Acute Pancreatitis and Pancreatic Cancer Risk: A Nationwide Matched-cohort Study in Denmark

Short title: Acute pancreatitis and pancreatic cancer risk

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Abbreviations: CI (confidence interval), CPR (Civil Personal Registration), DNPR (Danish National Patient Registry), HR (hazard ratio), ICD (International Classification of Diseases), IQR (inter-quartile range), SIR (standardized incidence ratio).

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ABSTRACT

Background & Aims

Acute pancreatitis may be a risk factor for pancreatic cancer. However, findings from studies on this association are conflicting. We investigated the association between acute pancreatitis and increased risk of pancreatic cancer.

Methods

We conducted a nationwide, population-based, matched cohort study of all patients admitted to a hospital in Denmark with a diagnosis of acute pancreatitis from January 1, 1980 through October 31, 2012. As many as 5 individuals from the general population without acute pancreatitis were matched for age and sex to each patient with acute pancreatitis. Pancreatic cancer risk was expressed as hazard ratios (HRs) with 95% CIs, calculated using the Cox proportional hazards model. Cox models were stratified by age, sex, and year of pancreatitis diagnosis and adjusted for alcohol- and smoking-related conditions, and Charlson Comorbidity Index score.

Results

We included 41,669 patients diagnosed with incident acute pancreatitis and 208,340 comparison individuals. Patients with acute pancreatitis had an increased risk of pancreatic cancer compared with the age- and sex-matched general population throughout the follow-up period. The risk decreased over time but remained high after more than 5 years of follow up (adjusted HR, 2.02; 95% CI, 1.57–2.61). Two- and 5-year absolute risks of pancreatic cancer among patients with acute pancreatitis were 0.68% (95% CI, 0.61%–0.77%) and 0.85% (95% CI, 0.76%–0.94), respectively.

Conclusions

In a nationwide, population-based, matched cohort study, we observed an association between diagnosis of acute pancreatitis and long-term risk of pancreatic cancer.

Keywords

Pancreas, etiology, epidemiology; risk factor

INTRODUCTION

Pancreatic cancer remains a major cause of cancer-related death worldwide and is associated with a dismal prognosis.[1, 2] Curative-intent surgery offers the only chance of survival from pancreatic cancer. However, less than 20% of patients are eligible for resection at the time of diagnosis due to locally advanced or metastatic disease.[1] To facilitate early diagnosis and thus increase resection rates of pancreatic cancer, knowledge on risk factors is essential.

Acute pancreatitis is a sudden-onset inflammatory disease of the pancreas.[3] Although experimental research suggests that acute pancreatitis can induce pancreatic cancer,[4, 5] findings from epidemiological studies are conflicting.[6-9] A case-control study of ~2,500 patients with pancreatic cancer within the US Veterans Affairs population,[6] and a British matched cohort study of ~6,000 patients with acute pancreatitis, both observed a positive association between acute pancreatitis and pancreatic cancer.[8] However, both studies only excluded pancreatic cancer cases occurring in the first year following acute pancreatitis, which may not allow sufficient time to eliminate reverse causation or surveillance bias. A US-based case-control study including ~300 patients with pancreatic cancer also found a positive association between acute pancreatitis and pancreatic cancer,[7] but did not include any lag-period from acute pancreatitis to pancreatic cancer. Furthermore, all three studies failed to report estimates of the association at different follow up times. In contrast, a Swedish cohort study of ~25,000 patients with acute pancreatitis reported no association with pancreatic cancer after more than ten years of follow up.[9] Thus, the association between acute pancreatitis and pancreatic cancer requires clarification.

We therefore conducted a nationwide population-based matched cohort study to examine the risk of pancreatic cancer in patients with acute pancreatitis compared with a matched comparison cohort from the general population.

METHODS

Setting and data sources

We conducted a nationwide, population-based, matched cohort study from January 1980 through October 2013, using data from the Danish National Patient Registry (DNPR), Civil Registration System, and Danish Cancer Registry. These registries can be linked on an individual level using the Civil Personal Registration (CPR)-number, which is assigned to every Danish resident at birth or immigration.

The DNPR was established in 1977 and contains information on all inpatient hospitalizations to Danish public hospitals.[10] Outpatient and emergency room visits have been included since 1995. Patients are registered in the DNPR with diagnoses according to the International Classification of Diseases (ICD) 8th revision (ICD-8) from 1977 through 1993 and ICD 10th revision (ICD-10) hereafter.

The Civil Registration System, which was established in 1968, is an administrative registry containing data on variables like birth date, sex, sequential dates of migration, and vital status for every resident in Denmark.[11] The Civil Registration System is updated daily and virtually complete.

The Danish Cancer Registry was established in 1943 and includes information on all cancers diagnosed in Denmark.[12] This registry contains information on date of diagnosis, cancer site, histology, dissemination, and other variables.

Acute pancreatitis cohort

From the DNPR, we identified a cohort of all individuals with an inpatient diagnosis of acute pancreatitis from January 1980 through October 2012 (n=44,589), allowing for at least one year of follow up for all patients. We applied a three-year washout period since the start of the DNPR (1977-1979) to reduce the likelihood of including prevalent cases of acute pancreatitis.

For each individual, we defined the date of the first diagnosis of acute pancreatitis as their index date. We did not include outpatient diagnoses of acute pancreatitis (n=680), as these are most likely to represent a post-admission follow-up consultation or miscoding. We excluded patients from the acute pancreatitis cohort if they had a diagnosis of pancreatic cancer (n=119), chronic pancreatitis/other exocrine pancreatic disease (n=2,367), or if they underwent pancreatic resection or transplantation (n=49) prior to the index date. Likewise, patients aged less than 18 years at the index date were also excluded (n=385). In total, 41,669 patients were included in this study. A detailed flowchart of the study population is provided in the supplementary material (Figure S1).

