Supplement

Table S1: Completeness of biomarker values used in five-year time trend analysis for each observation time period reported in number of observations (n) and percent (%) of total cohort (n=289,356)

Months prior to index month	BMI	%	HbA1c	%	ALT	%	AST	%	GGT	%	Bilirubin	%	Hb	%	WBC	%	Platelet	%
0 to <3	36,370	12.57	25,873	8.94	50,519	17.46	9,505	3.28	17,719	6.12	55,465	19.17	55,435	19.16	55,335	19.12	55,280	19.10
3 to <6	34,966	12.08	24,253	8.38	41,931	14.49	7,826	2.70	13,695	4.73	45,927	15.87	45,615	15.76	45,485	15.72	45,434	15.70
6 to <9	34,395	11.89	23,353	8.07	39,575	13.68	7,245	2.50	13,079	4.52	43,398	15.00	42,471	14.68	42,376	14.64	42,303	14.62
9 to <12	33,805	11.68	22,174	7.66	38,202	13.20	7,186	2.48	12,556	4.34	42,150	14.57	41,314	14.28	41,214	14.24	41,155	14.22
12 to <15	33,021	11.41	21,546	7.45	37,010	12.79	7,101	2.45	12,500	4.32	40,960	14.16	39,801	13.76	39,728	13.73	39,694	13.72
15 to <18	32,495	11.23	20,645	7.13	36,097	12.47	6,889	2.38	12,276	4.24	39,915	13.79	38,873	13.43	38,793	13.41	38,749	13.39
18 to <21	32,273	11.15	19,803	6.84	35,052	12.11	6,675	2.31	11,989	4.14	38,745	13.39	37,420	12.93	37,336	12.90	37,353	12.91
21 to <24	31,637	10.93	19,070	6.59	34,071	11.77	6,594	2.28	11,726	4.05	37,787	13.06	36,462	12.60	36,423	12.59	36,393	12.58
24 to <27	31,147	10.76	18,409	6.36	33,278	11.50	6,555	2.27	11,588	4.00	37,000	12.79	35,670	12.33	35,622	12.31	35,625	12.31
27 to <30	30,473	10.53	17,368	6.00	32,031	11.07	6,502	2.25	11,188	3.87	35,784	12.37	34,470	11.91	34,425	11.90	34,397	11.89
30 to <33	30,160	10.42	16,930	5.85	31,451	10.87	6,315	2.18	11,042	3.82	35,077	12.12	33,704	11.65	33,644	11.63	33,634	11.62
33 to <36	29,496	10.19	16,066	5.55	30,749	10.63	6,260	2.16	10,966	3.79	34,450	11.91	32,938	11.38	32,860	11.36	32,854	11.35
36 to <39	29,364	10.15	15,661	5.41	29,699	10.26	6,165	2.13	10,605	3.67	33,263	11.50	31,797	10.99	31,772	10.98	31,757	10.98
39 to <42	28,657	9.90	14,783	5.11	28,873	9.98	6,074	2.10	10,487	3.62	32,491	11.23	30,981	10.71	30,964	10.70	30,936	10.69
42 to <45	28,231	9.76	14,127	4.88	28,025	9.69	6,030	2.08	10,127	3.50	31,643	10.94	29,897	10.33	29,867	10.32	29,821	10.31
45 to <48	27,595	9.54	13,563	4.69	27,298	9.43	5,770	1.99	10,004	3.46	30,807	10.65	29,302	10.13	29,274	10.12	29,259	10.11
48 to <51	27,292	9.43	12,998	4.49	26,614	9.20	5,788	2.00	9,824	3.40	30,220	10.44	28,211	9.75	28,206	9.75	28,213	9.75
51 to <54	26,758	9.25	12,471	4.31	25,687	8.88	5,641	1.95	9,705	3.35	29,216	10.10	27,480	9.50	27,477	9.50	27,464	9.49
54 to <57	26,721	9.23	11,983	4.14	24,709	8.54	5,566	1.92	9,182	3.17	28,161	9.73	26,626	9.20	26,573	9.18	26,549	9.18
57 to <60	25,937	8.96	11,068	3.83	23,988	8.29	5,450	1.88	9,129	3.15	27,462	9.49	25,716	8.89	25,666	8.87	25,666	8.87

Table S2: Onset of comorbidities and initiation time of medication in PDAC cases versus controls

	Onset/initiation time	PDAC cases	Controls
Total, N	Onsey mination time	28137	261219
Comorbidities			
Type 2 diabetes	None	21212 (75.4)	228257 (87.4)
No. of the second	Start <=3 years ago	2731 (9.7)	6497 (2.5)
	Start >3 years ago	4194 (14.9)	26465 (10.1)
Prediabetes	None	26465 (94.1)	250052 (95.7)
-	Start <=3 years ago	808 (2.9)	4840 (1.9)
-	Start >3 years ago	864 (3.1)	6327 (2.4)
Acute pancreatitis	None	27400 (97.4)	259651 (99.4)
	Start <=3 years ago	446 (1.6)	328 (0.1)
	Start >3 years ago	291 (1.0)	1240 (0.5)
Chronic pancreatitis	None	27816 (98.9)	260863 (99.9)
	Start <=3 years ago	208 (0.7)	82 (0.0)
	Start >3 years ago	113 (0.4)	274 (0.1)
Hypercholesterolaemia	None	23226 (82.5)	216040 (82.7)
	Start <=3 years ago	705 (2.5)	7621 (2.9)
	Start >3 years ago	4206 (14.9)	37558 (14.4)
Venous thromboembolism	None	26491 (94.2)	252161 (96.5)
	Start <=3 years ago	693 (2.5)	2032 (0.8)
	Start >3 years ago	953 (3.4)	7026 (2.7)
Asthma	None	25147 (89.4)	234560 (89.8)
	Start <=3 years ago	284 (1.0)	2597 (1.0)
	Start >3 years ago	2706 (9.6)	24062 (9.2)
Inflammatory bowel disease	None	27800 (98.8)	258510 (99.0)
	Start <=3 years ago	47 (0.2)	262 (0.1)
	Start >3 years ago	290 (1.0)	2447 (0.9)
Celiac disease	None	27994 (99.5)	260362 (99.7)
	Start <=3 years ago	41 (0.1)	160 (0.1)
	Start >3 years ago	102 (0.4)	697 (0.3)
Breast cancer	None	27366 (97.3)	255262 (97.7)
	Start <=3 years ago	129 (0.5)	1095 (0.4)
	Start >3 years ago	642 (2.3)	4862 (1.9)
Ovarian cancer	None	28055 (99.7)	260808 (99.8)
	Start <=3 years ago	21 (0.1)	90 (0.0)
	Start >3 years ago	61 (0.2)	321 (0.1)
Prostate cancer	None	27459 (97.6)	255989 (98.0)
	Start <=3 years ago	235 (0.8)	1662 (0.6)
Departure the sust	Start >3 years ago	443 (1.6)	3568 (1.4)
Pancreatic cyst	None Start (2) years and	27945 (99.3)	261104 (100.0)
	Start <= 3 years ago	150 (0.5)	64 (0.0)
Rheumatoid arthritis	Start >3 years ago	42 (0.1)	51 (0.0)
Medinatola al tillitis	None Start <= 2 years ago	27597 (98.1)	256509 (98.2)
	Start <= 3 years ago	87 (0.3) 453 (1.6)	789 (0.3)
Systemic lupus erythematosus	Start >3 years ago	453 (1.6)	3921 (1.5)
Systemic rupus erythematosus	None Start <= 3 years ago	28113 (99.9)	260981 (99.9)
	Start <=3 years ago	<5	23 (0.0)

	Start >3 years ago	22 (0.1)	215 (0.1)
Multiple sclerosis	None	28065 (99.7)	260585 (99.8)
	Start <=3 years ago	<5	38 (0.0)
	Start >3 years ago	68 (0.2)	596 (0.2)
AIDS/HIV	None	28113 (99.9)	261096 (100.0)
	Start <=3 years ago	<5	20 (0.0)
	Start >3 years ago	22 (0.1)	103 (0.0)
Psoriatic arthritis	None	28062 (99.7)	260500 (99.7)
	Start <=3 years ago	9 (0.0)	103 (0.0)
	Start >3 years ago	66 (0.2)	616 (0.2)
Medications			
Insulin	None	26153 (92.9)	255242 (97.7)
	Start <=3 years ago	1180 (4.2)	1855 (0.7)
	Start >3 years ago	804 (2.9)	4122 (1.6)
Sulphonylurea	None	24332 (86.5)	245691 (94.1)
	Start <=3 years ago	1725 (6.1)	3666 (1.4)
	Start >3 years ago	2080 (7.4)	11862 (4.5)
Biguanides	None	22994 (81.7)	237137 (90.8)
	Start <=3 years ago	2275 (8.1)	6578 (2.5)
	Start >3 years ago	2868 (10.2)	17504 (6.7)
Alpha-glucosidase inhibitor	None	27979 (99.4)	260369 (99.7)
	Start <=3 years ago	31 (0.1)	130 (0.0)
	Start >3 years ago	127 (0.5)	720 (0.3)
Meglitinide	None	28016 (99.6)	260695 (99.8)
	Start <=3 years ago	41 (0.1)	133 (0.1)
	Start >3 years ago	80 (0.3)	391 (0.1)
Dipeptidyl-peptidase 4 inhibitor	None	27109 (96.3)	257215 (98.5)
	Start <=3 years ago	646 (2.3)	2110 (0.8)
	Start >3 years ago	382 (1.4)	1894 (0.7)
Thiazolidinedione	None	27185 (96.6)	256668 (98.3)
	Start <=3 years ago	321 (1.1)	1123 (0.4)
	Start >3 years ago	631 (2.2)	3428 (1.3)
Glucagon-like peptide-1	None	27976 (99.4)	260437 (99.7)
	Start <=3 years ago	67 (0.2)	334 (0.1)
	Start >3 years ago	94 (0.3)	448 (0.2)
Sodium-glucose transport protein 2 (SGLT2) inhibitors	None	27937 (99.3)	260501 (99.7)
	Start <=3 years ago	161 (0.6)	544 (0.2)
	Start >3 years ago	39 (0.1)	174 (0.1)
Proton pump inhibitor	None	10770 (38.3)	151382 (58.0)
	Start <=3 years ago	8115 (28.8)	29802 (11.4)
	Start >3 years ago	9252 (32.9)	80035 (30.6)
Histamine-2 receptor blocker	None	21611 (76.8)	216045 (82.7)
	Start <=3 years ago	1937 (6.9)	6649 (2.5)
	Start >3 years ago	4589 (16.3)	38525 (14.7)
Aspirin	None	17152 (61.0)	171569 (65.7)
	Start <=3 years ago	2545 (9.0)	20481 (7.8)
	Start >3 years ago	8440 (30.0)	69169 (26.5)

Statin	None	16197 (57.6)	161055 (61.7)
	Start <=3 years ago	3163 (11.2)	26408 (10.1)
	Start >3 years ago	8777 (31.2)	73756 (28.2)
Bisphosphonate	None	25495 (90.6)	238774 (91.4)
	Start <=3 years ago	946 (3.4)	8064 (3.1)
	Start >3 years ago	1696 (6.0)	14381 (5.5)
Immunosuppressant	None	27907 (99.2)	259622 (99.4)
	Start <=3 years ago	67 (0.2)	400 (0.2)
	Start >3 years ago	163 (0.6)	1197 (0.5)
Digoxin	None	26696 (94.9)	250904 (96.1)
	Start <=3 years ago	509 (1.8)	3466 (1.3)
	Start >3 years ago	932 (3.3)	6849 (2.6)

Sex-specific population

Onset/initiation time	PDAC cases	Controls
None	13335 (94.5)	125386 (95.5)
Start <=3 years ago	129 (0.9)	1094 (0.8)
Start >3 years ago	642 (4.6)	4858 (3.7)
None	14024 (99.4)	130929 (99.7)
Start <=3 years ago	21 (0.1)	90 (0.1)
Start >3 years ago	61 (0.4)	319 (0.2)
None	13353 (95.2)	124652 (96.0)
Start <=3 years ago	235 (1.7)	1661 (1.3)
Start >3 years ago	443 (3.2)	3568 (2.7)
	None Start <=3 years ago Start >3 years ago None Start <=3 years ago Start >3 years ago None Start <=3 years ago None Start <=3 years ago	None13335 (94.5)Start <=3 years ago

