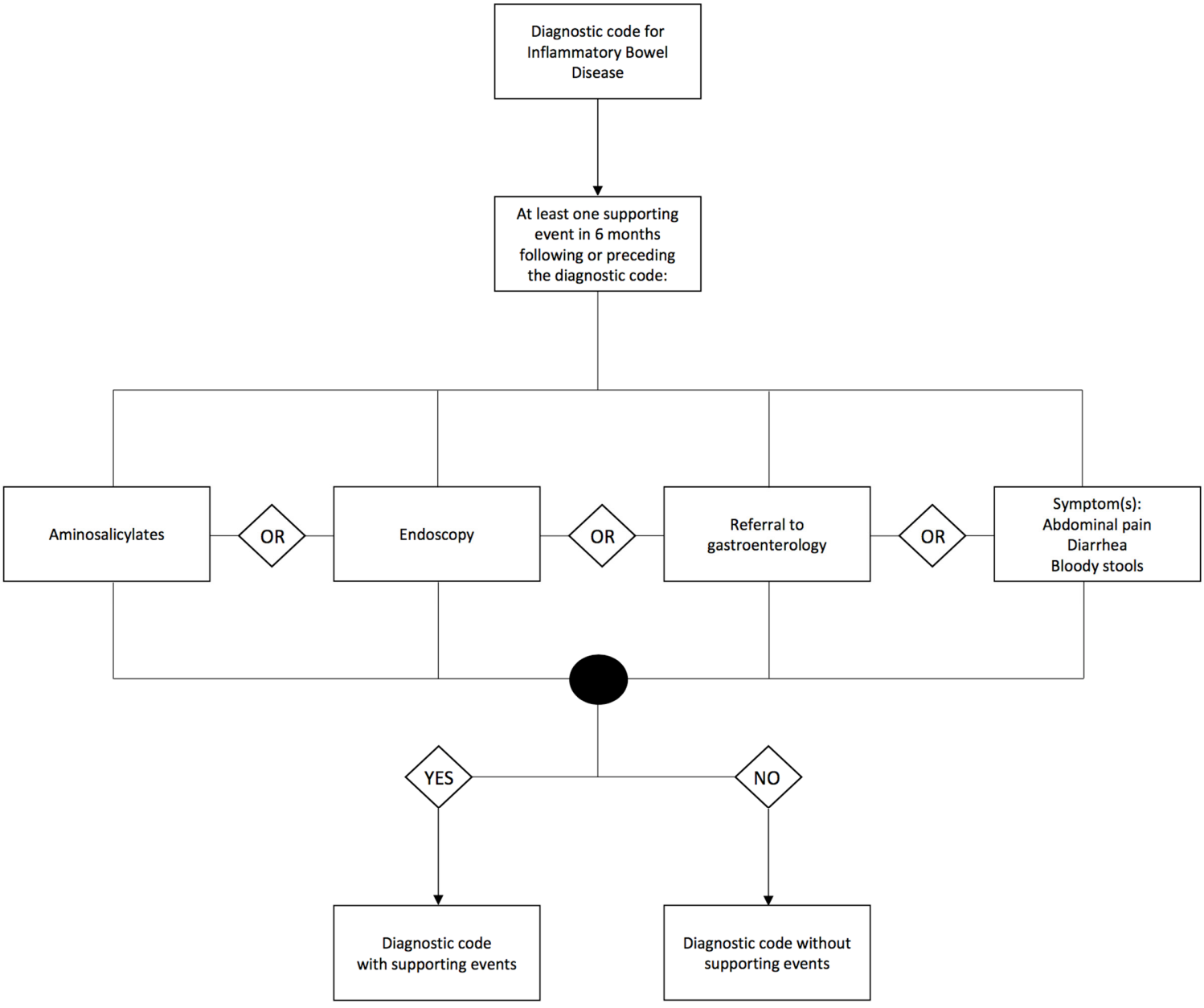
Supplementary Methods 1: Algorithm Used to Identify Supported Inflammatory Bowel Disease

We examined the validity of the outcome definition (inflammatory bowel disease (IBD), identified using Read codes) using the algorithm below. In this algorithm, IBD events qualified as an outcome only if they were accompanied by at least one supporting event in the 6 months preceding or following the IBD code. These consisted of prescriptions for aminosalicylates, referrals for endoscopy, referrals to gastroenterology, or IBD-related symptoms (abdominal pain, diarrhea or bloody stools). In the event that the date of a supporting code was before the date of the IBD diagnostic code, the index date became the date of the supporting code. Thus, we estimated hazard ratios of IBD with clinically-supporting events, comparing the use of DPP-4 inhibitors with use of other antidiabetic drugs, using a time-dependent Cox proportional hazards model (adjusted for confounders listed in the manuscript).



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.[1] [2] 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 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.[3] 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 IBD associated with the use of DPP-4 inhibitors, with 95% confidence intervals calculated using robust variance estimators.[2]

References

1. Robins, J., Hernán, M., & Brumback, B. (2000). Marginal Structural Models and Causal Inference in Epidemiology. *Epidemiology, 11*(5), 550-560.
2. Hernán, M. Á., Brumback, B., & Robins, J. M. (2000). Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology*, *11*(5), 561-570.
3. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol 2008;168:656-64.