Matched comparison cohort

For each patient in the acute pancreatitis cohort, we used the Civil Registration System to identify a pool of individuals from the general population with the same sex and year of birth, who were alive in Denmark on the patient's index date (*i.e.* the date of the first acute pancreatitis diagnosis). From this pool of eligible comparison subjects, we randomly selected five individuals, thereby constructing a matched comparison cohort. We sampled with replacement, *i.e.* individuals could act as comparison subjects to several acute pancreatitis patients, but no individual could be sampled more than once to the same patient.[13] Furthermore, we required that the comparison subjects were free of acute pancreatitis, chronic pancreatitis/other exocrine pancreatic disease, and pancreatic cancer, and that they had not undergone pancreatic resection or transplantation prior to the acute pancreatitis patient's index date. We defined the index date for the comparison subjects as the date of diagnosis of the acute pancreatitis patient to whom they were matched. Individuals in the matched comparison cohort entered the acute pancreatitis cohort if they developed acute pancreatitis during follow up (n=1,165), in which case they were censored from the comparison cohort.

Follow up and pancreatic cancer outcome

In order to investigate the risk of pancreatic cancer, we followed the acute pancreatitis patients and the comparison subjects from their respective index dates until pancreatic cancer as recorded in the Danish Cancer Registry; chronic pancreatitis/other exocrine pancreatic disease, pancreatic resection or transplantation (and for comparison subjects also acute pancreatitis); death; emigration; or 1 November 2013, whichever came first.

Comorbidity and surgical procedures

To assess the impact of comorbidity on the association between acute pancreatitis and pancreatic cancer, we retrieved a full medical history from the DNPR for the entire study population. We used this medical history to identify selected conditions that may modify pancreatic cancer risk (obesity, and alcohol- and smoking-related conditions) and to calculate the Charlson Comorbidity Index (CCI) score.[14] We defined three levels of comorbidity: Low (score 0), moderate (score 1-2), and severe (score ≥ 3) comorbidity. We excluded non-melanoma skin tumors from the CCI score. In addition, we also excluded selected medical conditions (alcohol- and smoking-related diagnoses) from the CCI score, as these covariates were assessed separately.

We identified surgical procedures of interest (cholecystectomy, pancreatic surgery, and endoscopic retrograde cholangiopancreatography [ERCP]) from the DNPR. Surgical procedures were identified using the *Danish Classification of Surgical Procedures and Therapy* for procedures performed during 1977-1995 and the *Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures* hereafter. See supplementary material for relevant ICD and procedure codes (Tables S1-S3).

Statistical analyses

We tabulated descriptive characteristics for the study population. Continuous variables were presented as medians with inter-quartile ranges (IQRs). We divided the follow-up time into three periods depending on the time from index date to termination of follow-up: 0-2 years (short term risk), >2-5 years (intermediate term risk), and >5 years (long term risk). At the start of a new follow-up period, we excluded all comparison subjects matched to an acute pancreatitis patient no longer at risk (*i.e.* the acute pancreatitis patient had met the outcome or any complication listed above, emigrated, or died).

For each follow-up period, we calculated the incidence rate of pancreatic cancer as the number of pancreatic cancers divided by the total person-time accrued in that period. Using stratified Cox proportional hazards regression models,[15] we computed crude and adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) as a measure of the incidence rate ratio. We developed a directed acyclic graph (DAG) to identify which confounders to adjust for in the multivariate models (Figure S2). In the multivariate model, we stratified on age, sex, calendar year of acute pancreatitis diagnosis, and adjusted for alcohol- and smoking-related conditions, and the CCI score. The proportional hazards assumptions were assessed using log-log plots. Cumulative incidence functions, treating death as a competing risk, were calculated as a measure of the absolute risk in the acute pancreatitis cohort. Data extraction and construction of the matched comparison cohort was performed by UH using SAS (SAS Institute Inc., Cary, North Carolina, USA). All data cleaning and statistical analyses were performed by JK using Stata 13.1 (StataCorp LP, College Station, Texas, USA).

Sensitivity analyses

We performed several sensitivity analyses to examine the robustness of our results. First, we restricted to individuals with at least one year of follow up. Second, we examined the association after a minimum of 10 years of follow up. In both analyses, we followed the individuals from the respective time point until the end of follow-up. Third, we allowed comparison subjects diagnosed with acute pancreatitis after the index date to contribute person-time in both cohorts, resembling an intention-to-treat (ITT) analysis.[16] Fourth, we recalculated the CCI score after five years of follow up (Table S4) to assess if additional comorbidity diagnosed within this period had an impact on our estimates. Fifth, we restricted to patients with recurrent acute pancreatitis, defined as two or more hospitalizations for acute pancreatitis, each at least 90 days from discharge until the next admission.[17] We followed these patients from the date of their second acute pancreatitis admission to avoid immortal time bias[18] and adjusted the follow-up start for their matched comparison subjects to the same date. Sixth, we examined the association between acute pancreatitis and pancreatic cancer beyond five years of follow up according to the acute pancreatitis etiology. As information on acute pancreatitis etiology is not routinely recorded in the DNPR, we used the following proxy measures: 1) alcoholic pancreatitis, if a diagnosis of an alcohol-related disease occurred before, or on the same date as the acute pancreatitis diagnosis; 2) biliary pancreatitis, if a diagnosis of gallstone, cholecystitis, cholangitis, or gallstone-pancreatitis was recorded simultaneously with the acute pancreatitis diagnosis; 3) ERCP-pancreatitis, if an ERCP was conducted less than 5 days before the acute pancreatitis diagnosis; and 4) idiopathic, if the etiology was unknown. Patients eligible in more than one of these groups were prioritized according to the listing above. Seventh, we restricted to individuals without a history of smoking-related disease before the index date to assess the impact of confounding from tobacco smoking. Finally, we restricted our analyses to individuals with no history of

smoking- or alcohol-related disease to assess the impact of residual confounding from exposure to these substances.

Ethical considerations

This study was approved by the Danish Data Protection Agency (*J.nr. 1-16-02-139-16*) and the Danish Health Data Authority. According to Danish law, ethical approval is not required for registry-based studies.

RESULTS

Baseline characteristics

We included 41,669 patients with a first-diagnosis of acute pancreatitis and 208,340 comparison individuals, matched on age and sex (Table 1). Median ages were 55.8 (IQR: 41.4-71.2) and 55.8 (IQR: 41.4-71.3) years in the respective cohorts. Approximately half (54.7%) were men. Median follow-up time for the two cohorts was 5.3 (IQR: 1.4-12.0) and 5.0 (IQR: 2.0-13.0) years, respectively. Compared with the comparison cohort, patients with acute pancreatitis had a higher burden of comorbidity, including alcohol- and smoking-related diseases, gallstones, obesity, and diabetes.