Table S3: E-values – sensitivity analysis for potential unmeasured confounding of statistically significant risk factors (large E-values imply a relatively large unmeasured confounding effect is needed to explain away residual confounding, whilst small E-values^{39,40} imply small unmeasured confounding effect is needed to explain away any residual confounding)

xpiairi away ariy residual co	OR (95% CI)	E-value (point estimate)	E-value (lower CI to span 1
Comorbidities	On (55% Ci)	2 value (point estimate)	2 Talue (lower of to spail 1
Recent-onset			
Pancreatic cyst	19.60 (14.36-26.76)	38.69	28.21
Chronic pancreatitis	11.93 (9.03-15.77)	23.35	17.55
Acute pancreatitis	10.94 (9.39-12.76)	21.37	18.27
Type 2 diabetes	4.93 (4.69-5.18)	9.33	8.85
Venous thromboembolism	3.19 (2.91-3.49)	5.83	5.27
Coeliac disease	2.35 (1.64-3.36)	4.13	2.66
Ovarian cancer	2.18 (1.34-3.56)	3.78	2.01
Prediabetes	1.63 (1.50-1.77)	2.64	2.37
Inflammatory bowel	1.44 (1.04-2.00)	2.24	1.24
, disease	,		
Prostate cancer	1.35 (1.17-1.55)	2.04	1.62
Hypercholesterolemia	0.83 (0.77-0.91)	1.70	1.43
Long-standing			
Pancreatic cyst	6.65 (4.33-10.23)	12.78	8.13
Chronic pancreatitis	2.01 (1.58-2.57)	3.43	2.54
AIDS/HIV	2.00 (1.24-3.22)	3.41	1.79
Ovarian cancer	1.94 (1.46-2.57)	3.29	2.28
Type 2 diabetes	1.89 (1.82-1.97)	3.19	3.04
Acute pancreatitis	1.57 (1.37-1.82)	2.52	2.08
Coeliac disease	1.32 (1.06-1.64)	1.97	1.31
Breast cancer	1.26 (1.15-1.37)	1.83	1.57
Venous thromboembolism	1.24 (1.16-1.34)	1.79	1.59
Prostate cancer	1.13 (1.02-1.25)	1.51	1.16
Medications			
Recent-initiation			
Insulin	3.66 (3.34-4.02)	6.78	6.14
Proton pump inhibitor	3.65 (3.52-3.77)	6.76	6.50
Sulphonylurea	2.28 (2.11-2.47)	3.99	3.64
Histamine-2 receptor	2.18 (2.06-2.31)	3.78	3.54
blocker	,		
SGLT-2 inhibitor	1.51 (1.22-1.85)	2.39	1.74
Metformin	1.49 (1.38-1.60)	2.34	2.10
DPP-4 inhibitor	1.45 (1.30-1.62)	2.26	1.92
Thiazolidinedione	1.27 (1.09-1.47)	1.86	1.40
Meglitinide	1.03 (0.69-1.54)	1.21	1.00
Aspirin	0.87 (0.83-0.92)	1.56	1.39
Statin	0.80 (0.76-0.84)	1.81	1.67
Bisphosphonate	0.78 (0.72-0.84)	1.88	1.67
	0.78 (0.72-0.84)		
Long-standing	0.78 (0.72-0.64)		
Long-standing Insulin	1.71 (1.56-1.88)	2.81	2.49
Insulin	1.71 (1.56-1.88)		2.49 2.49
Insulin Proton pump inhibitor	1.71 (1.56-1.88) 1.62 (1.56-1.68)	2.62	2.49
Insulin	1.71 (1.56-1.88)		

Table S4: Risk factors that remained significant after Bonferroni correction and corresponding p-values

Comorbidities

Bonferroni corrected p-value: 0.05/(18*2) tests = 0.0014

	р
Recent-onset	
Type-2 diabetes	<0.00001
Acute pancreatitis	<0.00001
VTE	<0.00001
Pancreatic cyst	<0.00001
Chronic pancreatitis	<0.00001
Pre-diabetes	<0.00001
Coeliac disease	<0.00001
Hypercholesterolaemia	0.000016
Prostate cancer	0.000050
Long-standing	
Type-2 diabetes	<0.00001
Pancreatic cyst	<0.00001
Acute pancreatitis	<0.00001
VTE	<0.00001
Chronic pancreatitis	<0.00001
Breast cancer	<0.00001
Ovarian cancer	<0.00001

Medications

Bonferroni correction: 0.05/(16*2) tests = 0.0016

Recent initiation	р
Proton-pump inhibitor	<0.00001
Insulin	<0.00001
Histamine-2 blocker	<0.00001
Sulphonylurea	<0.00001
Biguanide (metformin)	<0.00001
Statin	<0.00001
DPP4-inhibitor	<0.00001
Bisphosphonate	<0.00001
Aspirin	<0.00001
SGLT-2 inhibitor	0.000109
Long-standing	
Biguanide (metformin)	0.000046
Proton-pump inhibitor	<0.00001
Insulin	<0.00001
Sulphonylurea	0.000149

List S1: ICD-10 codes and ICD-0 codes used for PDAC cases

ICD-10 codes:

C250

C251

C252

C253

C257

C258

C259

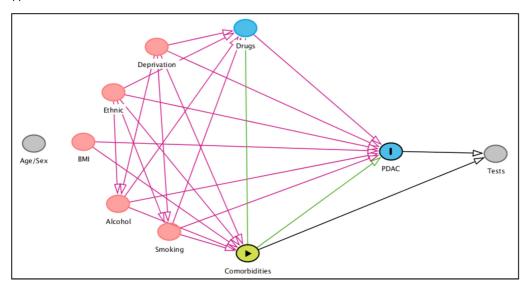
ICD-O histology codes:

List S2: Medical conditions and medications included as exposure variables in association analyses with risk of PDAC

- a. Medical conditions (18)^{7,8,19-22}: pancreatic cyst, chronic pancreatitis, acute pancreatitis, type-2 diabetes mellitus (T2D), prediabetes, venous thromboembolism (VTE), hypercholesterolemia breast cancer, ovarian cancer, prostate cancer, asthma, autoimmune conditions (coeliac disease, inflammatory bowel disease (IBD), rheumatoid arthritis, AIDS/HIV, multiple sclerosis, psoriatic arthritis, and systemic lupus erythematosus (SLE))
- b. Medications (16)²³⁻³²: insulin, metformin, sulphonylurea, SGLT2-inhibitor, DPP4-inhibitor, GLP-1 agonist, thiazolidinedione, meglitinide, alpha-glucosidase inhibitor, proton-pump inhibitor (PPI), histamine-2-receptor antagonist (H2RA), immunosuppressant, digoxin, aspirin, statin, and bisphosphonate.

Figure S1: Directed acyclic graphs (DAGs) for exposures (i) comorbidities and (ii) medications.

(i) Comorbidities



(ii) Medications

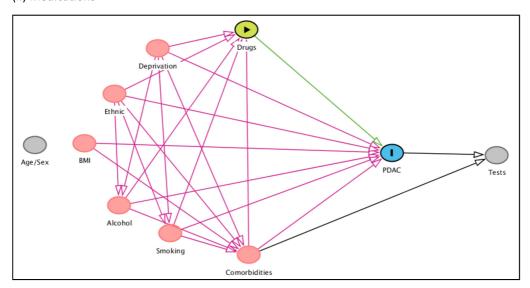


Figure S2 (a): Fractional polynomial plots for the association of BMI and biomarker levels with risk of PDAC up to 3 years versus 1 year prior to index date for other liver function markers (ALT, AST, GGT)

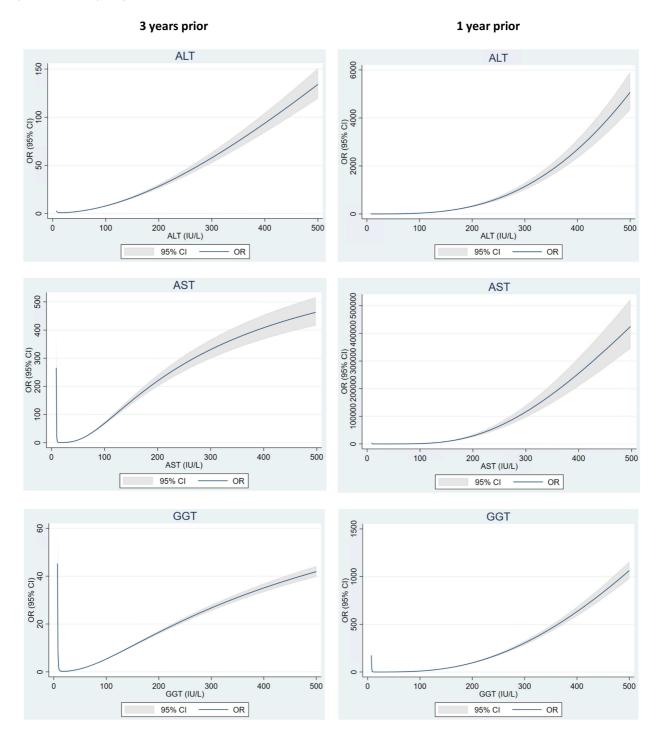
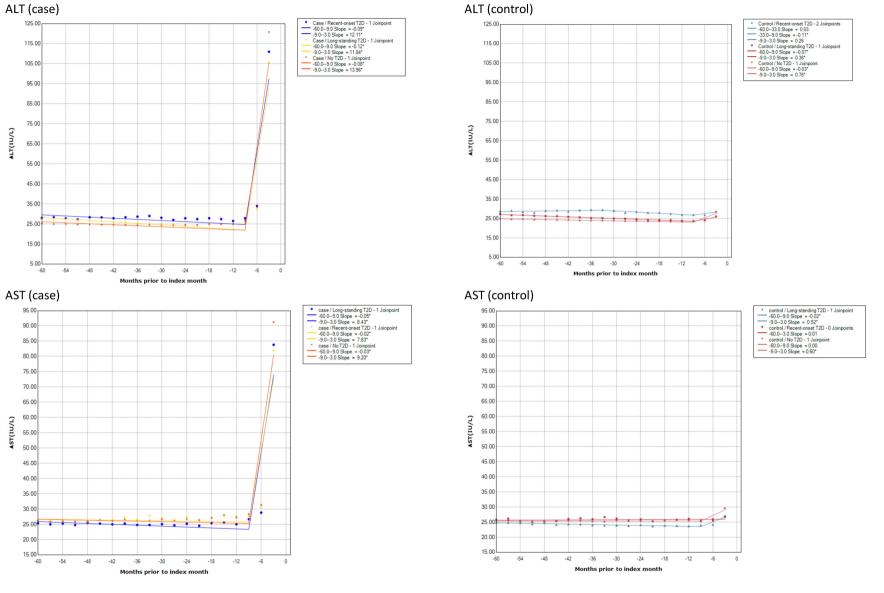
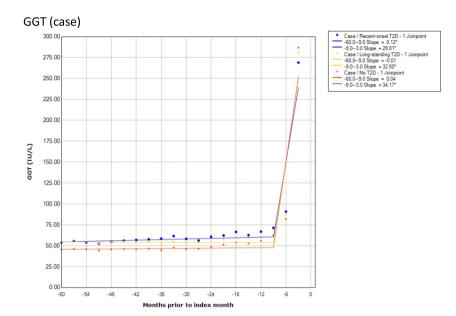


Figure S2 (b): Five year time-trends of mean liver function markers (ALT, AST, GGT) prior to index month in PDAC cases versus controls by type-2 diabetes status (recent-onset, long-standing, none) (imputed dataset)





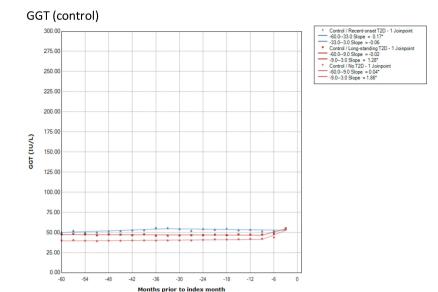
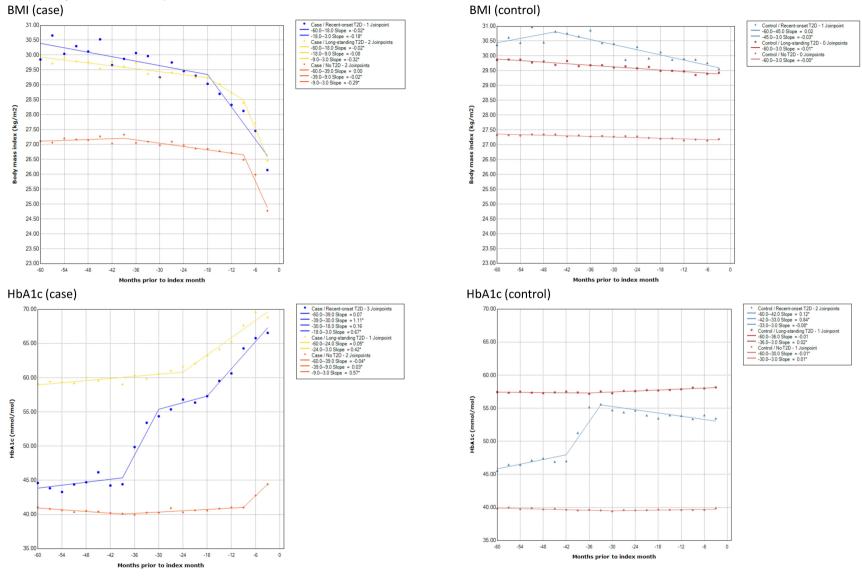
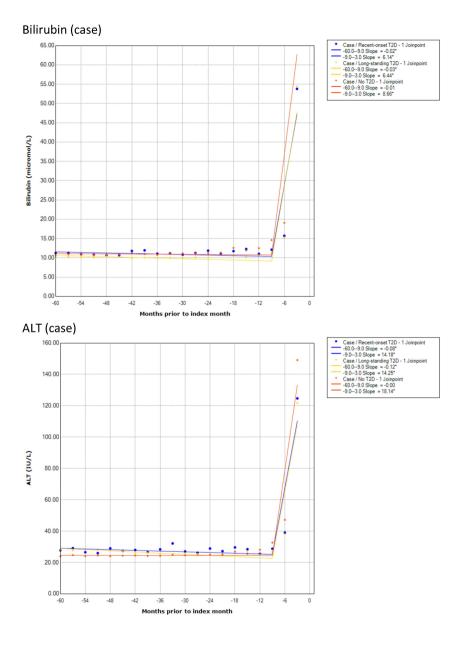
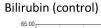