Supplementary Methods 3: Disease Risk Score Method

To address residual confounding, we employed a disease risk score (DRS) analysis, used as an alternative to the propensity score method.[1 2] To fit the DRS, we constructed a historical cohort[3] using data from the United Kingdom Clinical Practice Research Datalink, from January 1, 1997 to December 31, 2006 (before DPP-4 inhibitors were available). To enter the historical cohort, patients were required to have a new prescription for a non-insulin antidiabetic drug. All exclusions listed for the study cohort in the manuscript were applied to the historical cohort. As DPP-4 inhibitors were not available during the historical cohort, the DRS estimated the probability of IBD conditional on being unexposed to DPP-4 inhibitors. To calculate the DRS, we fitted a Cox proportional hazards model including all potential confounders (listed in the manuscript) and baseline exposure. The DRS was then applied to the study cohort to calculate the probability of IBD conditional on being unexposed to DPP-4 inhibitors. Stratified on deciles, the DRS was used as a summary statistic in place of all individual potential confounders to estimate hazard ratios of incident IBD associated with the use of DPP-4 inhibitors.

References

1. Arbogast, P. G., & Ray, W. A. (2011). Performance of disease risk scores, propensity scores, and traditional multivariable outcome regression in the presence of multiple confounders. *American journal of epidemiology*, *174*(5), 613-620.
2. Arbogast, P. G., & Ray, W. A. (2009). Use of disease risk scores in pharmacoepidemiologic studies. *Stat Methods Med Res* 18(1), 67–80, 2009.
3. Glynn RJ, Gagne JJ, Schneeweiss S. Role of disease risk scores in comparative effectiveness research with emerging therapies. *Pharmacoepidemiol Drug Saf*. 2012;21:138–47.

Supplementary Methods 4: Multiple Imputation

We repeated the primary analysis using multiple imputation for variables with incomplete data (i.e. missing values for haemoglobin A1c, BMI and smoking).[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 at cohort entry and all confounders listed in the manuscript. Using Rubin's rules, we combined the results of ten imputations to estimate the value of missing variables.[4]

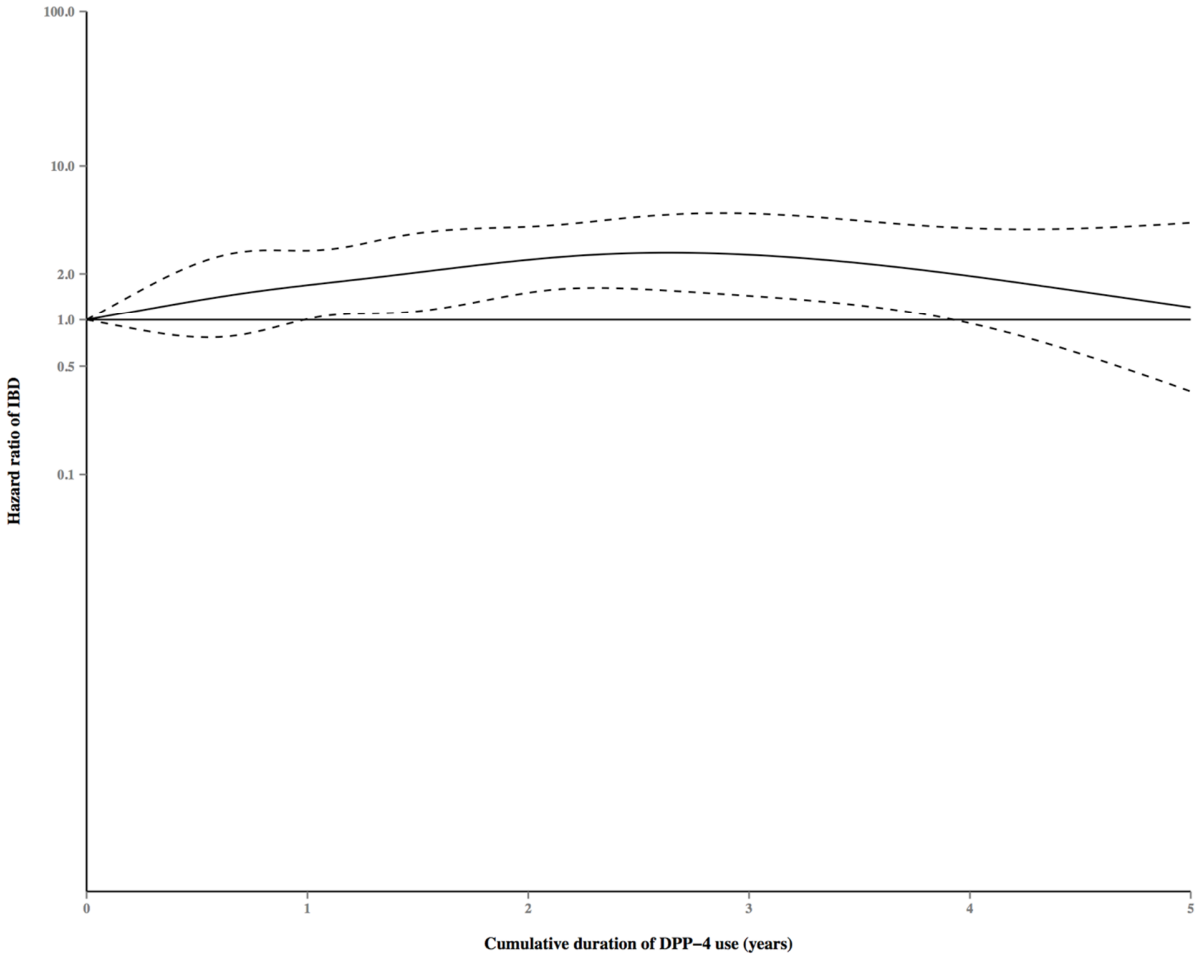
References

1. Schafer, J. L. (1997). *Analysis of incomplete multivariate data*. CRC press.
2. Rubin, D. B. (1987). Multiple Imputation for Nonresponse in Surveys Hoboken, NJ, USA, John Wiley & Sons, Inc.
3. White, I. R., & Royston, P. (2009). Imputing missing covariate values for the Cox model. *Stat Med*, *28*(15), 1982-1998.
4. Sterne, J. A., White, I. R., Carlin, J. B., Spratt, M., Royston, P., Kenward, M. G., ... & Carpenter, J. R. (2009). Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *Bmj*, *338*, b2393.