Pancreatic cancer risk

In total, 937 cancers occurred in the study population (Table S5). Patients with acute pancreatitis had increased risk of pancreatic cancer compared with the comparison subjects within the first two years of follow up (adjusted HR [aHR]: 19.52; 95% CI: 14.81-25.73; Table 2). Acute pancreatitis patients still had an increased risk of pancreatic cancer compared with the comparison subjects in the period from two to five years post pancreatitis diagnosis

(aHR: 2.43; 95% CI: 1.73-3.51). Patients followed for more than five years after the initial episode of acute pancreatitis still had a higher risk of pancreatic cancer than the comparison cohort (aHR: 2.02; 95% CI: 1.57-2.61). Absolute two- and five-year risks of pancreatic cancer among patients with acute pancreatitis were 0.68% (95% CI: 0.61%-0.77%) and 0.85% (95% CI: 0.76%-0.94%), respectively (Figure 1).

Sensitivity analyses

The first two sensitivity analysis, restricting to patients with acute pancreatitis followed for more than one and 10 years yielded adjusted HRs of 2.40 (95% CI: 1.99-2.88) and 2.21 (95% CI: 1.56-3.13) respectively. The sensitivity analyses, in which we resembled an ITT analysis and reassessed the burden of comorbidity after five years of follow up did not substantially change our estimates. When restricting to patients with recurrent acute pancreatitis (n=4,654; 11.2% of the acute pancreatitis population), our estimate beyond five years of follow up attenuated slightly (aHR: 1.81; 95% CI: 0.65-5.05), although this was imprecise due to few observations. When stratifying the patients according to the acute pancreatitis etiology, our sensitivity analysis suggested that, compared with the general population, patients with idiopathic pancreatitis have the highest pancreatic cancer risk, followed by patients with biliary pancreatitis. No meaningful interpretation can be made from the group of patients with alcoholic or ERCP-related pancreatitis (Table 3). Finally, our assessment of the impact of confounding from tobacco smoking and alcohol consumption showed no substantial effect on our estimates (Tables S6 and S7).

DISCUSSION

In the present study, patients hospitalized with incident acute pancreatitis had an increased risk of pancreatic cancer compared with the general population. Although the risk was highest in the first two years following acute pancreatitis diagnosis, it remained elevated throughout the follow-up period. After both five and ten years of follow up, pancreatic cancer risk in patients with acute pancreatitis was still double that of their matched comparison subjects. Our results were robust to various sensitivity analyses, except for some variation between subgroups based on the presumed acute pancreatitis etiology.

Several factors require consideration when interpreting our findings. First, our population-based design using Danish population-based and medical registries ensures long term and virtually complete follow up. Second, data in the nationwide registries used in this study has been prospectively registered for administrative and reimbursement purposes, allowing us to obtain a large study population with a high precision for most of our estimates. Third, although pancreatic cancer diagnoses in the Danish Cancer Registry have not been previously validated, this registry has a high overall validity (*e.g.* ~90% of all registered cancers are verified histologically) with compulsory reporting since 1987.[19, 20] Furthermore, the Danish Cancer Registry is cross-linked with the DNPR and the Danish National Pathology Registry to minimize the risk of coding errors. Fourth, we applied a three-year washout period from the start of the DNPR until the start of patient inclusion to minimize the risk of including prevalent acute pancreatitis diagnoses.

Some limitations should be considered when interpreting our findings. First, the accuracy of our findings depends on the validity of acute pancreatitis diagnoses in the DNPR. We have previously validated a subset of the acute pancreatitis diagnoses in the DNPR, showing a positive predictive value of 97.3% (manuscript submitted). Other authors have also reported a high validity of acute pancreatitis diagnoses in the DNPR.[21, 22] In addition, descriptive characteristics of the acute pancreatitis patients in our study are similar to previous

reports,[23-26] thus misclassification of exposure is of limited concern. Second, we did not have information on potential confounders such as tobacco smoking and alcohol consumption. However, to address this limitation we adjusted our estimates for selected smoking- and alcohol-related conditions. Our afore-mentioned validation study also suggests that alcohol-related conditions registered in the DNPR are a useful tool to capture alcohol exposure in patients with acute pancreatitis, whereas smoking-related conditions have lower validity. Residual confounding by tobacco smoking and, partly, alcohol consumption may thus have led to an overestimation of the association between acute pancreatitis and pancreatic cancer. However, our sensitivity analyses suggest that residual confounding is unlikely to substantially impact our findings. Third, acute pancreatitis etiology (*e.g.* alcoholic, biliary, ERCP-related, or idiopathic) is not routinely reported in the DNPR. Therefore, we were only able to assess the impact of etiology based on proxy-measures. Although our estimates indicate a lower risk of pancreatic cancer in patients with alcoholic pancreatitis, we emphasize the uncertainty in these proxy measures. This uncertainty is supported by the disproportionately large number of patients in the idiopathic acute pancreatitis group (51.6%) and the substantial variation in our estimates between men and women in the subgroups. Furthermore, in some of the subgroups, it was doubtful if the proportional hazards assumption was fulfilled.

Most previous studies investigating the association of acute pancreatitis and pancreatic cancer failed to report risk estimates by follow up time.[6-8] Such estimates are essential to thoroughly interpret and compare findings from different studies, as pancreatic cancer usually evolves over several years.[27] Thus, a pancreatic cancer observed shortly after the start of follow up is likely present at the time of acute pancreatitis diagnosis; acute pancreatitis is unlikely to be a causal factor. This is reflected in our observed 20-fold increased risk of pancreatic cancer within the first two years after acute pancreatitis diagnosis,

consistent with previous research.[28, 29] As such, failing to provide estimates of association at different follow up times leads to a spuriously strong overall association. A US-based pancreatic cancer case-control study by Duell *et al*.[7] failed to incorporate such a lag-period after acute pancreatitis diagnosis. They reported an odds ratio of 6.4 but the precision of their estimates was limited (95% CI: 2.7-15.0). Moreover, their effect estimates were similar in magnitude among patients with either acute or chronic pancreatitis. As chronic pancreatitis is more strongly associated with pancreatic cancer than acute pancreatitis,[30] their odds ratio of pancreatic cancer could be expected to differ between acute and chronic pancreatitis patients. In addition, pancreatitis diagnoses in their study were self-reported, thus recall bias and misclassification of acute and chronic pancreatitis seems likely. The study by Duell *et al*. may also be prone to selection bias as they conducted their study within a selected geographic area and had a response rate of only 67% among both cases and controls.