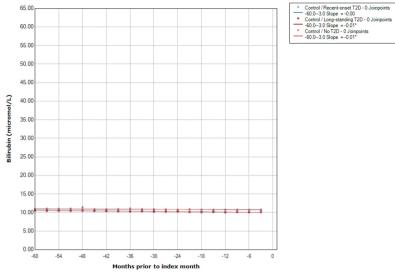
Figure S3: Five year time-trends of mean BMI and blood markers prior to index month in PDAC cases versus controls by type-2 diabetes status (recent-onset, long-standing, none) (complete-case dataset)



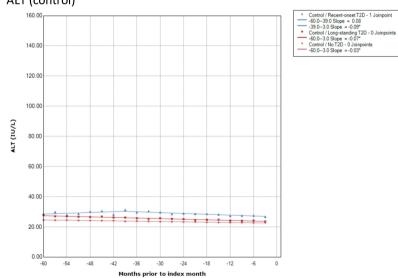


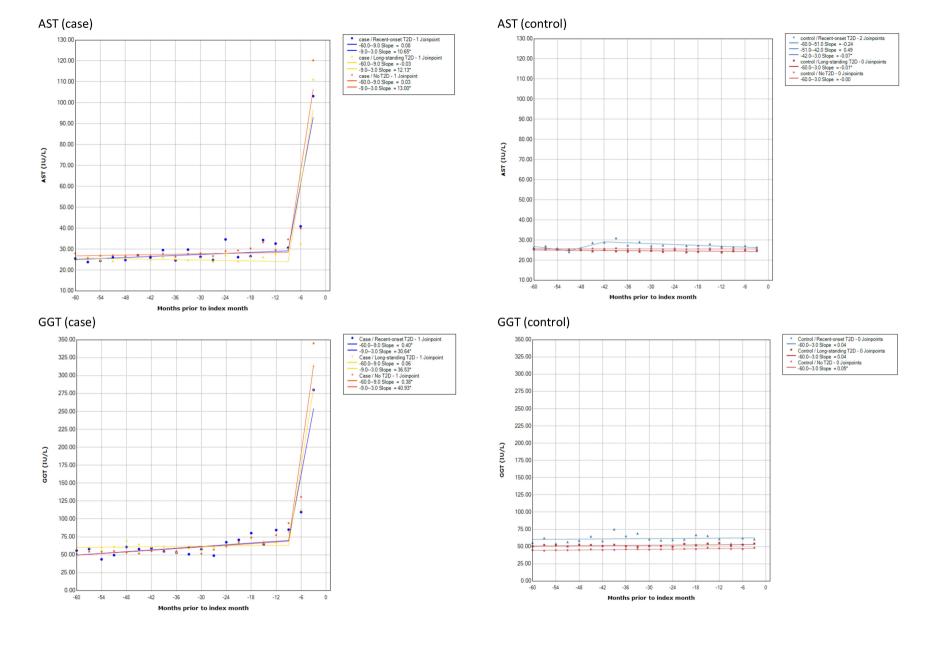
Supplemental material

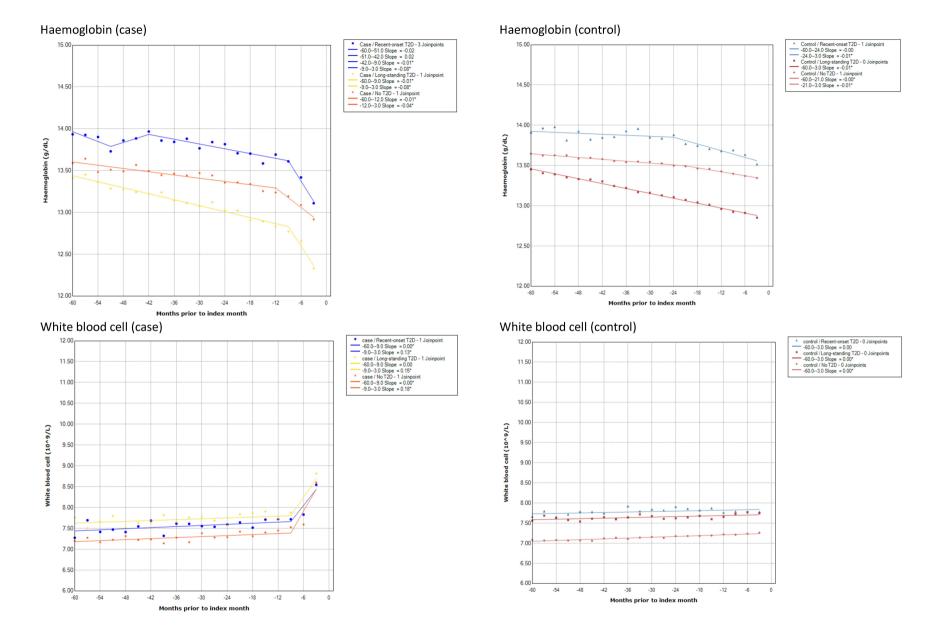


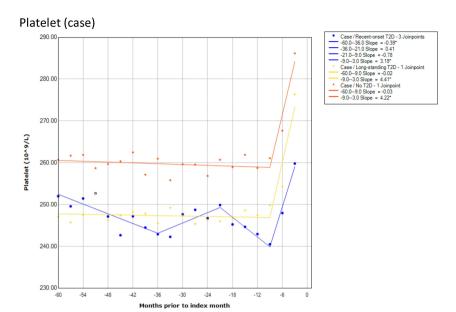


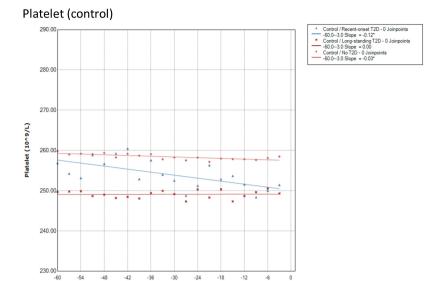
ALT (control)





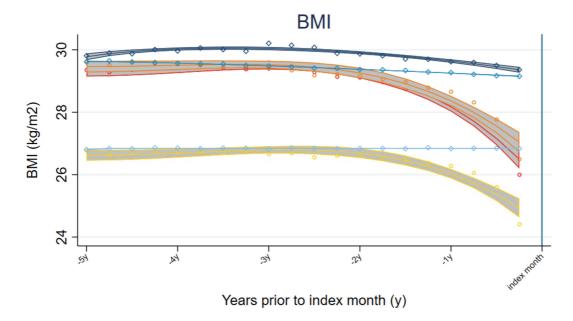


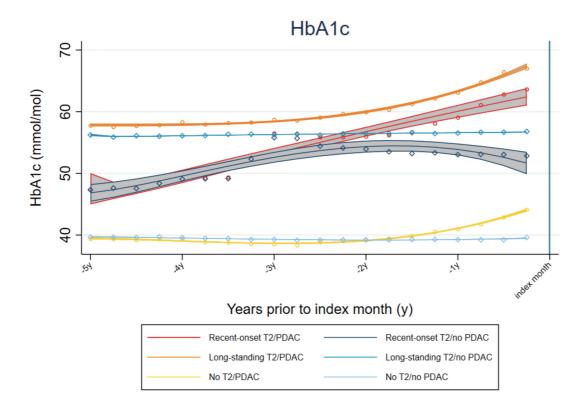


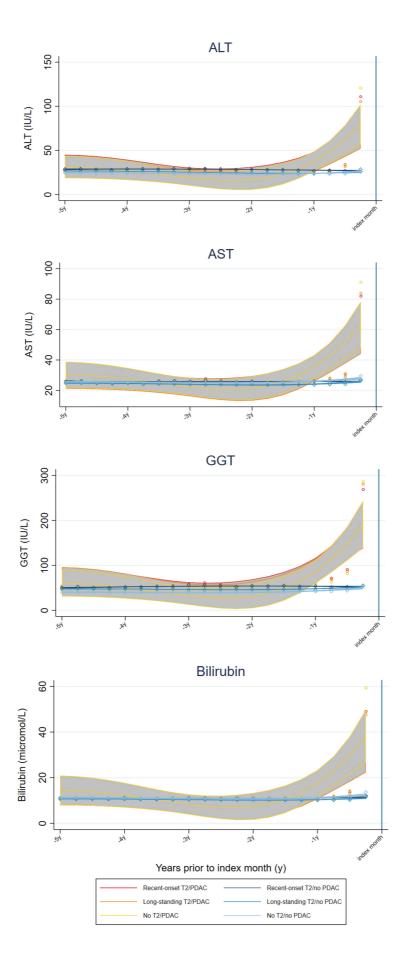


Months prior to index month

Figure S4: Five year time-trends of mean BMI and blood markers prior to index month for PDAC cases/controls by type-2 diabetes status using fractional polynomial fit and corresponding 95% CI (multiply imputed)







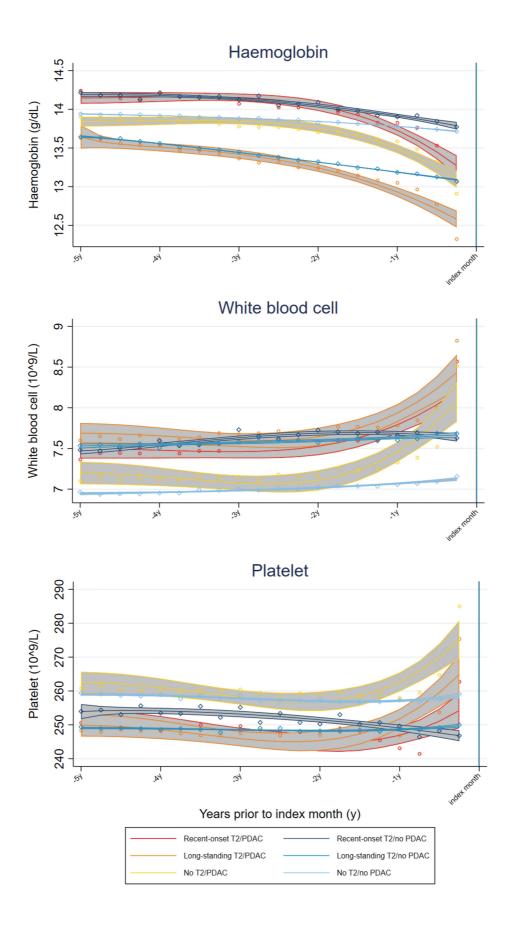
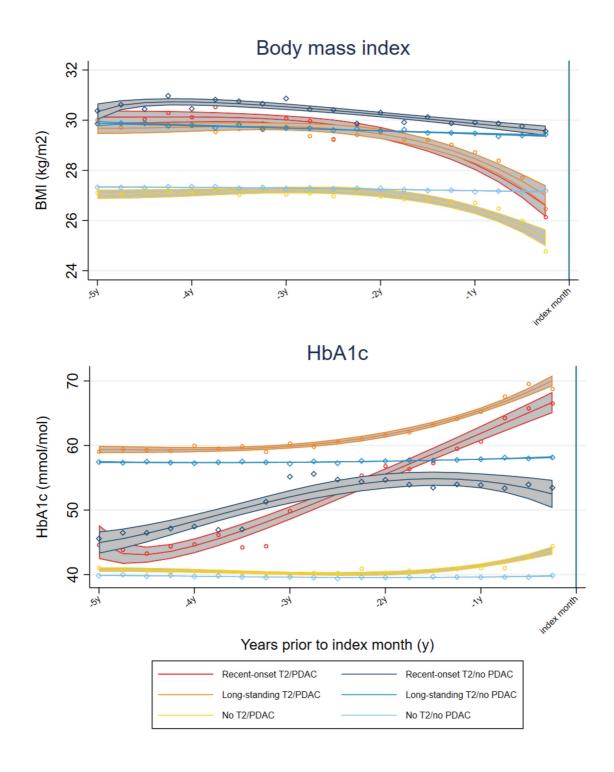
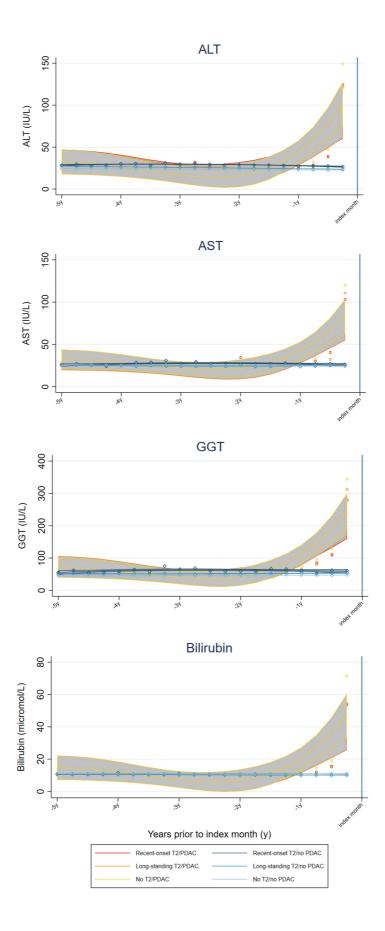