Supplementary Methods 5: Head-to-head Comparison of DPP-4 Inhibitors versus Insulin

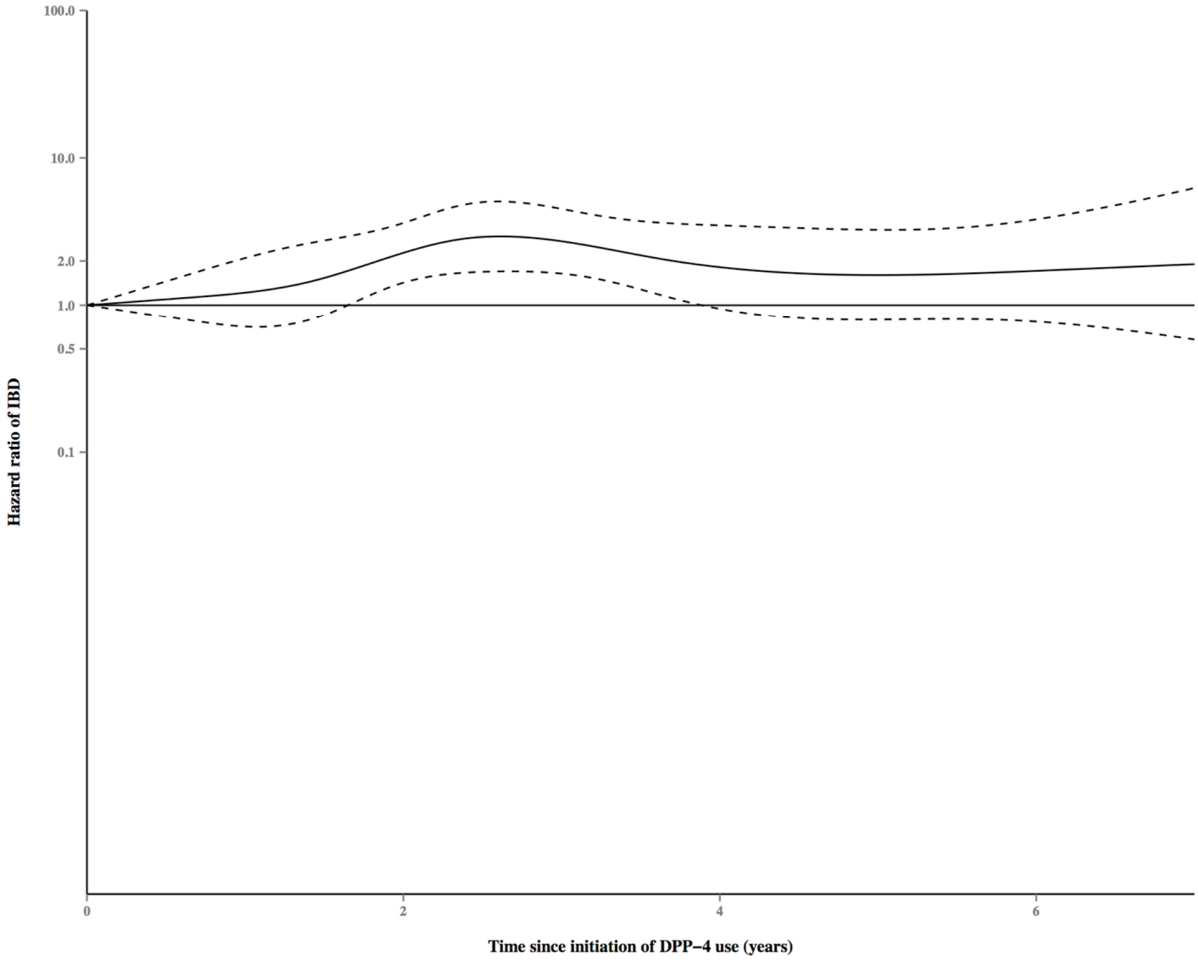
We conducted a head-to-head comparison of DPP-4 inhibitors versus insulin to further address the potential impact of confounding by indication. Using the study cohort described above, we assembled a subcohort of patients newly-treated with either DPP-4 inhibitors or insulin between January 1, 2007 and December 31, 2016. Patients with a history of insulin use prior to 2007 were excluded. Cohort entry corresponded to the date of either the first DPP-4 inhibitor or insulin prescription. As with the primary analysis, patients with a history of IBD, diverticulitis, ischaemic colitis, pseudo-membranous colitis or unspecified colitis, as well as those with prescriptions for mesalamine were excluded. Finally, patients with less than 6 months of follow-up after cohort entry were excluded. Patients were followed starting 6 months after cohort entry until an incident diagnosis of IBD, or censored on death from any cause, switching from a DPP-4 inhibitor to insulin or from insulin to a DPP-4 inhibitor, end of registration with the general practice, or end of the study period (June 30, 2017), whichever occurred first. Propensity scores were calculated as the predicted probability of receiving a DPP-4 inhibitor versus insulin conditional on the covariates listed previously. Patients in non-overlapping regions of the propensity score distributions were trimmed from the analysis. Finally, a Cox proportional hazards model stratified on propensity score quintiles was used to estimate the HR of IBD, comparing DPP-4 inhibitors with insulin.