Our finding of an approximately two-fold increased risk of pancreatic cancer among patients with pancreatitis concurs with other studies.[6, 8] In a Veterans Affairs-based case-control study, Bansal *et al*.[6] provided an unadjusted odds ratio for pancreatic cancer of 1.76 (95% CI: 1.28-2.41) among patients with acute pancreatitis after excluding cases of pancreatic cancer diagnosed within the first year of acute pancreatitis diagnosis. Likewise, Goldacre *et al*.[8] reported an effect estimate of 3.0 (95% CI: 2.2-4.0) in a British matched cohort study. Our results agree with these findings, but extend the current knowledge by reporting the association of acute pancreatitis and pancreatic cancer according to follow-up time.

Our observed elevated pancreatic cancer risk beyond five years of follow up compares to findings from a Swedish cohort study by Karlson *et al*.[9] They report an age-, sex-, and calendar year-standardized incidence ratio (SIR) of pancreatic cancer of 1.6 (95% CI: 1.1-2.2) in the period five to nine years following acute pancreatitis diagnosis but an attenuated SIR beyond ten years of follow up (SIR: 1.2; 95% CI: 0.7-1.7). In contrast to our study, they

included only a selection of the ICD codes used to classify pancreatitis diagnoses. Their study therefore may be prone to exposure misclassification and may be difficult to compare with other studies. In addition, although Karlson *et al*. reported the risk of pancreatic cancer for each type of pancreatitis (*i.e*. acute, recurrent acute, chronic, and unspecified), the magnitude of the risk of pancreatic cancer among patients with chronic pancreatitis differed substantially from other reports at different follow up periods.[31, 32] Although the overall estimate in the study by Karlson *et al*. was similar to one of the reports,[31] it was considerably lower than in the other,[32] suggesting that the study by Karlson *et al*. may be prone to misclassification.

In conclusion, patients admitted with acute pancreatitis had an increased risk of pancreatic cancer compared with age- and sex-matched comparison subjects from the general population.

FIGURE LEGENDS

Figure 1. Cumulative incidence of pancreatic cancer in 41,669 patients diagnosed with acute pancreatitis and 208,340 comparison subjects. Full line: Acute pancreatitis patients; dashed line: Matched comparison cohort.

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Table 1. Descriptive characteristics of 41,669 patients diagnosed with acute pancreatitis and 208,340 comparison subjects.

	Acute pancreatitis N=41,669		Comparison subjects N=208,340	
	N	**%**	**N**	**%**
Median age, years (IQR)	55.8 (41.4-71.2)		55.8 (41.4-71.3)	
Age group				
≤35 years	6,177	14.8%	30,824	14.8%
>35-45 years	6,849	16.4%	34,371	16.5%
>45-55 years	7,228	17.3%	35,963	17.3%
>55-65 years	6,820	16.4%	34,179	16.4%
>65-75 years	6,601	15.8%	33,049	15.9%
>75 years	7,994	19.2%	39,954	19.2%
Sex				
Women	18,861	45.3%	94,304	45.3%
Men	22,808	54.7%	114,036	54.7%
Total person-years	321,538		1,769,344	

Median follow-up time, years (IQR)	5.3 (1.4-12.0)		5.0 (2.0-13.0)	
Charlson Comorbidity Index				
Low (score 0)	28,133	67.5%	172,441	82.8%
Intermediate (score 1-2)	10,746	25.8%	30,642	14.7%
Severe (score >2)	2,790	6.7%	5,257	2.5%
Comorbidity diagnoses				
Alcohol-related	5,643	13.5%	4,112	2.0%
Smoking-related	3,200	7.7%	6,304	3.0%
Gallstone	13,148	31.6%	4,983	2.4%
Obesity	1,913	4.6%	3,226	1.5%
Diabetes mellitus	3,031	7.3%	6,174	3.0%
Operations at baseline				
ERCP	1,381	3.3%	1,117	0.5%
Cholecystectomy	1,816	4.4%	3,808	1.8%
Operations during follow-up				
ERCP	10,264	24.6%	1,392	0.7%

Cholecystectomy	9,526	22.9%	2,414	1.2%
Pancreatic resection	120	0.3%	36	<0.1%
Calendar period of index date				
1980-1993	14,215	34.1%	71,075	34.1%
1994-2003	14,298	34.3%	71,485	34.3%
2004-2012	13,156	31.6%	65,780	31.6%

Table 2. Hazard ratios of pancreatic cancer in 41,669 patients diagnosed with acute pancreatitis compared with 208,340 comparison subjects stratified by follow-up time.

Follow-up	Acute pancreatitis N=41,669			Comparison subjects N=208,340			Hazard ratio	
	Events	No. at risk	Person-years	Events	No. at risk	Person-years	Crude	Adjusted
0-2 years								
All	276	41,669	65,951	97	208,340	399,509	16.42 (13.02-20.69)	**19.28 (14.62-25.41)**
Women	114	18,861	30,385	41	94,304	180,548	15.85 (11.09-22.65)	**20.52 (13.09-30.95)**
Men	162	22,808	35,566	56	114,036	218,962	16.86 (12.44-22.85)	**19.28 (13.26-27.60)**
>2-5 years								
All	56	29,254	75,080	109	138,842	375,765	2.57 (1.87-3.55)	**2.43 (1.73-3.41)**
Women	25	13,659	35,336	52	64,861	174,209	2.37 (1.47-3.83)	**2.36 (1.40-3.99)**
Men	31	15,595	39,743	57	73,981	201,557	2.76 (1.78-4.27)	**2.73 (1.72-4.35)**
>5 years								
All	103	21,413	180,506	296	95,537	994,069	1.96 (1.57-2.46)	**2.02 (1.57-2.61)**