Figure S5: Five year time-trends of mean blood counts (haemoglobin, white blood cell, platelet) prior to index month for PDAC cases/controls by type-2 diabetes status using fractional polynomial fit and corresponding 95% Ci (complete-case)





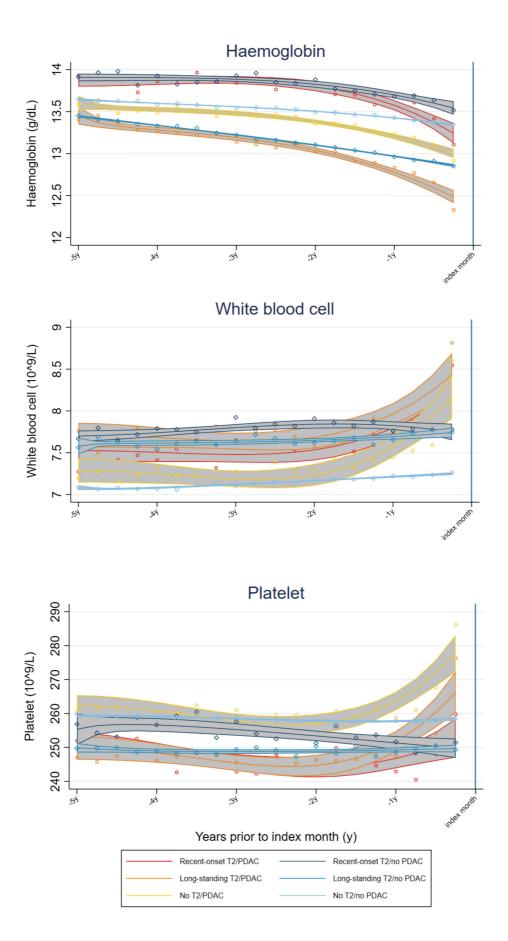
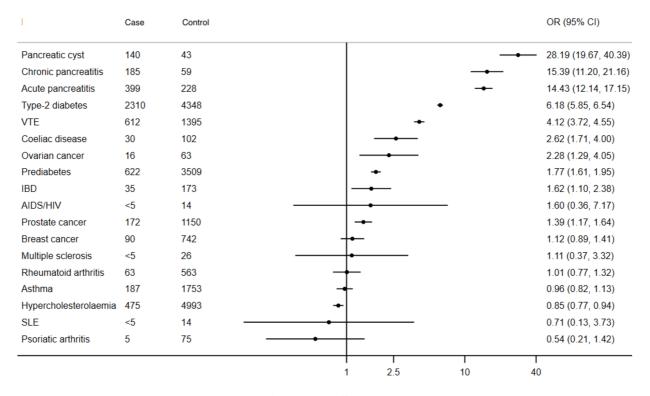


Figure S6: Association of comorbidities with risk of PDAC by onset time; recent-onset defined as within 2 years prior to index date, long-standing defined as more than 2 years prior to index date.^a

Recent-onset



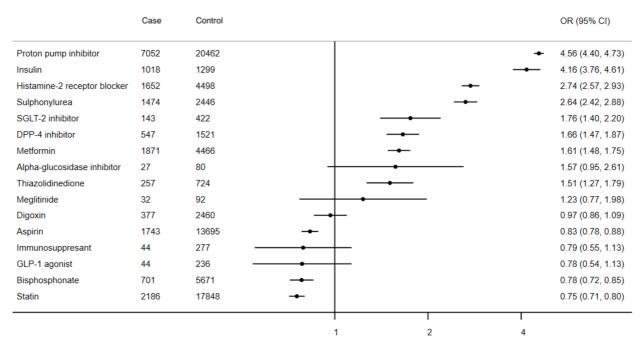
Long-standing

	Case	Control					OR (95% CI)
Pancreatic cyst	52	72			-	-	5.51 (3.77, 8.07)
Chronic pancreatitis	136	297		—			2.22 (1.77, 2.79)
Type-2 diabetes	4615	28614					1.92 (1.85, 2.00)
Ovarian cancer	66	348					1.92 (1.47, 2.52)
AIDS/HIV	22	109					1.86 (1.16, 3.00)
Acute pancreatitis	338	1340		-			1.70 (1.49, 1.95)
Coeliac disease	113	755		 -			1.38 (1.12, 1.70)
Breast cancer	681	5215		-			1.25 (1.14, 1.36)
VTE	1034	7663					1.23 (1.15, 1.32)
Prostate cancer	506	4080		-			1.15 (1.04, 1.26)
IBD	302	2536		 -			1.09 (0.96, 1.24)
Prediabetes	1050	7658		•			1.07 (1.00, 1.15)
Multiple sclerosis	68	608		-			1.06 (0.82, 1.37)
Asthma	2803	24906		•			1.05 (1.00, 1.09)
Rheumatoid arthritis	477	4147		+			1.04 (0.94, 1.14)
Hypercholesterolaemia	4436	40186		+			0.99 (0.96, 1.03)
Psoriatic arthritis	70	644		+			0.97 (0.76, 1.26)
SLE	22	224	_				0.93 (0.60, 1.46)
				1 2.5		T 10	1 40

^aEstimates are odds ratios adjusted for ethnic group, deprivation quintile, BMI, smoking and alcohol consumption. Reference group represent those with no corresponding comorbidities.

Figure S7: Association of medications with risk of PDAC by onset time; recent-onset defined as within 2 years prior to index date, long-standing defined as more than 2 years prior to index date.^a

Recent-onset



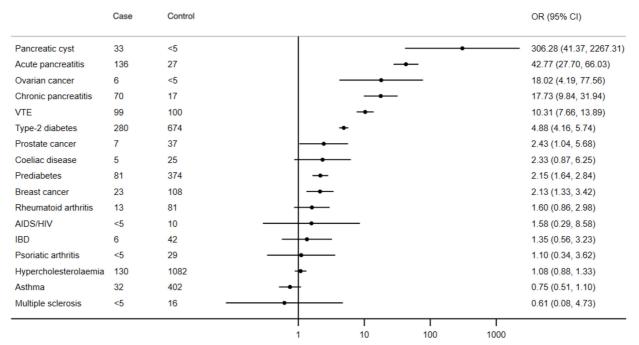
Long-standing

	Case	Control		OR (95% CI)
Insulin	966	4678	-	1.75 (1.60, 1.91)
Proton pump inhibitor	10315	89375	•	1.59 (1.53, 1.64)
Metformin	3272	19616	-	1.21 (1.11, 1.31)
Sulphonylurea	2331	13082	-	1.17 (1.09, 1.27)
Immunosuppresant	186	1320	—	1.17 (0.99, 1.39)
Meglitinide	89	432		1.10 (0.85, 1.41)
DPP4- inhibitor	481	2483	 • -	1.09 (0.97, 1.24)
Digoxin	1064	7855	-	1.09 (1.01, 1.17)
GLP-1 agonist	117	546		1.06 (0.84, 1.33)
Histamine-2 receptor blocker	4874	40676	•	1.04 (1.00, 1.08)
Aspirin	9242	75955	+	1.02 (0.99, 1.06)
SGLT-2 inhibitor	57	296		1.02 (0.74, 1.40)
Thiazolidinedione	695	3827	-	0.98 (0.88, 1.09)
Statin	9754	82316	→	0.96 (0.93, 1.00)
Bisphosphonate	1941	16774	-	0.95 (0.90, 1.00)
Alpha-glucosidase inhibitor	131	770	→	0.83 (0.68, 1.02)

^aEstimates are odds ratios adjusted for ethnic group, deprivation quintile, BMI, smoking, alcohol consumption and comorbidities. Reference group represent those with no corresponding medications.

Figure S8 (a): Subgroup analysis by age - association of comorbidities and risk of PDAC in age < 60 at index date

Recent-onset (age <60)



Long-standing (age <60)

	Case	Control	OR (95% CI)
Ovarian cancer	6	17	4.16 (1.55, 11.13
Pancreatic cyst	<5	<5	2.73 (0.57, 13.14
Chronic pancreatitis	28	39	2.71 (1.53, 4.79)
Breast cancer	49	217	2.46 (1.77, 3.42)
Type-2 diabetes	292	1543	→ 2.34 (2.02, 2.72)
Acute pancreatitis	52	107	2.31 (1.54, 3.48)
Coeliac disease	16	78	1.90 (1.04, 3.45)
Prostate cancer	<5	21	1.53 (0.43, 5.47)
VTE	58	388	1.29 (0.95, 1.75)
Asthma	415	3544	◆ 1.15 (1.03, 1.29)
IBD	36	296	1.15 (0.79, 1.66)
AIDS/HIV	6	52	1.10 (0.45, 2.66)
Hypercholesterolaemia	272	2475	0.99 (0.86, 1.15)
Multiple sclerosis	11	108	0.95 (0.50, 1.81)
Prediabetes	44	316	0.90 (0.63, 1.29)
Rheumatoid arthritis	24	257	0.87 (0.56, 1.35)
Psoriatic arthritis	8	99	0.68 (0.32, 1.47)
SLE	<5	34 ←	0.27 (0.04, 2.04)

Figure S8 (b): Subgroup analysis by age - association of comorbidities and risk of PDAC in age >=60 at index date

Recent-onset (age >=60)

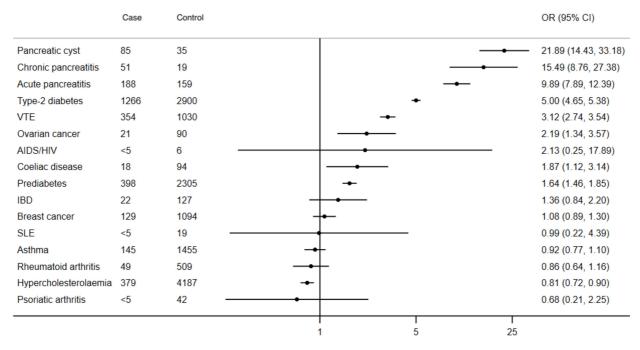
	Case	Control		OR (95% CI)
Pancreatic cyst	117	63		- 15.12 (10.90, 20.98)
Chronic pancreatitis	138	65		10.33 (7.49, 14.24)
Acute pancreatitis	310	301	-	8.21 (6.92, 9.75)
Type-2 diabetes	2451	5823	•	4.93 (4.68, 5.20)
VTE	594	1932	+	2.84 (2.58, 3.14)
Coeliac disease	36	135		2.37 (1.61, 3.49)
Ovarian cancer	15	87	 • • • • • • • • • • • • • • • • • • •	1.61 (0.92, 2.83)
Prediabetes	727	4466	+	1.58 (1.45, 1.73)
IBD	41	220		1.47 (1.03, 2.09)
Prostate cancer	228	1625	-	1.33 (1.15, 1.53)
Asthma	252	2195	-	1.04 (0.91, 1.20)
Multiple sclerosis	<5	22		1.01 (0.29, 3.53)
Breast cancer	106	987	+	0.98 (0.79, 1.20)
Rheumatoid arthritis	74	708	-	0.93 (0.73, 1.19)
Hypercholesterolaemia	575	6539	+	0.79 (0.72, 0.87)
SLE	<5	17		0.71 (0.15, 3.33)
Psoriatic arthritis	5	74		0.64 (0.25, 1.62)

Long-standing (age >=60)

	Case	Control		OR (95% CI)
Pancreatic cyst	39	47		7.05 (4.52, 11.01)
AIDS/HIV	16	51		2.95 (1.64, 5.30)
Type-2 diabetes	3902	24922	•	1.87 (1.79, 1.95)
Chronic pancreatitis	85	235		1.83 (1.40, 2.41)
Ovarian cancer	55	304		1.82 (1.35, 2.44)
Acute pancreatitis	239	1133	-	1.49 (1.28, 1.74)
Coeliac disease	86	619		1.25 (0.99, 1.58)
VTE	895	6638	•	1.24 (1.15, 1.33)
Breast cancer	593	4645	-	1.20 (1.10, 1.32)
Prostate cancer	440	3547	→	1.13 (1.01, 1.25)
Multiple sclerosis	57	488	- •	1.11 (0.84, 1.46)
SLE	21	181		1.10 (0.70, 1.74)
IBD	254	2151	 •-	1.09 (0.95, 1.24)
Rheumatoid arthritis	429	3664	+	1.04 (0.94, 1.16)
Prediabetes	820	6011	+	1.03 (0.95, 1.12)
Asthma	2291	20518	+	1.03 (0.98, 1.08)
Hypercholesterolaemia	3934	35083	†	1.00 (0.96, 1.04)
Psoriatic arthritis	58	517	+	1.00 (0.76, 1.32)
			1 5	25