Supplementary Figure A: Restricted Cubic Spline of Cumulative Duration of Dipeptidyl Peptidase-4 Inhibitor Use



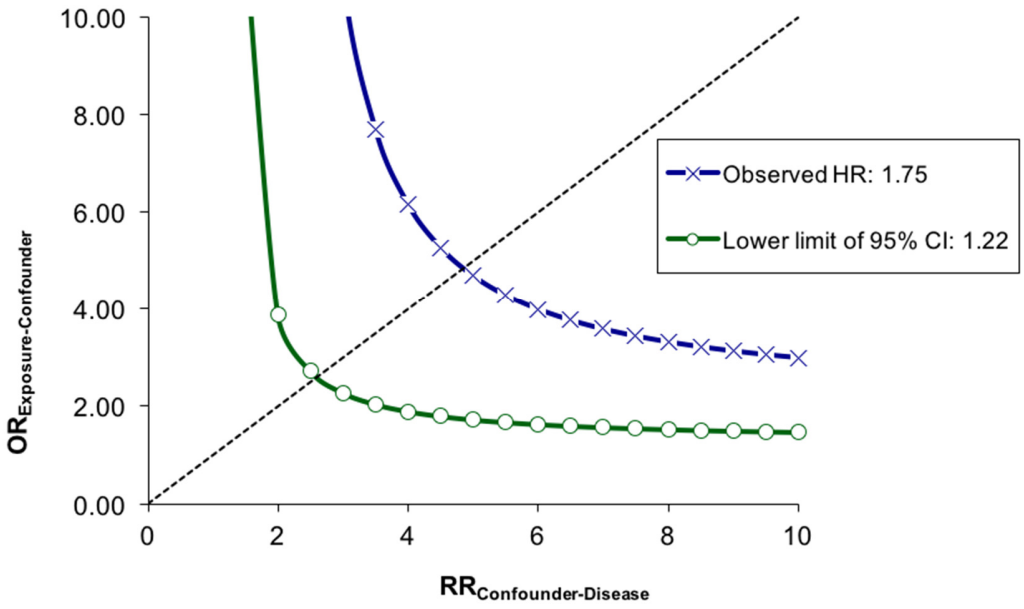
Smooth restricted spline curve of adjusted hazard ratio of inflammatory bowel disease (solid line) and 95% confidence limits (dashed lines) as function of cumulative duration of dipeptidyl peptidase-4 inhibitor use.

Supplementary Figure B: Restricted Cubic Spline of Time Since Dipeptidyl Peptidase-4 Inhibitor Initiation



Smooth restricted spline curve of adjusted hazard ratio of inflammatory bowel disease (solid line) and 95% confidence limits (dashed lines) as function of time since dipeptidyl peptidase-4 inhibitor initiation.

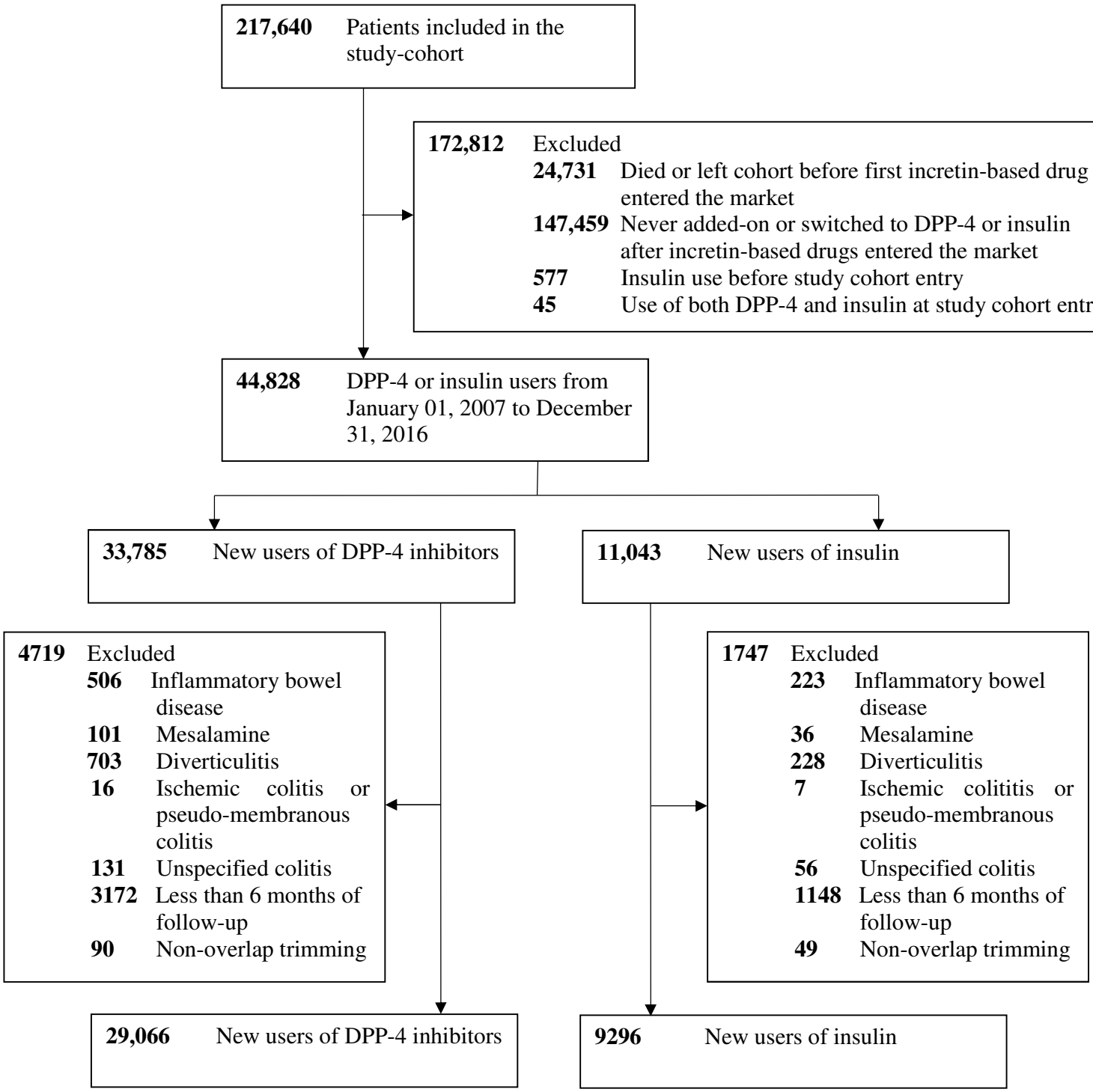
Supplementary Figure C: Strength of Unmeasured Confounder Required to Move the Hazard Ratio Towards the Null Using the Rule Out Method