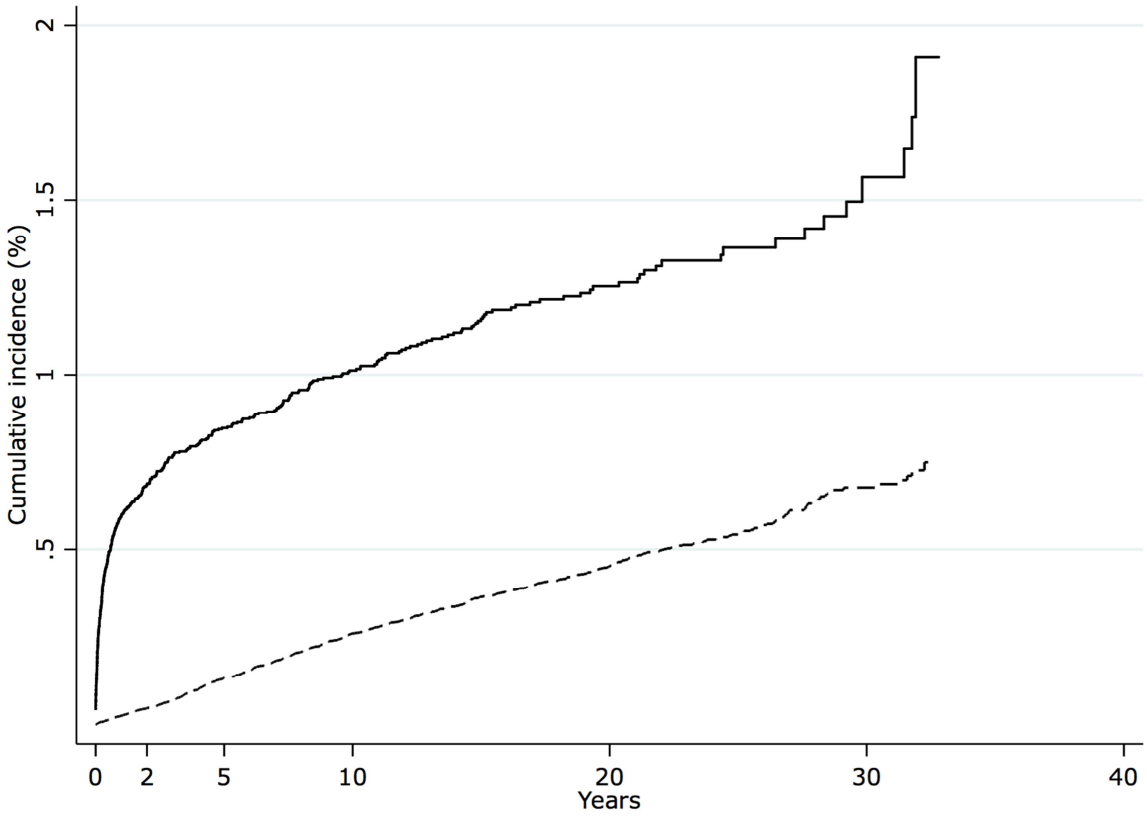
Women	55	10,157	83,679	129	45,471	430,604	2.21 (1.61-3.03)	**2.23 (1.58-3.17)**
Men	48	11,256	96,827	167	50,066	563,465	1.74 (1.26-2.41)	**1.87 (1.28-2.71)**

Table 3. Hazard ratios of pancreatic cancer in 21,413 patients diagnosed with acute pancreatitis compared with 95,537 comparison subjects alive and at risk after five years of follow-up, stratified by presumed etiology of acute pancreatitis.

Etiology	Acute pancreatitis N=21,413			Comparison subjects N=95,537			Hazard ratio	
	Events	No. at risk	Person-years	Events	No. at risk	Person-years	Crude	Adjusted
Alcohol								
All	3	2,225	16,784	41	10,537	127,468	0.64 (0.20-2.09)	**0.63 (0.18-2.19)**
Women	0	534	4,165	4	2,565	30,093	-	**-**
Men	3	1,691	12.619	37	7,972	97,374	0.71 (0.22-2.32)	**0.8 (0.23-2.82)**
Biliary								
All	29	6,650	47,381	76	29,067	215,543	1.75 (1.14-2.68)	**1.80 (1.13-2.89)**
Women	23	4,442	32,815	50	19,798	150,515	2.12 (1.29-3.47)	**2.07 (1.20-3.58)**
Men	6	2,208	14,566	26	9,269	65,028	1.04 (0.43-2.52)	**1.28 (0.49-3.35)**

ERCP								
All	3	605	5,737	12	2,629	28,008	1.20 (0.34-4.26)	**1.23 (0.32-4.72)**
Women	1	387	3,743	9	1,699	18,192	0.52 (0.07-4.10)	**0.50 (0.06-4.25)**
Men	2	218	1,993	3	930	9,816	3.39 (0.57-20.32)	**3.97 (0.54-29.42)**
Idiopathic								
All	68	11,933	110,605	167	53,304	623,050	2.33 (1.76-3.09)	**2.52 (1.83-3.47)**
Women	31	4,794	42,955	66	21,409	231,804	2.52 (1.64-3.86)	**2.85 (1.77-4.59)**
Men	37	7,139	67,650	101	31,895	391,246	2.20 (1.50-3.20)	**2.29 (1.48-3.55)**

ERCP: Endoscopic retrograde cholangiopancreatography



APPENDIX

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Figure S1. Flowchart of the study population