Figure S9 (a): Subgroup analysis by sex - association of comorbidities and risk of PDAC in female

Recent-onset (female)

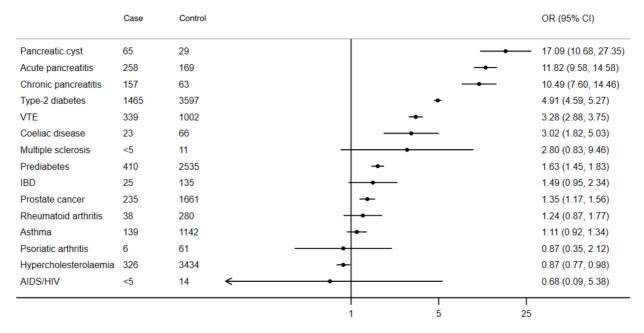


Long-standing (female)

	Case	Contro I		OR (95% CI)
Pancreatic cyst	25	30		7.33 (4.22, 12.72
Chronic pancreatitis	48	101	_ 	2.59 (1.77, 3.78)
AIDS/HIV	5	25		2.07 (0.76, 5.62)
Ovarian cancer	61	319		1.96 (1.48, 2.59)
Type-2 diabetes	1803	11541	•	1.83 (1.72, 1.93)
Coeliac disease	65	431		1.36 (1.03, 1.78)
Acute pancreatitis	109	619		1.29 (1.03, 1.61)
Breast cancer	642	4858	-	1.26 (1.16, 1.38)
IBD	154	1214	 • -	1.15 (0.97, 1.37)
VTE	485	3847	+	1.13 (1.02, 1.24)
Multiple sclerosis	48	397	- •	1.10 (0.81, 1.50)
Rheumatoid arthritis	305	2652	+	1.05 (0.93, 1.19)
Asthma	1500	13333	<u>+</u>	1.03 (0.98, 1.10)
SLE	20	190		1.02 (0.64, 1.62)
Hypercholesterolaemia	2153	19533	+	0.98 (0.93, 1.04)
Psoriatic arthritis	33	300	—	0.94 (0.65, 1.36)
Prediabetes	358	2909	-	0.90 (0.79, 1.01)

Figure S9 (b): Subgroup analysis by sex - association of comorbidities and risk of PDAC in male

Recent-onset (male)

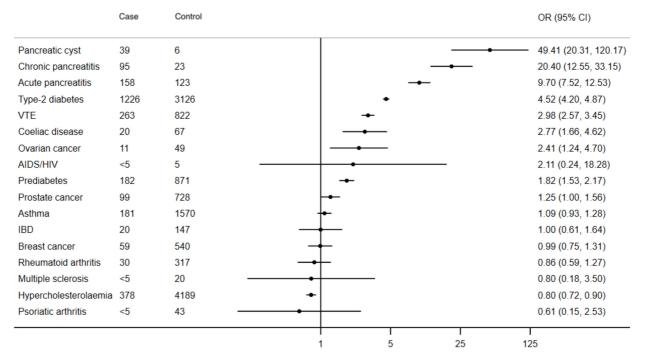


Long-standing (male)

	Case	Control		OR (95% CI)
Pancreatic cyst	17	21		5.75 (2.89, 11.46)
Type-2 diabetes	2391	14924	•	1.96 (1.86, 2.07)
AIDS/HIV	17	78		1.91 (1.11, 3.29)
Acute pancreatitis	182	621	-	1.84 (1.52, 2.21)
Chronic pancreatitis	65	173		1.66 (1.21, 2.28)
VTE	468	3179	-	1.39 (1.25, 1.54)
Coeliac disease	37	266	 • 	1.27 (0.89, 1.82)
Prediabetes	506	3418	-	1.15 (1.03, 1.27)
Prostate cancer	443	3568	•	1.13 (1.02, 1.25)
Asthma	1206	10729	+	1.06 (0.99, 1.13)
IBD	136	1233	-	1.03 (0.86, 1.24)
Hypercholesterolaemia	2053	18025	•	1.03 (0.97, 1.09)
Rheumatoid arthritis	148	1269	+	1.00 (0.84, 1.20)
Multiple sclerosis	20	199		1.00 (0.63, 1.60)
Psoriatic arthritis	33	316	-	0.98 (0.68, 1.42)
SLE	<5	25	<u> </u>	0.82 (0.19, 3.52)

Figure S10 (a): Subgroup analysis by year of diagnosis - association of comorbidities and risk of PDAC in diagnosis year 2000-2010 (or matching year in controls)

Recent-onset (2000-2010)

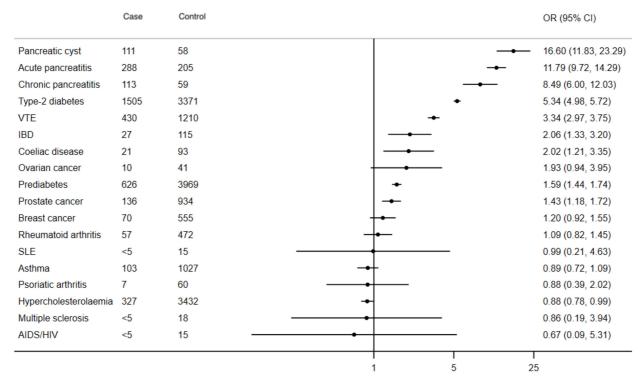


Long-standing (2000 to 2010)

	Case	Control							OR (95% CI)
AIDS/HIV	8	13			_	•	_		5.31 (2.09, 13.47)
Pancreatic cyst	9	9					_		4.90 (1.82, 13.24)
Chronic pancreatitis	51	105			-	-			2.43 (1.67, 3.52)
Type-2 diabetes	1407	8914			•				1.82 (1.71, 1.94)
Coeliac disease	41	206							1.82 (1.29, 2.57)
Acute pancreatitis	118	437			-				1.79 (1.42, 2.25)
Ovarian cancer	21	118			— —				1.77 (1.10, 2.85)
VTE	361	2661			-				1.27 (1.13, 1.42)
Prostate cancer	137	1016		ł	•				1.19 (0.98, 1.44)
Multiple sclerosis	30	240		-	•				1.13 (0.77, 1.67)
Breast cancer	206	1768		+	•-				1.08 (0.93, 1.25)
Asthma	1043	9298		ŀ	•				1.07 (1.00, 1.15)
IBD	110	939		+	-				1.06 (0.86, 1.30)
Rheumatoid arthritis	178	1578		+	-				1.02 (0.87, 1.20)
Prediabetes	94	695		-	_				0.96 (0.76, 1.21)
Hypercholesterolaemia	1097	10696		•					0.91 (0.85, 0.98)
SLE	5	60	_						0.84 (0.33, 2.10)
Psoriatic arthritis	15	185		-	_				0.75 (0.44, 1.28)
				1		1 5	1 25	12	5

Figure S10 (b): Subgroup analysis by year of diagnosis- association of comorbidities and risk of PDAC in diagnosis year 2011-2020 (or matching year in controls)

Recent-onset (2011-2020)

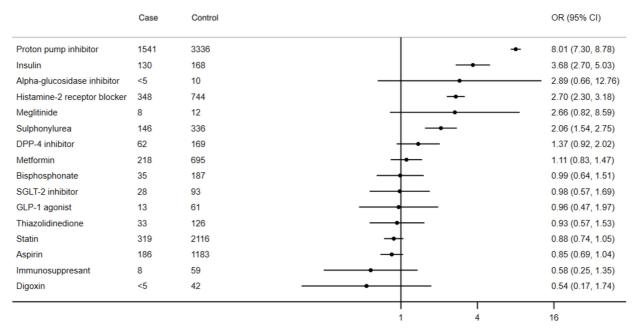


Long-standing (2011-2010)

	Case	Control		OR (95% CI)
Pancreatic cyst	33	42		7.19 (4.47, 11.59)
Ovarian cancer	40	203		2.05 (1.45, 2.91)
Type-2 diabetes	2787	17551	•	1.95 (1.85, 2.05)
Chronic pancreatitis	62	169		1.77 (1.28, 2.45)
AIDS/HIV	14	90	+	1.47 (0.82, 2.63)
Acute pancreatitis	173	803		1.47 (1.22, 1.76)
Breast cancer	436	3094	-	1.37 (1.23, 1.52)
VTE	592	4365	-	1.23 (1.12, 1.35)
IBD	180	1508	 -	1.11 (0.94, 1.30)
Prostate cancer	306	2552	 -	1.11 (0.98, 1.26)
Coeliac disease	61	491		1.10 (0.83, 1.46)
Hypercholesterolaemia	3109	26862	•	1.05 (1.00, 1.10)
Psoriatic arthritis	51	431		1.04 (0.77, 1.41)
Rheumatoid arthritis	275	2343	 -	1.04 (0.91, 1.19)
SLE	17	155	—	1.03 (0.62, 1.72)
Asthma	1663	14764	•	1.03 (0.97, 1.09)
Multiple sclerosis	38	356		1.02 (0.73, 1.44)
Prediabetes	770	5632	+	1.02 (0.94, 1.11)
			1 5	T 25

Figure S11 (a): Subgroup analysis by age - association of medications and risk of PDAC in age < 60 at index date

Recent-initiation (age <60)

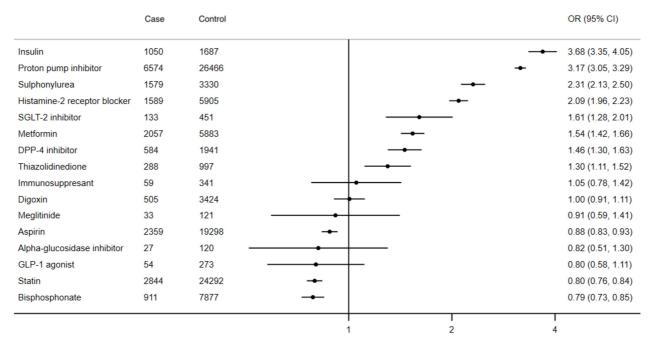


Long-standing (age <60)

	Case	Control		OR (95% CI)
Proton pump inhibitor	850	7055	+	2.20 (1.98, 2.45)
GLP-1 agonist	16	44	 	1.82 (0.85, 3.90)
Digoxin	16	68	 • • • • • • • • • • • • • • • • • • •	1.70 (0.90, 3.21)
Insulin	82	356	 -	1.54 (1.11, 2.12)
Sulphonylurea	146	614	—	1.42 (1.01, 2.00)
Alpha-glucosidase inhibitor	6	23		1.39 (0.49, 3.92)
Bisphosphonate	33	210	 •	1.34 (0.88, 2.04)
Thiazolidinedione	60	203	—	1.26 (0.84, 1.91)
Statin	467	3111		1.21 (1.02, 1.43)
Metformin	220	1124	 •	1.19 (0.84, 1.69)
Immunosuppresant	25	138		1.09 (0.64, 1.85)
DPP4- inhibitor	41	154		1.04 (0.64, 1.67)
Histamine-2 receptor blocker	407	3226	+	0.99 (0.87, 1.13)
Aspirin	306	2069	-	0.95 (0.80, 1.13)
Meglitinide	6	31		0.71 (0.26, 1.98)
SGLT-2 inhibitor	5	31		0.27 (0.08, 0.95)

Figure S11 (b): Subgroup analysis by age - association of medications and risk of PDAC in age >= 60 at index date

Recent-initiation (age >=60)



Long-standing (age >=60)

	Case	Control		OR (95% CI)
Insulin	722	3766		1.73 (1.57, 1.91)
Proton pump inhibitor	8402	72980	+	1.53 (1.47, 1.59)
SGLT-2 inhibitor	34	143	+	1.46 (0.97, 2.21)
Metformin	2648	16380		1.20 (1.10, 1.31)
Sulphonylurea	1934	11248	-	1.16 (1.06, 1.26)
Meglitinide	74	360		1.15 (0.88, 1.51)
DPP4- inhibitor	341	1740	—	1.15 (0.99, 1.32)
Immunosuppresant	138	1059		1.10 (0.91, 1.33)
Digoxin	916	6781	-	1.08 (1.00, 1.16)
Aspirin	8134	67100	 •	1.03 (0.99, 1.07)
Histamine-2 receptor blocker	4182	35299	 ←	1.03 (0.99, 1.07)
Thiazolidinedione	571	3225	-	0.99 (0.88, 1.11)
GLP-1 agonist	78	404		0.96 (0.73, 1.26)
Bisphosphonate	1663	14171	→	0.96 (0.91, 1.02)
Statin	8310	70645	+	0.95 (0.91, 0.99)
Alpha-glucosidase inhibitor	121	697		0.89 (0.72, 1.10)

Figure S12 (a): Subgroup analysis by sex - association of medications and risk of PDAC in female