Based on an observed hazard ratio (HR) of 1.75, a dipeptidyl peptidase-4 inhibitor exposure prevalence of 21.6% and a confounder prevalence of 20%. Blue line: observed HR Green line: lower bound of 95% confidence interval (CI). $OR_{Exposure\text{-}Confounder}$: odds ratio for the exposure-confounder association; $RR_{Confounder\text{-}Disease}$: relative risk for the confounder-disease association.

Exposure-confounder and confounder-disease associations to the right of the curves would be necessary to bring the association down to the null. Thus, a hypothetical confounder would need to be strongly associated with both the exposure (OR > 4.7) and the outcome (RR > 5.0) to affect the point estimate.

Supplementary Figure D: Flowchart for the Dipeptidyl Peptidase-4 Inhibitor and Insulin Head-to-head Comparison



Supplementary Table A: Read Codes for Inflammatory Bowel Disease	
Read Code	**Read Term**
J40..00	Regional enteritis - Crohn's disease
J40..11	Crohn's disease
J401z00	Crohn's disease of the large bowel NOS
J401z11	Crohn's colitis
J40z.11	Crohn's disease NOS
Jyu4000	[X]Other Crohn's disease
J41..12	Ulcerative colitis and/or proctitis
J410.00	Ulcerative proctocolitis
J410000	Ulcerative ileocolitis
J410100	Ulcerative colitis
J410z00	Ulcerative proctocolitis NOS
J411.00	Ulcerative (chronic) enterocolitis
J412.00	Ulcerative (chronic) ileocolitis
J413.00	Ulcerative pancolitis
Jyu4100	[X]Other ulcerative colitis
J436.00	Microscopic colitis
J436000	Collagenous colitis
J436100	Lymphocytic colitis
J4z6.00	Indeterminate colitis
J4...12	Inflammatory bowel disease

NOS=not otherwise specified.

Supplementary Table B: Algorithm for Inflammatory Bowel Disease: Cases Accompanied by Clinically-Relevant Supporting Events	
Number of supporting events	**N=208**
None, n (%)	**15 (7.2%)**
One, n (%)	**33 (15.9%)**
Symptoms	7
Referral to gastroenterology	10
Endoscopy	5
Use of aminosalicylates	11
Two, n (%)	**54 (26.0%)**
Symptoms, referral to gastroenterology	14
Symptoms, endoscopy	s‡
Symptoms, use of aminosalicylates	8
Referral to gastroenterology, endoscopy	7
Referral to gastroenterology, use of aminosalicylates	17
Endoscopy, use of aminosalicylates	s‡
Three, n (%)	**66 (31.7%)**
Symptoms, referral to gastroenterology, endoscopy	15
Symptoms, referral to gastroenterology, use of aminosalicylates	23
Symptoms, endoscopy, use of aminosalicylates	13
Referral to gastroenterology, endoscopy, use of aminosalicylates	15
Four, n (%)	**40 (19.2%)**
Symptoms, referral to gastroenterology, endoscopy, use of aminosalicylates,	40

‡Numbers <5 are not shown, as per confidentiality policies of Clinical Practice Research Datalink.

Supplementary Table C. Crude and Adjusted Hazard Ratios for the Association between the Use of Specific DPP-4 Inhibitors and the Risk of Inflammatory Bowel Disease

Exposure	Events	Person years	Incidence rate (95% CI)*	Hazard Ratio (95% CI)	
				Crude	Adjusted†
Use of other antidiabetic drugs	159	460 623	34.5 (29.4 to 40.3)	1.00	1.00 (reference)
Sitagliptin only	30	66 453	45.1 (30.5 to 64.4)	1.34	1.45 (0.95 to 2.21)
Saxagliptin only	6	9263	64.8 (23.8 to 141.0)	1.92	2.23 (0.98 to 5.12)
Other combinations	13	16 075	80.9 (43.1 to 138.3)	2.42	2.76 (1.53 to 4.99)

DPP-4=dipeptidyl peptidase-4. CI=confidence interval.

*Per 100 000 person years.