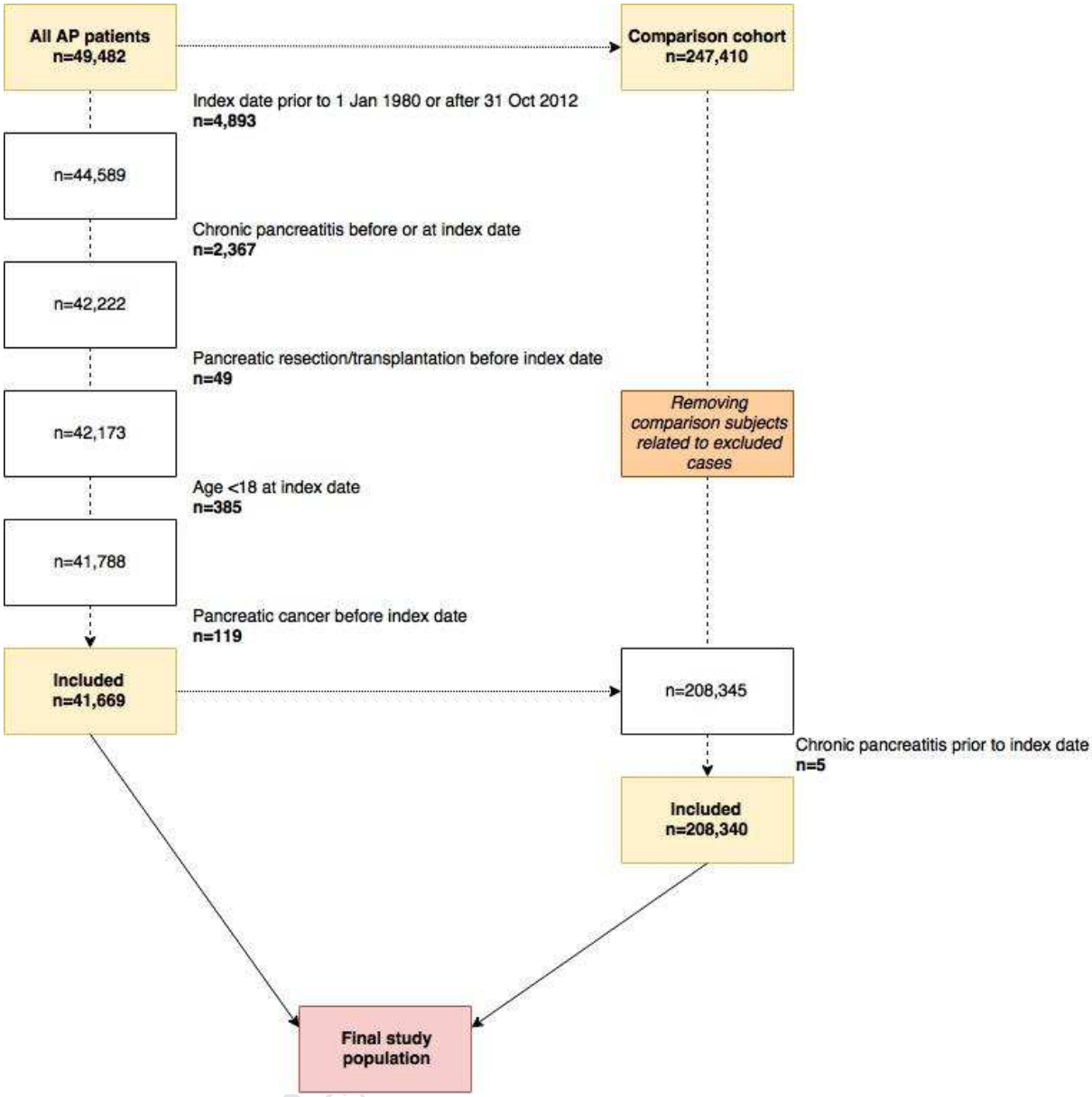
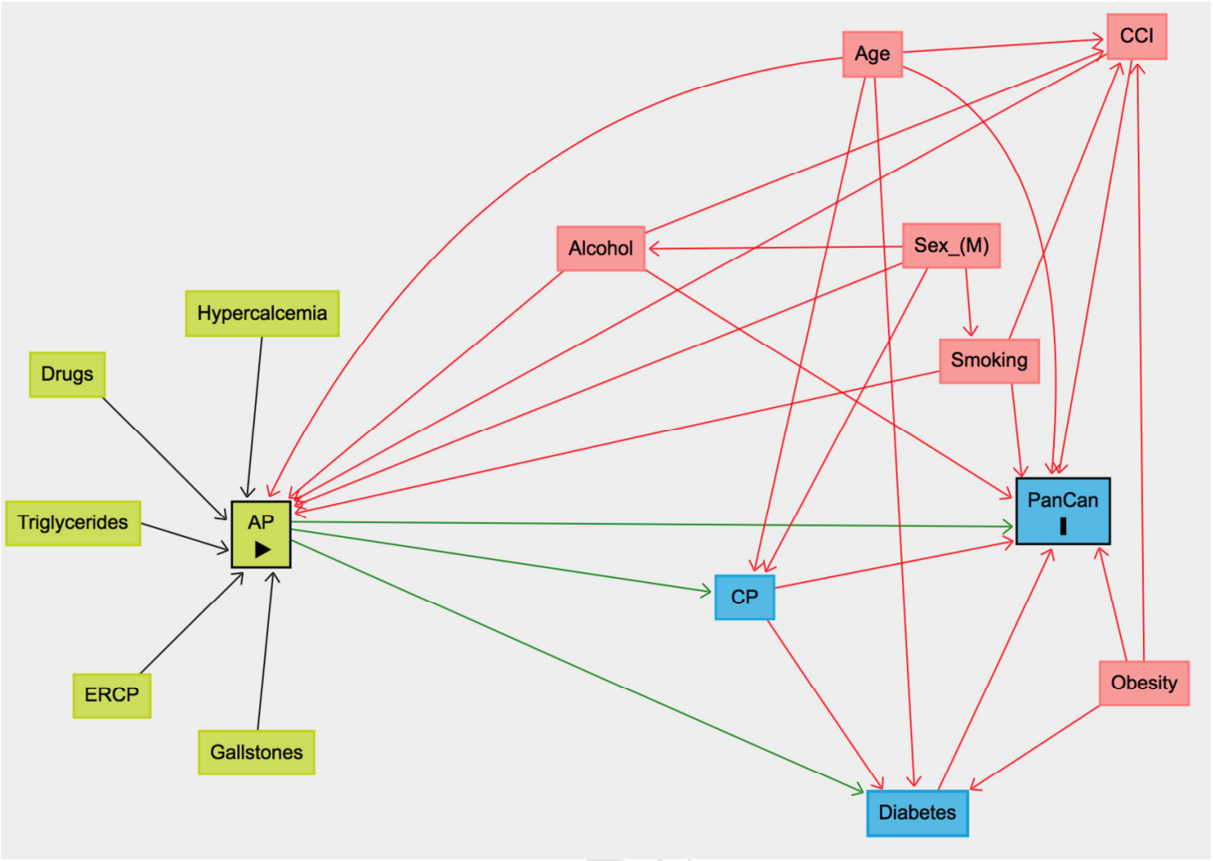