Recent-initiation (female)

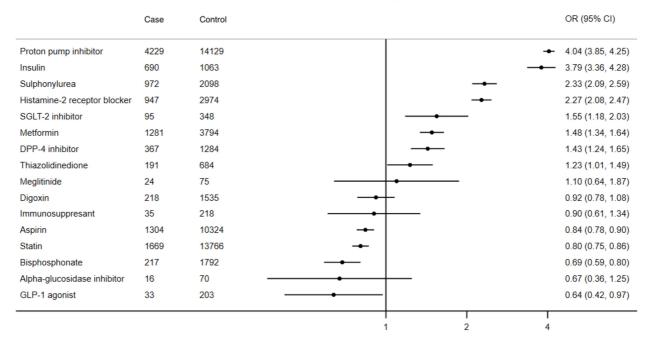
	Case	Control		OR (95% CI)
Insulin	490	792		3.55 (3.09, 4.08)
Proton pump inhibitor	3886	15673	-	3.30 (3.14, 3.46)
Sulphonylurea	753	1568		2.22 (1.97, 2.50)
Histamine-2 receptor blocker	990	3675	-	2.11 (1.95, 2.29)
DPP-4 inhibitor	279	826		1.50 (1.27, 1.77)
Metformin	994	2784	—	1.49 (1.33, 1.67)
SGLT-2 inhibitor	66	196		1.44 (1.04, 1.99)
Thiazolidinedione	130	439		1.34 (1.06, 1.69)
Alpha-glucosidase inhibitor	15	60		1.24 (0.66, 2.34)
Immunosuppresant	32	182		1.09 (0.73, 1.65)
GLP-1 agonist	34	131		1.05 (0.69, 1.60)
Digoxin	291	1931	-	1.04 (0.90, 1.19)
Meglitinide	17	58		0.95 (0.52, 1.74)
Aspirin	1241	10157	→	0.90 (0.83, 0.97)
Bisphosphonate	729	6272	→	0.82 (0.75, 0.89)
Statin	1494	12642	→	0.79 (0.74, 0.85)

Long-standing (female)

	Case	Control		OR (95% CI)
Insulin	377	1740	-	1.94 (1.69, 2.23)
Proton pump inhibitor	4922	42762	-	1.61 (1.53, 1.69)
Metformin	1245	7455		1.26 (1.11, 1.44)
Sulphonylurea	894	4993		1.16 (1.02, 1.31)
Thiazolidinedione	274	1403		1.10 (0.93, 1.29)
Immunosuppresant	83	628		1.09 (0.85, 1.39)
DPP4- inhibitor	160	805		1.06 (0.86, 1.30)
Digoxin	455	3446	 -	1.04 (0.94, 1.16)
Histamine-2 receptor blocker	2492	21178	 -	1.04 (0.99, 1.09)
Aspirin	3886	32230	+	1.01 (0.96, 1.06)
Bisphosphonate	1374	12018	-• 	0.95 (0.89, 1.02)
Statin	3983	33723	→	0.95 (0.89, 1.01)
GLP-1 agonist	44	205		0.95 (0.65, 1.38)
Alpha-glucosidase inhibitor	60	337		0.92 (0.68, 1.25)
SGLT-2 inhibitor	11	72	• 	0.87 (0.44, 1.71)
Meglitinide	34	196		0.86 (0.58, 1.28)

Figure S12 (b): Subgroup analysis by sex - association of medications and risk of PDAC in male

Recent-initiation (male)

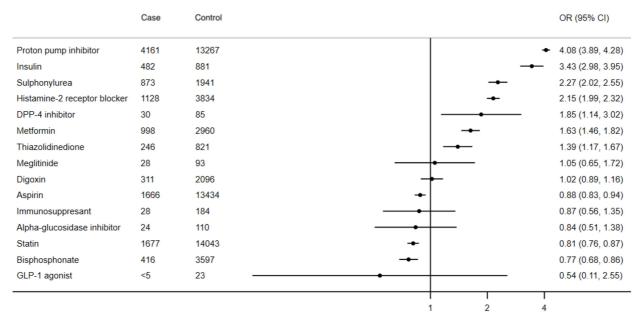


Long-standing (male)

I	Case	Control		OR (95% CI)
Proton pump inhibitor	4330	37273	+	1.62 (1.54, 1.70)
Insulin	427	2382	—	1.55 (1.36, 1.76)
SGLT-2 inhibitor	28	102	+	1.47 (0.90, 2.39)
Meglitinide	46	195	——	1.40 (0.98, 2.00)
DPP4- inhibitor	222	1089		1.25 (1.04, 1.50)
Sulphonylurea	1186	6869		1.18 (1.06, 1.32)
Metformin	1623	10049		1.14 (1.01, 1.28)
Immunosuppresant	80	569		1.14 (0.87, 1.48)
Digoxin	477	3403		1.13 (1.02, 1.26)
GLP-1 agonist	50	243		1.11 (0.79, 1.58)
Aspirin	4554	36939	 	1.04 (0.99, 1.10)
Bisphosphonate	322	2363		1.03 (0.91, 1.18)
Histamine-2 receptor blocker	2097	17347	+	1.00 (0.94, 1.06)
Statin	4794	40033	→	0.98 (0.92, 1.04)
Thiazolidinedione	357	2025		0.95 (0.82, 1.10)
Alpha-glucosidase inhibitor	67	383		0.87 (0.65, 1.17)

Figure S13 (a): Subgroup analysis year of diagnosis - association of medications and risk of PDAC in diagnosis year 2000-2010 (or matching year in controls)

Recent-initiation (2000-2010)

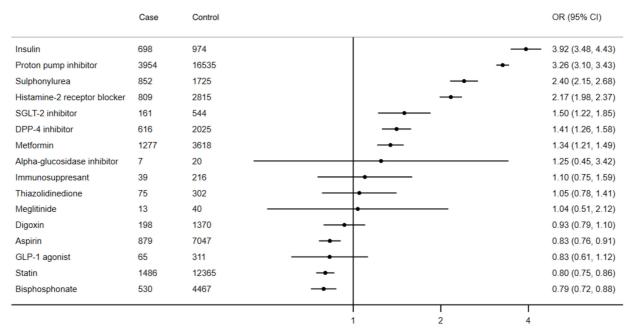


Long-standing (2000-2010)

	Case	Control						OR (95% CI)
Insulin	232	1146			-	•		1.93 (1.63, 2.29)
Proton pump inhibitor	2383	20479			•			1.64 (1.55, 1.74)
Immunosuppresant	57	387		+	-			1.30 (0.96, 1.76)
Sulphonylurea	775	4469			—			1.28 (1.12, 1.46)
Metformin	758	4664		ł	•			1.12 (0.98, 1.30)
Digoxin	495	3630		}	•			1.11 (1.00, 1.23)
Thiazolidinedione	131	668		+	•—			1.11 (0.88, 1.39)
Meglitinide	21	101			•	_		1.10 (0.65, 1.86)
Aspirin	3168	26817		+				0.98 (0.93, 1.04)
Alpha-glucosidase inhibitor	70	352						0.96 (0.72, 1.30)
Histamine-2 receptor blocker	1995	17191		•				0.94 (0.89, 1.00)
Statin	2119	18370		-				0.94 (0.87, 1.01)
Bisphosphonate	442	4031		-				0.88 (0.79, 0.98)
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Figure S13 (b): Subgroup analysis year of diagnosis - association of medications and risk of PDAC in diagnosis year 2011-2020 (or matching year in controls)

Recent-initiation (2011-2020)

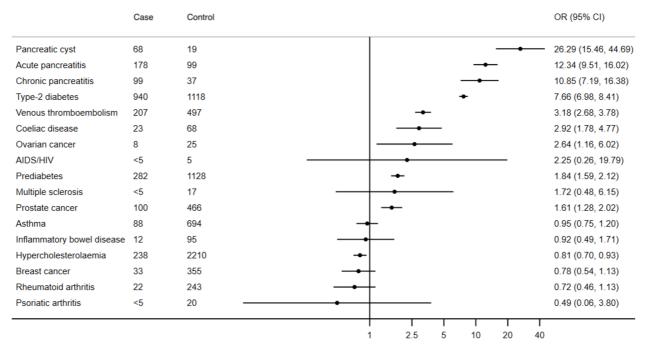


Long-standing (2011-2020)

	Case	Control		OR (95% CI)
Insulin	572	2976		1.66 (1.48, 1.85)
Proton pump inhibitor	6869	59556	-	1.56 (1.49, 1.63)
SGLT-2 inhibitor	39	174		1.21 (0.82, 1.78)
Metformin	2110	12840	 -	1.19 (1.07, 1.33)
Meglitinide	59	290		1.14 (0.84, 1.55)
Sulphonylurea	1305	7393		1.13 (1.02, 1.26)
DPP4- inhibitor	382	1894	 • 	1.13 (0.98, 1.30)
Histamine-2 receptor blocker	2594	21334	-	1.09 (1.03, 1.14)
Digoxin	437	3219	 	1.06 (0.95, 1.19)
Aspirin	5272	42352	+	1.05 (1.00, 1.11)
Immunosuppresant	106	810		1.05 (0.84, 1.31)
GLP-1 agonist	94	448		1.03 (0.80, 1.34)
Bisphosphonate	1254	10350	+	0.99 (0.93, 1.06)
Thiazolidinedione	500	2760		0.99 (0.87, 1.12)
Statin	6658	55386	-•	0.97 (0.92, 1.02)
Alpha-glucosidase inhibitor	57	368		0.81 (0.60, 1.09)
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Figure S14 (a): Subgroup analysis by body mass index (BMI) - association of comorbidities and risk of PDAC in individuals with BMI $<25 \text{kg/m}^2$ *

Recent-onset (BMI <25 kg/m2)



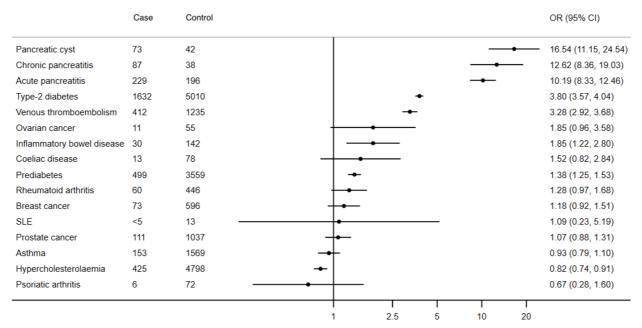
Long-standing (BMI <25 kg/m2)

	Case	Control							OR (95% CI)
Pancreatic cyst	9	14			•	_			3.85 (1.60, 9.26)
AIDS/HIV	10	37	-	-	_				2.55 (1.23, 5.27)
Type-2 diabetes	1295	5517		•					2.19 (2.05, 2.35)
Chronic pancreatitis	68	121	-	-					2.08 (1.49, 2.90)
Acute pancreatitis	123	331	-	•					1.84 (1.45, 2.33)
Coeliac disease	58	327	-	—					1.53 (1.15, 2.05)
Ovarian cancer	20	120	+-•						1.46 (0.90, 2.38)
Psoriatic arthritis	26	150	+•	_					1.24 (0.80, 1.91)
Breast cancer	246	1733	-						1.20 (1.05, 1.39)
Venous thromboembolism	270	1661	-						1.18 (1.03, 1.36)
SLE	10	81							1.18 (0.61, 2.28)
Prediabetes	262	1313	•						1.15 (0.99, 1.33)
Inflammatory bowel disease	118	842	 •−						1.10 (0.90, 1.35)
Asthma	967	7052	•						1.09 (1.02, 1.18)
Prostate cancer	154	1057	 						1.09 (0.91, 1.31)
Multiple sclerosis	24	208							1.04 (0.68, 1.61)
Rheumatoid arthritis	177	1308	+						1.03 (0.88, 1.22)
Hypercholesterolaemia	1458	10501	+						1.01 (0.95, 1.08)
			1	2.5	5	10	20	1 40	

^{*} Subgrouping variables were not matching factors in the case-control study design, hence, these subgroup analysis were performed without matching but instead analysed using mixed effects logistic regression using practice as a random-effect variable and additionally adjusted for other matching factors (age, sex, year of diagnosis).