†Adjusted for age, sex, year of cohort entry, body mass index, alcohol related disorders (including alcoholism, alcoholic cirrhosis of liver, alcoholic hepatitis, and hepatic failure), smoking status, haemoglobin A_{1c}, microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (myocardial infarction, stroke, peripheral arteriopathy) complications of diabetes, duration of treated diabetes, antidiabetic drugs used before cohort entry, use of aspirin, non-steroidal anti-inflammatory drugs, hormonal replacement therapy, oral contraceptives, other autoimmune conditions, total number of unique non-diabetic drugs in year before cohort entry.

Supplementary Table D. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors and the Risk of Crohn's Disease, Ulcerative Colitis and Unspecified Disease

IBD type	Events	Person years	Incidence rate (95% CI)*	Hazard Ratio (95% CI)	
				Crude	Adjusted†
Crohn's disease					
Use of other antidiabetic drugs	37	460 623	8.0 (5.6 to 11.1)	1.00	1.00 (reference)
DPP-4 inhibitors	7	91 790	7.6 (3.1 to 15.7)	0.95	0.87 (0.37 to 2.09)
Ulcerative colitis					
Use of other antidiabetic drugs	73	460 623	15.8 (12.4 to 19.9)	1.00	1.00 (reference)
DPP-4 inhibitors	23	91 790	25.1 (15.9 to 37.6)	1.72	2.23 (1.32 to 3.76)
Unspecified disease					
Use of other antidiabetic drugs	49	460 623	10.6 (7.9 to 14.1)	1.00	1.00 (reference)
DPP-4 inhibitors	19	91 790	20.7 (12.5 to 32.3)	1.88	1.86 (1.03 to 3.36)

DPP-4=dipeptidyl peptidase-4. CI=confidence interval.
*Per 100 000 person years.
†Adjusted for age, sex, year of cohort entry, body mass index, alcohol related disorders (including alcoholism, alcoholic cirrhosis of liver, alcoholic hepatitis, and hepatic failure), smoking status, haemoglobin A_{1c}, microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (myocardial infarction, stroke, peripheral arteriopathy) complications of diabetes, duration of treated diabetes, antidiabetic drugs used before cohort entry, use of aspirin, non-steroidal anti-inflammatory drugs, hormonal replacement therapy, oral contraceptives, other autoimmune conditions, total number of unique non-diabetic drugs in year before cohort entry.

Supplementary Table E. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors lagged by 1 year and the Risk of Inflammatory Bowel Disease

Exposure	Events	Person years	Incidence rate (95% CI)*	Hazard Ratio (95% CI)	
				Crude	Adjusted†
Use of other antidiabetic drugs	143	406 686	35.2 (29.6 to 41.4)	1.00	1.00 (reference)
DPP-4 inhibitors	46	77 214	59.6 (43.6 to 79.5)	1.81	2.02 (1.39 to 2.93)

DPP-4=dipeptidyl peptidase-4. CI=confidence interval.

*Per 100 000 person years.

†Adjusted for age, sex, year of cohort entry, body mass index, alcohol related disorders (including alcoholism, alcoholic cirrhosis of liver, alcoholic hepatitis, and hepatic failure), smoking status, haemoglobin A_{1c}, microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (myocardial infarction, stroke, peripheral arteriopathy) complications of diabetes, duration of treated diabetes, antidiabetic drugs used before cohort entry, use of aspirin, non-steroidal anti-inflammatory drugs, hormonal replacement therapy, oral contraceptives, other autoimmune conditions, total number of unique non-diabetic drugs in year before cohort entry.

Supplementary Table F. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors and the Risk of Clinically Supported Inflammatory Bowel Disease

Exposure	Events	Person years	Incidence rate (95% CI)*	Hazard Ratio (95% CI)	
				Crude	Adjusted†
Use of other antidiabetic drugs	139	460 594	30.2 (25.4 to 35.6)	1.00	1.00 (reference)
DPP-4 inhibitors	45	91 781	49.0 (35.8 to 65.6)	1.71	1.94 (1.33 to 2.82)

DPP-4=dipeptidyl peptidase-4. CI=confidence interval.
*Per 100 000 person years.
†Adjusted for age, sex, year of cohort entry, body mass index, alcohol related disorders (including alcoholism, alcoholic cirrhosis of liver, alcoholic hepatitis, and hepatic failure), smoking status, haemoglobin A_{1c}, microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (myocardial infarction, stroke, peripheral arteriopathy) complications of diabetes, duration of treated diabetes, antidiabetic drugs used before cohort entry, use of aspirin, non-steroidal anti-inflammatory drugs, hormonal replacement therapy, oral contraceptives, other autoimmune conditions, total number of unique non-diabetic drugs in year before cohort entry.

Supplementary Table G. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors and the Risk of Inflammatory Bowel Disease using a Sub-distribution Hazard

Exposure	Events	Person years	Incidence rate (95% CI)*	Sub-distribution Hazard Ratio (95% CI)	
				Crude	Adjusted†
Use of other antidiabetic drugs	159	460 623	34.5 (29.4 to 40.3)	1.00	1.00 (reference)
DPP-4 inhibitors	49	91 790	53.4 (39.5 to 70.6)	1.62	1.78 (1.24 to 2.56)

DPP-4=dipeptidyl peptidase-4. CI=confidence interval.
*Per 100 000 person years.
†Adjusted for age, sex, year of cohort entry, body mass index, alcohol related disorders (including alcoholism, alcoholic cirrhosis of liver, alcoholic hepatitis, and hepatic failure), smoking status, haemoglobin A_{1c}, microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (myocardial infarction, stroke, peripheral arteriopathy) complications of diabetes, duration of treated diabetes, antidiabetic drugs used before cohort entry, use of aspirin, non-steroidal anti-inflammatory drugs, hormonal replacement therapy, oral contraceptives, other autoimmune conditions, total number of unique non-diabetic drugs in year before cohort entry.