Figure S2. Directed acyclic graph



AP: Acute pancreatitis; CP: Chronic pancreatitis; CCI: Charlson Comorbidity Index; ERCP: Endoscopic retrograde cholangio-pancreaticography; M: Men; PanCan: Pancreatic cancer

Green: Exposure/ancestor of exposure

Red: Confounder

Blue: Outcome /ancestor of outcome

Table S1. List of ICD codes used in the study

Condition	ICD-8	ICD-10
Pancreatic disorders		
Acute pancreatitis	577.0	K85
Chronic pancreatitis	577.1	K86.0, K86.1
Other exocrine pancreatic disease	577.9	K86.2-K86.9
Gallstones		
Gallstone	574	K80
Diabetes mellitus		
Diabetes mellitus	249, 250	E10-E14, O24
Glomerulopathy in diabetes	-	N08.3
Diabetic mononeuropathy	-	G59.0
Diabetic polyneuropathy	-	G63.2
Diabetic cataract	-	H28.0
Diabetic retinal traction amotio	-	H33.4B
Diabetic retinopathy	-	H36.0
Diabetic artropathy	-	M14.2
Anamnesis with type-2 diabetes	-	Z86.3D
Obesity		
Obesity	277	E66
Alcohol		
Directly related to alcohol		
Alcohol dependence	291, 303	F10
Pregnancy with alcoholic foster damage	-	O35.4
Alcohol abuse in maternity with sequelae for newborn	-	P04.3
Antabus-alcohol reaction	-	T50.0A
Self-damage with alcohol	-	X65
Alcohol consumption during pregnancy	-	Z35.8M10
Postpartum examination due to alcohol consumption in pregnancy	-	Z39.310
Postpartum examination due to alcohol consumption before pregnancy	-	Z39.320

Rehabilitation from alcohol abuse	-	Z50.2
Advise due to alcohol abuse	-	Z71.4
Problems related to alcohol use	-	Z72.1
Alcohol poisoning	-	T51.9
Alcohol-related diseases		
Alcoholic liver disease	571.09, 571.10	K70
Changes in the nervous system due to alcohol	-	G31.2
Alcoholic polyneuropathy	303.91	G62.1
Alcoholic myopathy	-	G72.1
Alcoholic cardiomyopathy	-	I42.6
Alcoholic gastritis	-	K29.2
Alcohol dermatitis	-	L27.8A
Alcoholic pellagra	-	E52.9A
Alcohol-induced pseudo-Cushing syndrome	-	E24.4
Esophageal varices	456.0	I85, I98.2
Smoking		
Directly related to smoking		
Mental and behavioral disorders due to use of tobacco	-	F17
Fetus and newborn affected by maternal use of tobacco	-	P04.2
Toxic effect of tobacco or nicotine	-	T65.2
Tobacco smoking in pregnancy	-	Z35.8M18
Postpartum examination due to tobacco smoking in pregnancy	-	Z39.318
Exposure to tobacco smoking	-	Z58.7 (not A)
Advice due to tobacco smoking	-	Z71.6
Problems related to tobacco smoking	-	Z72.0 (not B)
Smoking-related lung diseases		
Bronchitis, not specified as acute or chronic	490	J40
Chronic bronchitis	491	J41, J42
Emphysema	492	J43

Other chronic obstructive pulmonary disease	-	J44
Bronchiectasia	518	J47
Lung cancer	162	C34

All sublevels of a given ICD code are included.

Table S2. List of ICD codes in the Charlson Comorbidity Index

Condition	ICD-8	ICD-10
Score 1		
Myocardial infarction	410	I21-I23
Congestive heart failure	427.09-427.19, 428.99, 782.49	I50, I11.0, I13.0, I13.2
Peripheral vascular disease	440-445	I70-I74, I77
Cerebrovascular disease	430-438	I60-I69, G45, G46
Dementia	290, 293.09	F00-F03, F05.1, G30
Chronic pulmonary disease	490-493, 515-518	J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease	712, 716, 734, 446, 135.99	M05, M06, M08, M09, M30-M36, D86
Ulcer disease	530.91, 530.98, 531-534	K22.1, K25-K28
Mild liver disease	571, 573.01, 573.04	B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0
Diabetes types 1 and 2	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9
Score 2		
Hemiplegia	344	G81, G82
Moderate to severe renal disease	403, 404, 580-584, 590.09, 593.19, 753.10-753.19, 792	I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Diabetes with end-organ damage	249.01-249.05, 249.08, 250.01-250.05, 250.08	E10.2-E10.8, E11.2-E11.8
Any tumor (except skin and pancreatic cancer)	140-194	C00-C75
Leukemia	204-207	C91-C95
Lymphoma	200-203, 275.59	C81-C85, C88, C90, C96
Score 3		

Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Score 6		
Metastatic solid tumor	195-199	C76-C80
AIDS	079.83	B21-B24

Table S3. List of surgical and procedure codes used in the study

Operation/procedure	Danish Classification of Surgical Procedures	NOMESCO Classification
ERCP	47702, 47711, 47770, 47860, 47870, 48040, 48080, 48090, 48095, 48361, 48362, 48651, 48652, 48653, 48661, 48663, 53050, 54000, 91050, 91051, 91055, 91120, 91121, 91123, 91125, 92301, 92305	KJKE02, KJKE12, KJKE15, KJKE18, KJKE18A, KJKE22, KJKE25, KJKE32, KJKE98, KJLB12, KJLB25, KJLB35, KJLB38, KJLB42, KJLB98, KUJK02, KUJK05, KUJK12, KUJK15, KUJK42, KUJK45
Cholecystectomy	47360, 47365, 53500	KJKA20, KJAKA21
Pancreatic resection	48380, 48410, 48420, 48460, 48480, 48500, 48550	KJLC00, KJLC10, KJLC20, KJLC30, KJLC40, KJLC50, KJLC96
Pancreatic transplantation	48840, 48849	KJLE

All sublevels of a given code are included.

Table S4. Comorbidity among study subjects re-assessed at five years of follow-up.