Figure S14 (b): Subgroup analysis by body mass index (BMI) - association of comorbidities and risk of PDAC in individuals with BMI $>=25 \text{kg/m}^2$ *

Recent-onset (BMI >=25 kg/m2)



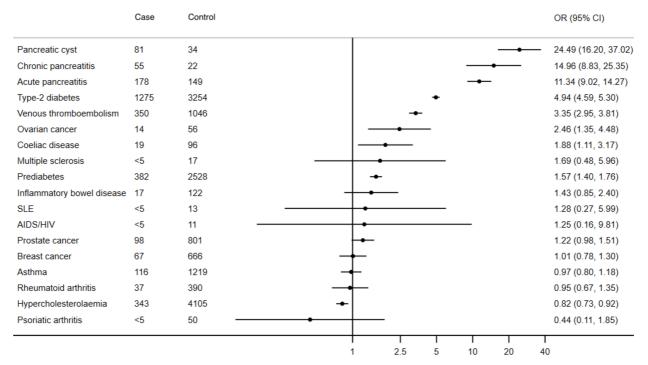
Long-standing (BMI >=25 kg/m2)

	Case	Control		OR (95% CI)
Pancreatic cyst	28	34		7.10 (4.23, 11.94)
Ovarian cancer	32	169		1.92 (1.31, 2.82)
AIDS/HIV	10	58	 	1.79 (0.90, 3.54)
Type-2 diabetes	2763	20028	•	1.62 (1.55, 1.70)
Chronic pancreatitis	35	131		1.54 (1.02, 2.31)
Acute pancreatitis	145	790		1.40 (1.16, 1.70)
Breast cancer	341	2539	-	1.32 (1.17, 1.48)
Multiple sclerosis	34	262	 • •	1.27 (0.88, 1.83)
Venous thromboembolism	608	4569	+	1.27 (1.16, 1.39)
Prostate cancer	251	2225	 • 	1.12 (0.98, 1.28)
Inflammatory bowel disease	148	1339	 -	1.07 (0.90, 1.27)
Rheumatoid arthritis	238	2180	-	1.04 (0.91, 1.20)
Asthma	1595	15216	+	1.01 (0.96, 1.07)
Coeliac disease	32	312		0.99 (0.68, 1.44)
Prediabetes	588	4845	+	0.96 (0.87, 1.05)
Hypercholesterolaemia	2595	25235	•	0.94 (0.90, 0.99)
SLE	11	121		0.91 (0.49, 1.71)
Psoriatic arthritis	35	428		0.77 (0.54, 1.09)

^{*} Subgrouping variables were not matching factors in the case-control study design, hence, these subgroup analysis were performed without matching but instead analysed using mixed effects logistic regression using practice as a random-effect variable and additionally adjusted for other matching factors (age, sex, year of diagnosis).

Figure S15 (a): Subgroup analysis by smoking status - association of comorbidities and risk of PDAC in never smokers*

Recent-onset (never-smokers)



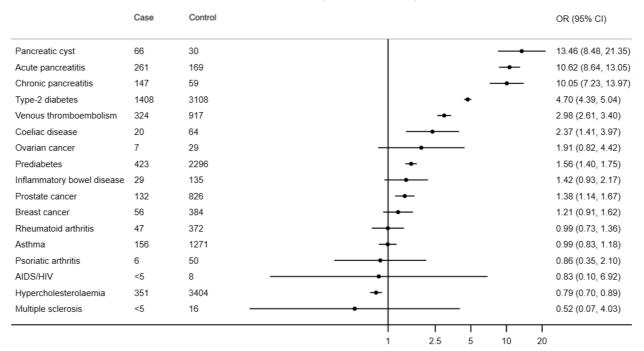
Long-standing (never-smokers)

	Case	Control									OR (95% CI)
Pancreatic cyst	26	26						•	_		8.78 (5.00, 15.43)
Chronic pancreatitis	32	96			_	•—					2.09 (1.35, 3.22)
Ovarian cancer	42	218			_	•					2.02 (1.44, 2.83)
AIDS/HIV	10	64		\vdash		•	-				1.99 (1.00, 3.96)
Type-2 diabetes	1954	13514			•	•					1.84 (1.74, 1.94)
Acute pancreatitis	107	596			—						1.46 (1.17, 1.82)
Breast cancer	376	2998		-	•						1.26 (1.13, 1.41)
Venous thromboembolism	475	3695		-	•						1.25 (1.13, 1.38)
Multiple sclerosis	34	293		+	•—						1.23 (0.86, 1.78)
Prostate cancer	215	1699		-	•						1.21 (1.04, 1.41)
Inflammatory bowel disease	140	1222		H	•						1.18 (0.98, 1.41)
Coeliac disease	50	425		+	—						1.14 (0.84, 1.55)
Asthma	1248	12410		•							1.04 (0.98, 1.11)
Rheumatoid arthritis	204	1925		+	-						1.03 (0.89, 1.20)
SLE	11	125	_	-+							0.98 (0.53, 1.83)
Prediabetes	388	3204		+							0.97 (0.86, 1.08)
Hypercholesterolaemia	1937	20048		•							0.92 (0.87, 0.97)
Psoriatic arthritis	19	281		•+							0.72 (0.45, 1.15)
				1		2.5	5 5	10	20	1 40	

^{*} Subgrouping variables were not matching factors in the case-control study design, hence, these subgroup analysis were performed without matching but instead analysed using mixed effects logistic regression using practice as a random-effect variable and additionally adjusted for other matching factors (age, sex, year of diagnosis).

Figure S15 (b): Subgroup analysis by smoking status - association of comorbidities and risk of PDAC in ever smokers (ex and current smokers)*

Recent-onset (ever-smokers)



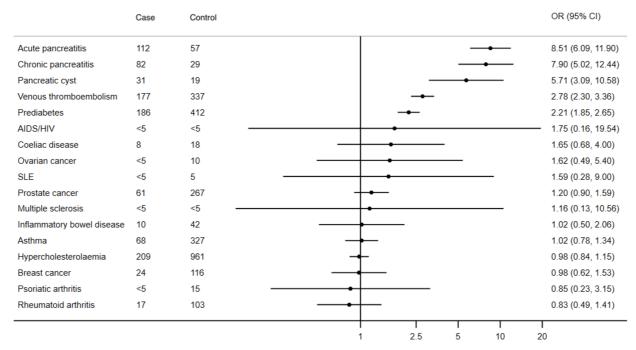
Long-standing (ever-smokers)

	Case	Control		OR (95% CI)
Pancreatic cyst	16	24		4.28 (2.20, 8.34)
AIDS/HIV	12	39		2.07 (1.07, 4.01)
Chronic pancreatitis	79	173	-	1.87 (1.39, 2.51)
Type-2 diabetes	2200	12698	•	1.86 (1.76, 1.96)
Acute pancreatitis	180	609	-	1.70 (1.41, 2.05)
Coeliac disease	50	257		1.50 (1.10, 2.05)
Ovarian cancer	16	92		1.44 (0.83, 2.48)
Breast cancer	255	1696	-	1.23 (1.07, 1.41)
Venous thromboembolism	457	3129	+	1.21 (1.09, 1.34)
Prostate cancer	220	1808	 -	1.05 (0.91, 1.22)
Prediabetes	476	3114	→	1.05 (0.94, 1.16)
SLE	11	87		1.04 (0.55, 1.96)
Psoriatic arthritis	44	331	-	1.04 (0.75, 1.43)
Rheumatoid arthritis	238	1841	+	1.02 (0.89, 1.18)
Hypercholesterolaemia	2247	17272	•	1.02 (0.97, 1.07)
Asthma	1423	11218	+	1.01 (0.95, 1.07)
Multiple sclerosis	31	271		0.93 (0.64, 1.35)
Inflammatory bowel disease	139	1150		0.91 (0.76, 1.10)
			1 1 1	1

^{*} Subgrouping variables were not matching factors in the case-control study design, hence, these subgroup analysis were performed without matching but instead analysed using mixed effects logistic regression using practice as a random-effect variable and additionally adjusted for other matching factors (age, sex, year of diagnosis).

Figure S16 (a): Subgroup analysis by type-2 diabetes status - association of comorbidities and risk of PDAC in individuals with type-2 diabetes*

Recent-onset (with type-2 diabetes)



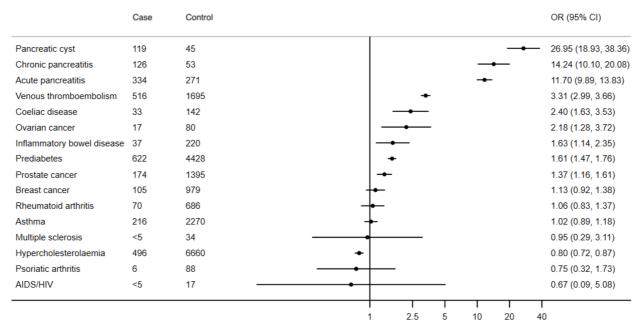
Long-standing (with type-2 diabetes)

	Case	Control		OR (95% CI)
Pancreatic cyst	15	14		4.74 (2.20, 10.22)
AIDS/HIV	5	12		1.79 (0.61, 5.23)
Ovarian cancer	12	36	 	1.78 (0.91, 3.47)
Chronic pancreatitis	66	103	_ 	1.64 (1.16, 2.31)
Coeliac disease	24	58		1.57 (0.96, 2.58)
Acute pancreatitis	124	331		1.38 (1.10, 1.74)
Venous thromboembolism	328	1293		1.35 (1.18, 1.53)
Breast cancer	148	599	 •	1.17 (0.97, 1.41)
Rheumatoid arthritis	134	531	 •	1.16 (0.95, 1.42)
Prostate cancer	132	606	 • 	1.15 (0.95, 1.40)
Prediabetes	509	2336	-	1.14 (1.02, 1.26)
Asthma	769	3768	+	1.01 (0.93, 1.10)
Inflammatory bowel disease	79	352		1.00 (0.78, 1.29)
Psoriatic arthritis	24	118		0.98 (0.62, 1.54)
Hypercholesterolaemia	1572	8098	•	0.93 (0.87, 0.99)
Multiple sclerosis	12	57		0.86 (0.45, 1.64)
SLE	<5	22 —	<u> </u>	0.72 (0.21, 2.46)

^{*} Subgrouping variables were not matching factors in the case-control study design, hence, these subgroup analysis were performed without matching but instead analysed using mixed effects logistic regression using practice as a random-effect variable and additionally adjusted for other matching factors (age, sex, year of diagnosis).

Figure S16 (b): Subgroup analysis by type-2 diabetes status - association of comorbidities and risk of PDAC in individuals with no type-2 diabetes*

Recent-onset (no type-2 diabetes)



Long-standing (no type-2 diabetes)

	Case	Control		OR (95% CI)
Pancreatic cyst	27	37		7.07 (4.26, 11.75)
AIDS/HIV	17	91		2.14 (1.26, 3.64)
Chronic pancreatitis	47	171		1.94 (1.38, 2.73)
Ovarian cancer	49	285		1.88 (1.38, 2.55)
Acute pancreatitis	167	909	-	1.65 (1.38, 1.97)
Coeliac disease	78	639	•	1.27 (1.00, 1.62)
Breast cancer	494	4263	•	1.24 (1.12, 1.36)
Venous thromboembolism	625	5733	•	1.18 (1.08, 1.28)
Prostate cancer	311	2962	→	1.14 (1.01, 1.29)
Multiple sclerosis	56	539	 • -	1.11 (0.84, 1.46)
Inflammatory bowel disease	211	2095	+	1.07 (0.92, 1.23)
SLE	19	193		1.06 (0.66, 1.71)
Asthma	1937	20294	•	1.04 (0.99, 1.09)
Prediabetes	355	3991	+	1.02 (0.91, 1.14)
Rheumatoid arthritis	319	3390	+	0.96 (0.85, 1.08)
Hypercholesterolaemia	2634	29460	4	0.96 (0.92, 1.00)
Psoriatic arthritis	42	498	-	0.91 (0.66, 1.25)

^{*} Subgrouping variables were not matching factors in the case-control study design, hence, these subgroup analysis were performed without matching but instead analysed using mixed effects logistic regression using practice as a random-effect variable and additionally adjusted for other matching factors (age, sex, year of diagnosis).