Supplementary Table H. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors and the Risk of Inflammatory Bowel Disease by Interaction with Age Group

	Age less than 60	**Age 60 and above**
Use of other antidiabetic drugs	1.00 (reference)	1.00 (reference)
DPP-4 inhibitors	1.68 (1.03 to 2.72)	1.86 (1.16 to 3.00)
		p-interaction: 0.75

DPP-4=dipeptidyl peptidase-4. CI=confidence interval.

Supplementary Table I. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors‡ and the Risk of Inflammatory Bowel Disease

Exposure	Events	Person years	Incidence rate (95% CI)*	Hazard Ratio (95% CI)	
				Crude	Adjusted†
Use of other antidiabetic drugs	161	478 347	33.7 (28.7 to 39.3)	1.00	1.00 (reference)
DPP-4 inhibitors	47	74 066	63.5 (46.6 to 84.4)	1.97	2.21 (1.54 to 3.18)

DPP-4=dipeptidyl peptidase-4. CI=confidence interval.

*Per 100 000 person years.

†Adjusted for age, sex, year of cohort entry, body mass index, alcohol related disorders (including alcoholism, alcoholic cirrhosis of liver, alcoholic hepatitis, and hepatic failure), smoking status, haemoglobin A_{1c}, microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (myocardial infarction, stroke, peripheral arteriopathy) complications of diabetes, duration of treated diabetes, antidiabetic drugs used before cohort entry, use of aspirin, non-steroidal anti-inflammatory drugs, hormonal replacement therapy, oral contraceptives, other autoimmune conditions, total number of unique non-diabetic drugs in year before cohort entry.

‡Exposure defined by receiving 4 prescriptions within a 12-month moving window.

Supplementary Table J. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors[‡] and the Risk of Inflammatory Bowel Disease

Exposure [a]	Events	Person years	Incidence rate (95% CI)*	Hazard Ratio (95% CI)	
				Crude	Adjusted†
Use of other antidiabetic drugs	153	445 478	34.3 (29.1 to 40.2)	1.00	1.00 (reference)
DPP-4 inhibitors	43	80 057	53.7 (38.9 to 72.3)	1.60	1.78 (1.23 to 2.59)
GLP-1 receptor agonists	6	15 145	39.6 (14.5 to 86.2)	1.18	1.18 (0.50 to 2.83)
DPP-4 inhibitors and GLP-1 receptor agonists	6	11 733	51.1 (18.8 to 111.3)	1.57	1.66 (0.70 to 3.92)

DPP-4=dipeptidyl peptidase-4. CI=confidence interval.
*Per 100 000 person years.
†Adjusted for age, sex, year of cohort entry, body mass index, alcohol related disorders (including alcoholism, alcoholic cirrhosis of liver, alcoholic hepatitis, and hepatic failure), smoking status, haemoglobin A_{1c}, microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (myocardial infarction, stroke, peripheral arteriopathy) complications of diabetes, duration of treated diabetes, antidiabetic drugs used before cohort entry, use of aspirin, non-steroidal anti-inflammatory drugs, hormonal replacement therapy, oral contraceptives, other autoimmune conditions, total number of unique non-diabetic drugs in year before cohort entry.
‡Four mutually exclusive categories are created: DPP-4 inhibitors (alone or in combination with other antidiabetic drugs other than GLP-1 receptor agonists), use of GLP-1 receptor agonists (alone or in combination with other antidiabetic drugs other than DPP-4 inhibitors), use of both DPP-4 inhibitors and GLP-1 receptor agonists, and finally use of all other antidiabetic drugs. All categories are considered in the model, but not all presented in the table.

Supplementary Table K. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors‡ and the Risk of Inflammatory Bowel Disease

Exposure	Events	Person years	Incidence rate (95% CI)*	Hazard Ratio (95% CI)	
				Crude	Adjusted†
Use of other antidiabetic drugs	141	396 565	35.6 (29.9 to 41.9)	1.00	1.00 (reference)
DPP-4 inhibitors	31	62 676	49.5 (33.6 to 70.2)	1.48	1.60 (1.04 to 2.45)

DPP-4=dipeptidyl peptidase-4. CI=confidence interval.

*Per 100 000 person years.

†Adjusted for age, sex, year of cohort entry, body mass index, alcohol related disorders (including alcoholism, alcoholic cirrhosis of liver, alcoholic hepatitis, and hepatic failure), smoking status, haemoglobin A_{1c}, microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (myocardial infarction, stroke, peripheral arteriopathy) complications of diabetes, duration of treated diabetes, antidiabetic drugs used before cohort entry, use of aspirin, non-steroidal anti-inflammatory drugs, hormonal replacement therapy, oral contraceptives, other autoimmune conditions, total number of unique non-diabetic drugs in year before cohort entry.

‡Exclude and censor on thiazolidinedione use.

Supplementary Table L. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors and the Risk of Inflammatory Bowel Disease using a Marginal Structural Model

Exposure	Events	Person months	Incidence rate (95% CI)*	Marginal Hazard Ratio (95% CI)	
				Crude	Adjusted†
Use of other antidiabetic drugs	159	5 646 887	2.8 (2.4 to 3.3)	1.00	1.00 (reference)
DPP-4 inhibitors	49	1 142 457	4.3 (3.2 to 5.7)	1.53	1.71 (1.12 to 2.61)

DPP-4=dipeptidyl peptidase-4. CI=confidence interval.