	Acute pancreatitis N=21,413		Comparison subjects N=95,537	
	N	**%**	**N**	**%**
Charlson Comorbidity Index				
Low (score 0)	14,505	67.7%	78762	82.4%
Intermediate (score 1-2)	5,566	26.0%	14287	15.0%
Severe (score >2)	1,342	6.3%	2488	2.6%
Co-morbidity diagnoses				
Alcohol-related	3,029	14.1%	2209	2.35
Smoking-related	1,444	6.7%	3045	3.2%
Gallstone	9,295	43.4%	2617	2.7%
Obesity	1,242	5.8%	1876	2.0%
Diabetes mellitus	2,001	9.3%	3106	3.3%

Table S5. Characteristics of pancreatic cancers diagnosed in the study population

	Acute pancreatitis N=435		Comparison subjects N=502	
	N	**%**	**N**	**%**
Time from index date to cancer, years	0.7 (0.1-4.5)		6.9 (3.0-13.6)	
Age at cancer diagnosis, years	67.6 (59.2-76.3)		72.6 (64.9-81.2))	
Location				
Head	191	43.9%	212	42.2%
Body	21	4.8%	34	6.8%
Tail	14	3.2%	18	3.6%
Islet of Langerhans	22	5.1%	22	4.4%
Other	2	0.5%	2	0.4%
Unknown	185	42.5%	214	42.6%
Stage				
Localized	57	13.1%	60	12.0%
Regional	111	25.5%	114	22.7%
Metastatic	181	41.6%	233	46.4%
Unknown	86	19.8%	95	18.9%
Morphology				
Adenocarcinoma	270	62.1%	299	59.6%
Not adenocarcinoma	52	12.0%	60	12.0%
Unknown	113	26.0%	143	28.5%

Table S6. Results from the sensitivity analysis assessing the impact of confounding from tobacco smoking.

Follow-up	Acute pancreatitis N=38,469			Comparison subjects N=186,801			Hazard ratio	
	Events	No. at risk	Person-years	Events	No. at risk	Person-years	Crude	Adjusted
0-2 years								
All	244	38,469	61,752	86	186,801	360,040	15.8 (12.36-20.22)	**18.71 (13.97-25.05)**
Women	99	17,475	28,568	38	84,891	163,201	14.33 (9.86-20.83)	**17.93 (11.53-27.90)**
Men	145	20,994	33,184	48	101,910	196,839	17.02 (12.28-23.59)	**19.91 (13.38-29.63)**
>2-5 years								
All	51	27,617	71,560	97	128,400	350,710	2.58 (1.84-3.62)	**2.40 (1.68-3.43)**
Women	20	12,940	33,767	47	60,128	162,894	2.06 (1.22-3.47)	**1.89 (1.07-3.34)**
Men	31	14,677	37,793	50	68,272	187,816	3.08 (1.97-4.82)	**2.87 (1.79-4.60)**
>5 years								
All	101	20,601	176,994	283	90,735	964,221	1.99 (1.59-2.50)	**2.05 (1.59-2.65)**
Women	54	9,786	81,952	127	43,198	416,599	2.18 (1.58-2.99)	**2.18 (1.54-3.10)**
Men	47	10,815	95,042	156	47,537	547,622	1.82 (1.31-2.52)	**1.95 (1.33-2.86)**

Table S7. Results from the sensitivity analysis assessing the impact of residual confounding from tobacco smoking and alcohol consumption.

Follow-up	Acute pancreatitis N=33,540			Comparison subjects N=159,701			Hazard ratio	
	Events	No. at risk	Person-years	Events	No. at risk	Person-years	Crude	Adjusted
0-2 years								
All	234	33,540	54,378	79	159,701	307,303	16.07 (12.45-20.74)	**18.84 (14.00-25.35)**
Women	98	16,339	26,832	37	78,454	150,663	14.34 (9.82-20.93)	**17.78 (11.43-27.66)**
Men	136	17,201	27,545	42	81,247	156,640	17.59 (12.45-24.87)	**20.34 (13.51-30.65)**
>2-5 years								
All	47	24,495	63,920	92	111,447	303,695	2.43 (1.71-3.45)	**2.29 (1.59-3.30)**
Women	19	12,201	31,970	43	55,937	151,339	2.09 (1.22-3.59)	**2.00 (1.13-3.53)**
Men	28	12,294	31,950	49	55,510	152,356	2.73 (1.71-4.34)	**2.55 (1.56-4.16)**
>5 years								
All	98	18,517	160,690	242	79,753	833,667	2.14 (1.69-2.70)	**2.19 (1.68-2.84)**
Women	54	9,294	77,965	123	40,465	385,629	2.18 (1.58-3.00)	**2.22 (1.56-3.16)**
Men	44	9,223	82,725	119	39,288	448,039	2.08 (1.47-2.94)	**2.20 (1.49-3.26)**

STROBE checklist.

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract ***p. 1-3***
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ***p. 3-4***
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ***p. 5***
Objectives	3	State specific objectives, including any prespecified hypotheses ***p. 5***
Methods		
Study design	4	Present key elements of study design early in the paper ***p. 5-6***
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ***p. 6-8***
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ***p. 6-8***
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed ***p. 7+10***
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable ***p. 6-8***
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group ***p. 8-8***
Bias	9	Describe any efforts to address potential sources of bias ***p. 9-10***
Study size	10	Explain how the study size was arrived at ***p. 6-7, Figure S1***
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why ***p. 9***
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding ***p. 9***
		(*b*) Describe any methods used to examine subgroups and interactions ***p. 9***
		(*c*) Explain how missing data were addressed ***N/A***
		(*d*) If applicable, explain how loss to follow-up was addressed ***p. 6***
		(*e*) Describe any sensitivity analyses ***p. 10***
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ***Figure S1***

		(b) Give reasons for non-participation at each stage ***Figure S1***
		(c) Consider use of a flow diagram ***Figure S1***
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ***p. 11, Figure S2***
		(b) Indicate number of participants with missing data for each variable of interest ***N/A***
		(c) Summarise follow-up time (eg, average and total amount) ***p. 11, Table 1***
Outcome data	15*	Report numbers of outcome events or summary measures over time ***p. 11-12, Table 2***
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ***p. 9, 11-12, Table 2, Figure S2***
		(*b*) Report category boundaries when continuous variables were categorized ***p. 11, Table 1***
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period ***p. 12, Figure 1***
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ***p. 12***
Discussion		
Key results	18	Summarise key results with reference to study objectives ***p. 12-12***
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ***p. 13-14***
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ***p. 13-16***
Generalisability	21	Discuss the generalisability (external validity) of the study results ***p. 13-16***
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ***p. 1***