Figure S17 (a): Subgroup analysis by body mass index (BMI) - association of medications and risk of PDAC in individuals with BMI $<25 \text{kg/m}^{2^*}$

Recent-initiation (BMI <25 kg/m2)

	Case	Control	OR (95%	CI)
Insulin	406	339	4.46 (3.7	4, 5.33)
Proton pump inhibitor	2901	8832	◆ 3.72 (3.5	1, 3.94)
Sulphonylureas	599	659	2.34 (2.0	1, 2.72)
H2RA	701	1988	2.30 (2.0	8, 2.53)
SGLT2 inhibitor	38	53	1.96 (1.1	9, 3.23)
Biguanides	714	1078	1.84 (1.6	0, 2.13)
Thiazolidinedione	106	144	1.60 (1.1	7, 2.17)
Meglitinide	16	24	1.52 (0.7	4, 3.13)
DPP-4 inhibitor	181	336	1.50 (1.2	.0, 1.87)
Immunosuppresant	24	111	1.22 (0.7	5, 1.99)
GLP-1 agonist	<5	<5	1.10 (0.1	4, 8.71)
Digoxin	180	1031	1.06 (0.8	9, 1.26)
Aspirin	853	5658	0.85 (0.7	8, 0.93)
Statin	1065	7131	0.81 (0.7	4, 0.88)
Bisphosphonate	415	3284	0.76 (0.6	8, 0.85)
Alpha-glucosidase	11	29	0.67 (0.2	9, 1.53)
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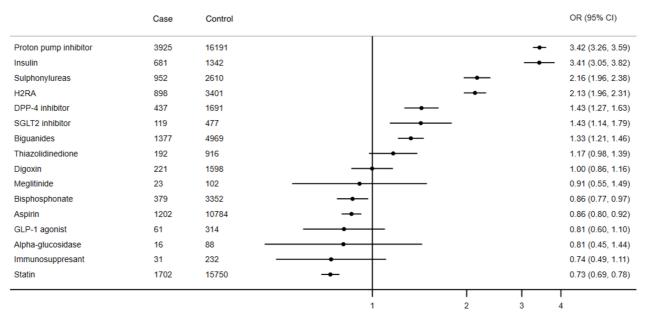
Long-standing (BMI <25 kg/m2)

	Case	Control		OR (95% CI)
GLP-1 agonist	5	8		3.25 (1.02, 10.36
SGLT2 inhibitor	10	13	-	2.03 (0.80, 5.17)
Proton pump inhibitor	3178	22946	•	1.61 (1.52, 1.71)
Biguanides	787	3077	-	1.36 (1.16, 1.58)
Meglitinide	21	74		1.32 (0.78, 2.24)
Insulin	171	776		1.32 (1.09, 1.60)
Immunosuppresant	61	386	+• -	1.14 (0.85, 1.54)
Digoxin	377	2305	 • 	1.11 (0.98, 1.25)
Thiazolidinedione	144	471		1.08 (0.85, 1.36)
Histamine-2 receptor blocker	1645	11345	+	1.05 (0.99, 1.12)
DPP4 inhibitor	94	303		1.05 (0.79, 1.40)
Sulphonylureas	633	2509	 -	1.04 (0.90, 1.21)
Aspirin	2886	19659	+	1.00 (0.94, 1.07)
Bisphosphonate	785	6235	- 	0.95 (0.87, 1.04)
Statin	2853	19176	→	0.95 (0.88, 1.01)
Alpha-glucosidase	29	143		0.64 (0.41, 1.00)

^{*} Subgrouping variables were not matching factors in the case-control study design, hence, these subgroup analysis were performed without matching but instead analysed using mixed effects logistic regression using practice as a random-effect variable and additionally adjusted for other matching factors (age, sex, year of diagnosis).

Figure S17 (b): Subgroup analysis by body mass index (BMI) - association of medications and risk of PDAC in individuals with BMI $>=25 \text{kg/m}^{2*}$

Recent-initiation (BMI >=25 kg/m2)



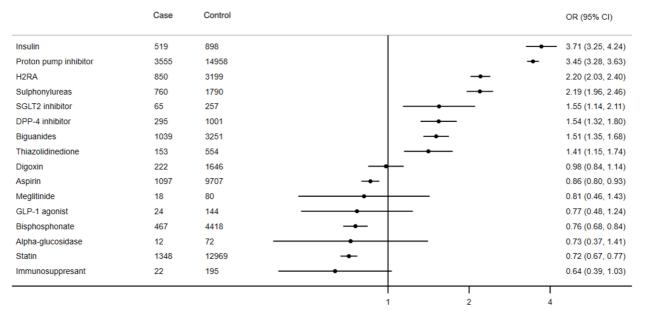
Long-standing (BMI >=25 kg/m2)

	Case	Control		OR (95% CI)
Insulin	588	3152	-	1.84 (1.65, 2.05)
Proton pump inhibitor	5291	49819	-	1.53 (1.46, 1.61)
DPP4 inhibitor	279	1555	——	1.17 (1.00, 1.36)
Sulphonylureas	1343	8774		1.17 (1.05, 1.29)
Biguanides	1960	13720	 • -	1.09 (0.98, 1.22)
Immunosuppresant	86	689		1.09 (0.85, 1.38)
SGLT2 inhibitor	29	156		1.07 (0.70, 1.66)
Digoxin	415	3500	 -	1.04 (0.93, 1.16)
Bisphosphonate	756	6660	 	1.03 (0.95, 1.12)
Meglitinide	55	302		1.03 (0.76, 1.40)
Aspirin	4817	42761	 -	1.03 (0.98, 1.08)
Histamine-2 receptor blocker	2457	22718	+	0.99 (0.94, 1.05)
Thiazolidinedione	462	2831	-	0.99 (0.88, 1.12)
Alpha-glucosidase	92	545		0.94 (0.74, 1.20)
GLP-1 agonist	84	428		0.94 (0.72, 1.23)
Statin	5423	50013	-	0.88 (0.83, 0.93)

^{*} Subgrouping variables were not matching factors in the case-control study design, hence, these subgroup analysis were performed without matching but instead analysed using mixed effects logistic regression using practice as a random-effect variable and additionally adjusted for other matching factors (age, sex, year of diagnosis).

Figure S18 (a): Subgroup analysis by smoking status - association of medications and risk of PDAC in never smokers*

Recent-initiation (Never-smokers)



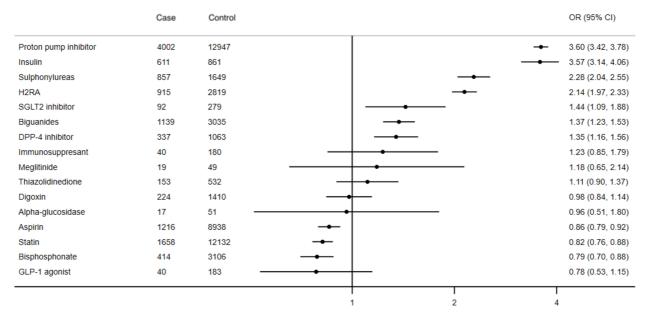
Long-standing (Never-smokers)

	Case	Control		OR (95% CI)
Insulin	333	2006		1.59 (1.38, 1.83)
Proton pump inhibitor	4242	41000	-	1.55 (1.47, 1.63)
Biguanides	1320	8768		1.23 (1.08, 1.39)
Immunosuppresant	81	595	 • • • • • • • • • • • • • • • • • • •	1.22 (0.95, 1.57)
Sulphonylureas	971	5993		1.18 (1.05, 1.33)
Digoxin	469	3422		1.16 (1.04, 1.29)
Meglitinide	37	193		1.13 (0.77, 1.66)
GLP-1 agonist	37	195		1.11 (0.75, 1.65)
DPP4 inhibitor	174	994		1.04 (0.85, 1.27)
Histamine-2 receptor blocker	2063	18937	 •	1.03 (0.97, 1.09)
Thiazolidinedione	280	1697		1.01 (0.87, 1.18)
Aspirin	3797	33863	+	1.00 (0.95, 1.05)
Bisphosphonate	931	8562	-• 	0.94 (0.87, 1.02)
Statin	3842	36067	→	0.91 (0.86, 0.97)
SGLT2 inhibitor	12	84		0.89 (0.46, 1.71)
Alpha-glucosidase	65	406		0.85 (0.63, 1.13)

^{*} Subgrouping variables were not matching factors in the case-control study design, hence, these subgroup analysis were performed without matching but instead analysed using mixed effects logistic regression using practice as a random-effect variable and additionally adjusted for other matching factors (age, sex, year of diagnosis).

Figure S18 (b): Subgroup analysis by smoking status - association of medications and risk of PDAC in ever smokers (ex and current smokers)*

Recent-initiation (Ever-smokers)



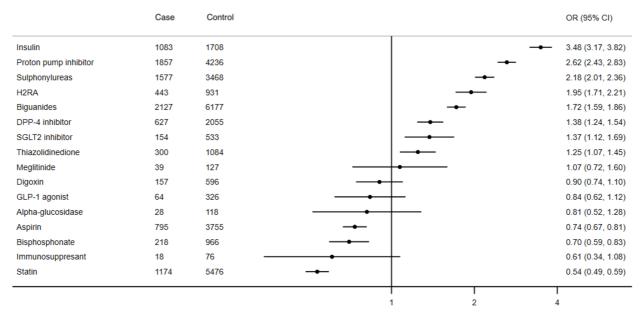
Long-standing (Ever-smokers)

	Case	Control		OR (95% CI)
Insulin	440	2015		1.76 (1.55, 2.00)
Proton pump inhibitor	4663	36264	-	1.57 (1.49, 1.65)
SGLT2 inhibitor	27	90	•	1.39 (0.86, 2.24)
DPP4 inhibitor	204	877		1.25 (1.04, 1.50)
Sulphonylureas	1037	5501	—	1.13 (1.01, 1.26)
Biguanides	1469	8315		1.12 (0.99, 1.26)
Meglitinide	40	187		1.06 (0.74, 1.54)
Aspirin	4279	32208	 • 	1.04 (0.99, 1.10)
Histamine-2 receptor blocker	2297	17575	-	1.01 (0.96, 1.07)
Thiazolidinedione	333	1651	—	1.01 (0.87, 1.18)
Immunosuppresant	71	543		0.99 (0.76, 1.30)
Bisphosphonate	701	5294	→	0.98 (0.89, 1.07)
Digoxin	378	2964		0.95 (0.84, 1.06)
Statin	4662	35607		0.93 (0.88, 0.98)
GLP-1 agonist	52	250		0.92 (0.66, 1.30)
Alpha-glucosidase	58	293		0.92 (0.67, 1.25)

^{*} Subgrouping variables were not matching factors in the case-control study design, hence, these subgroup analysis were performed without matching but instead analysed using mixed effects logistic regression using practice as a random-effect variable and additionally adjusted for other matching factors (age, sex, year of diagnosis).

Figure S19 (a): Subgroup analysis by type-2 diabetes status - association of medications and risk of PDAC in individuals with type-2 diabetes*

Recent-initiation (with type-2 diabetes)



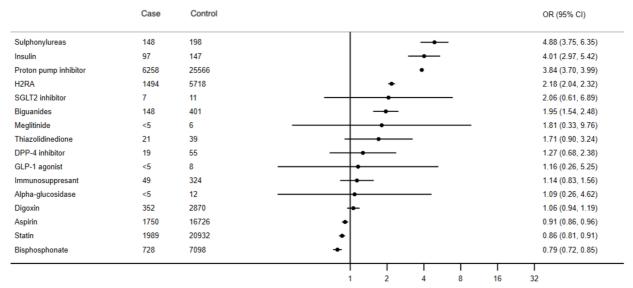
Long-standing (with type-2 diabetes)

	Case	Control		OR (95% CI)
Insulin	730	3808		1.49 (1.35, 1.64)
Proton pump inhibitor	2727	13567	-	1.40 (1.31, 1.51)
Meglitinide	77	379		1.14 (0.88, 1.49)
GLP-1 agonist	88	444		1.13 (0.87, 1.46)
DPP4 inhibitor	377	1869	 • -	1.12 (0.98, 1.29)
SGLT2 inhibitor	38	174		1.12 (0.76, 1.64)
Histamine-2 receptor blocker	1317	6061	 -	1.11 (1.03, 1.20)
Thiazolidinedione	614	3345	 • 	1.09 (0.98, 1.21)
Aspirin	3291	16862	+-	1.04 (0.97, 1.11)
Sulphonylureas	2006	11458	-	0.98 (0.90, 1.06)
Alpha-glucosidase	120	687		0.97 (0.79, 1.20)
Immunosuppresant	48	215		0.97 (0.68, 1.37)
Digoxin	303	1580	→	0.88 (0.77, 1.01)
Bisphosphonate	362	1791	—	0.84 (0.74, 0.96)
Biguanides	2765	16835		0.83 (0.76, 0.90)
Statin	3863	21066	→	0.68 (0.63, 0.74)

^{*} Subgrouping variables were not matching factors in the case-control study design, hence, these subgroup analysis were performed without matching but instead analysed using mixed effects logistic regression using practice as a random-effect variable and additionally adjusted for other matching factors (age, sex, year of diagnosis).

Figure S19 (b): Subgroup analysis by type-2 diabetes status - association of medications and risk of PDAC in individuals with no type-2 diabetes*

Recent-initiation (no type-2 diabetes)



Long-standing (no type-2 diabetes)

I	Case	Control	OR (95% CI)
GLP-1 agonist	6	<5	5.69 (1.15, 28.18)
Insulin	74	314	2.24 (1.68, 2.99)
Alpha-glucosidase	7	33	1.72 (0.70, 4.21)
Proton pump inhibitor	6525	66468	• 1.66 (1.59, 1.73)
Sulphonylureas	74	404	1.31 (0.92, 1.85)
Thiazolidinedione	17	83	1.28 (0.68, 2.41)
Digoxin	629	5269	← 1.21 (1.11, 1.33)
Meglitinide	<5	12	1.17 (0.26, 5.15)
Immunosuppresant	115	982	1.15 (0.94, 1.42)
Bisphosphonate	1334	12590	1.00 (0.94, 1.07)
Aspirin	5149	52307	1.00 (0.96, 1.04)
Histamine-2 receptor blocker	3272	32464	0.99 (0.94, 1.03)
Statin	4914	52690	0.94 (0.90, 0.98)
Biguanides	103	669	0.87 (0.64, 1.18)
DPP4 inhibitor	5	25	0.68 (0.21, 2.25)

^{*} Subgrouping variables were not matching factors in the case-control study design, hence, these subgroup analysis were performed without matching but instead analysed using mixed effects logistic regression using practice as a random-effect variable and additionally adjusted for other matching factors (age, sex, year of diagnosis).