*Per 100 000 person months.

†Adjusted for age, sex, year of cohort entry, body mass index, alcohol related disorders (including alcoholism, alcoholic cirrhosis of liver, alcoholic hepatitis, and hepatic failure), smoking status, haemoglobin A_{1c}, microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (myocardial infarction, stroke, peripheral arteriopathy) complications of diabetes, duration of treated diabetes, antidiabetic drugs used before cohort entry, use of aspirin, non-steroidal anti-inflammatory drugs, hormonal replacement therapy, oral contraceptives, other autoimmune conditions, total number of unique non-diabetic drugs in year before cohort entry.

Supplementary Table M. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors and the Risk of Inflammatory Bowel Disease Using the Disease Risk Score

Exposure	Events	Person years	Incidence rate (95% CI)*	Hazard Ratio (95% CI)	
				Crude	Adjusted†
Use of other antidiabetic drugs	159	460 623	34.5 (29.4 to 40.3)	1.00	1.00 (reference)
DPP-4 inhibitors	49	91 790	53.4 (39.5 to 70.6)	1.59	1.79 (1.26 to 2.55)

DPP-4=dipeptidyl peptidase-4. CI=confidence interval.
*Per 100 000 person years.
†Stratified on disease risk score

Supplementary Table N. Crude and Adjusted Hazard Ratios for the Association between the Use of DPP-4 Inhibitors and the Risk of Inflammatory Bowel Disease Using Multiple Imputation

Exposure	Events	Person years	Incidence rate (95% CI)*	Hazard Ratio (95% CI)	
				Crude	Adjusted†
Use of other antidiabetic drugs	159	460 623	34.5 (29.4 to 40.3)	1.00	1.00 (reference)
DPP-4 inhibitors	49	91 790	53.4 (39.5 to 70.6)	1.59	1.73 (1.21 to 2.47)

DPP-4=dipeptidyl peptidase-4. CI=confidence interval.

*Per 100 000 person years.

†Adjusted for age, sex, year of cohort entry, body mass index, alcohol related disorders (including alcoholism, alcoholic cirrhosis of liver, alcoholic hepatitis, and hepatic failure), smoking status, haemoglobin A_{1c}, microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (myocardial infarct ion, stroke, peripheral arteriopathy) complications of diabetes, duration of treated diabetes, antidiabetic drugs used before cohort entry, use of aspirin, non-steroidal anti-inflammatory drugs, hormonal replacement therapy, oral contraceptives, other autoimmune conditions, total number of unique non-diabetic drugs in year before cohort entry.

Supplementary Table O. Baseline Demographic and Clinical Characteristics of the Cohort and Stratified by Drug Use at Cohort Entry Using a Head-to-head Comparison of DPP-4 Inhibitors versus Insulin. Values are numbers (percentages) unless stated otherwise.

Characteristic	Use at Cohort Entry	
	DPP-4 inhibitors (n=29 066)	**Insulin (n=9296)**
Mean (SD) age, years	62.8 (12.1)	60.4 (15.0)
Male sex	17 092 (58.8)	5188 (55.8)
Alcohol-related disorders	5558 (19.1)	1788 (19.2)
Smoking status:		
Current smoker	4117 (14.2)	1680 (18.1)
Past smoker	11 245 (38.7)	3558 (38.3)
Never smoker	13 680 (47.1)	4036 (43.4)
Unknown	24 (0.1)	22 (0.2)
Body mass index:		
< 25	2353 (8.1)	1870 (20.1)
25-30	7835 (27.0)	2650 (28.5)
≥30.0	18 770 (64.5)	4671 (50.3)
Unknown	108 (0.4)	105 (1.1)
Haemoglobin A_{1c}:		
≤7.0%	5812 (20.0)	1037 (11.2)
7.1%-8.0%	8692 (29.9)	1171 (12.6)
>8.0%	11 644 (40.1)	6073 (65.3)
Unknown	2918 (10.0)	1015 (10.9)
Mean (SD) duration of treated diabetes, years	4.9 (3.7)	4.8 (3.9)
Nephropathy	9063 (31.2)	3214 (34.6)
Neuropathy	5515 (19.0)	1703 (18.3)
Retinopathy	7121 (24.5)	1953 (21.0)
Myocardial infarction	2051 (7.1)	897 (9.7)
Stroke	1483 (5.1)	597 (6.4)
Peripheral arteriopathy	1149 (4.0)	583 (6.3)
Aspirin	15 215 (52.4)	5135 (55.2)
Nonsteroidal anti-inflammatory drugs	17 495 (60.2)	5380 (57.9)
Hormonal replacement therapy	4044 (13.9)	1141 (12.3)
Oral contraceptives	2229 (7.7)	1073 (11.5)
Other autoimmune conditions	1002 (3.4)	373 (4.0)
No of non-antidiabetic drugs:		
Mean (SD)	9.6 (6.1)	11.9 (7.1)
0	211 (0.7)	52 (0.6)
1	623 (2.1)	82 (0.9)
2	1076 (3.7)	203 (2.2)
3	1505 (5.2)	323(3.5)
≥4	25 651 (88.3)	8636 (92.9)
Class of unique antidiabetic drugs*		
Metformin	28 013 (96.4)	8501 (91.5)
Sulfonylurea	15 713 (54.1)	7464 (80.3)
Thiazolidinediones	6382 (22.0)	3105 (33.4)
Other	833 (2.9)	476 (5.1)

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

*Non-mutually exclusive groups measured any time before (not including) cohort entry.