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GASTRO-INTESTINAL DISEASES

Smoking as the most important risk factor for chronic pancreatitis in the general population

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Abstract

We tested the hypothesis that six toxic risk factors from the TIGAR-O classification system are equally important for risk of chronic pancreatitis, at the level of the individual patient and in the general population. 108,438 women and men aged 20–100 years participating in the Copenhagen General Population Study from 2003 to 2015 were included. Associations of smoking, alcohol intake, waist/hip ratio, kidney function, plasma triglycerides, plasma Ca^{2+}, and diseases within the causal pathway with risk of chronic pancreatitis, and corresponding population attributable risks were estimated. Information on chronic pancreatitis was from national Danish health registries. During median 9 years (range: 0–15) of follow-up, 313 individuals had a first diagnosis of chronic pancreatitis; the incidence of chronic pancreatitis per 10,000 person-years were 3.1 overall, 2.8 in women, and 3.5 in men. Of the six toxic risk factors and relative to individuals with low values, individuals in the top 5% had hazard ratios for chronic pancreatitis of 3.1(95% CI 2.1–4.5) for pack-years smoked, 2.5(1.5–4.0) for alcohol intake, and 1.6(1.1–2.6) for plasma triglycerides. Corresponding values versus those without the baseline disease were 12.6 (7.9–20.2) for acute pancreatitis, 1.9 (1.2–2.8) for gallstone disease, and 1.9 (1.3–2.7) for diabetes mellitus. The highest population attributable fractions were for women (1) ever smoking (31%), (2) gallstone disease (5%), and (3) diabetes mellitus (4%), and for men (1) ever smoking (38%), (2) acute pancreatitis (7%)/high alcohol intake (7%), and (3) high plasma triglycerides (5%). Smoking is the most important risk factor for chronic pancreatitis in the general population.

Keywords Epidemiology · Cohort study · Pancreas · Gastroenterology · Prevention · Smoking · Pancreatitis

Introduction

Chronic pancreatitis is an irreversible condition caused by prolonged inflammatory processes resulting in fibrotic, atrophic pancreatic tissue, with impairment of exo- and/or endocrine functions and with the potential to obstruct local vascular and luminal anatomy [1]. Individuals suffering from chronic pancreatitis are tormented with intense intermittent or constant abdominal pain, nausea, malabsorption, fatigue, and markedly reduced quality of life [2, 3]. Also, life expectancy is reduced and individuals with chronic pancreatitis have high risk of developing pancreatic cancer [1], one of the most lethal cancers globally [4]. The treatment of chronic pancreatitis is primarily symptomatic consisting of conservative or early surgical pain relief and oral and/or injected supplements to compensate exo- and/or endocrine insufficiency [5, 6]. Intrahepatic transplantation of autologous pancreatic islets after total pancreatectomy has recently shown intriguing results, offering hope of improvement in quality of life for individuals suffering from chronic pancreatitis [7, 8].

The incidence of chronic pancreatitis per 10,000 person-years is approximately 1.1 in Europe and 0.8 in North America [9]. The corresponding prevalence varies from 3.6 to 12.5 per 10,000 individuals, with the highest prevalence found in India [10].

Chronic pancreatitis is a complex multifactorial disease often preceded by episode(s) of acute pancreatitis [11, 12]. To help clinicians navigate in potential etiologies/risk

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factors, when disentangling medical history for each patient, tools such as TIGAR-O [13] (Toxic-metabolic, Idiopathic, Genetic, Autoimmune, Recurrent acute pancreatitis, and Obstructive) and M-ANNHEIM [14] (Multiple risk, Alcohol, Nicotine, Nutritional, Hereditary, Efferent pancreatic duct, Immunological, and Miscellaneous/Metabolic factors) scores have been created. These acronyms are classification systems comprising the most accepted risk factors/etiologies of chronic pancreatitis.

TIGAR-O Version 1 has been used [15] and validated [16] in the North American Pancreas Study 2 (NAPS2 [15], a case–control study from 2000 to 2006 with 540 chronic pancreatitis cases/695 controls, NAPS2-CV [16] from 2008 to 2011 with 521 chronic pancreatitis cases/no controls), and is recommend by both European [17] and American [18] guidelines in the diagnostic work-up of individuals with chronic pancreatitis. In 2019 TIGAR-O Version 2 implementing new knowledge regarding risk factors and aetiology of chronic pancreatitis was suggested by Dr. Whitcomb [19].

We tested the hypothesis that six toxic risk factors from TIGAR-O are equally important for risk of chronic pancreatitis, at the level of individual patients and in the entire general population. For this purpose, we studied 108,438 individuals from the white Danish general population, the Copenhagen General Population Study. Diabetes mellitus, gallstone disease, acute pancreatitis, and non-alcoholic fatty liver disease were not considered confounders but on the causal pathway from one or more of the six toxic risk factors to chronic pancreatitis, and therefore not included in main regression analyses; however, for comparison we also examined risk of chronic pancreatitis as a function of these four diseases.

Methods

Study population

108,438 women and men aged 20–100 years from the Copenhagen General Population Study recruited between 2003 and 2015 were included (participation rate 45%). Participants, randomly selected based on their unique Central Person Registry-number from the white Danish general population, filled in a questionnaire, underwent a physical examination, and had blood samples drawn for biochemical analyses at the baseline visit. The study was conducted in accordance with the Declaration of Helsinki and approved by local institutional reviews boards and a Danish ethical committee (H-KF-01-144/01). Written informed consent was obtained from all individuals.

Six toxic risk factors

Based on TIGAR-O Version 2 [19] long duration of smoking, high alcohol intake, high plasma triglycerides, high waist-hip ratio, high plasma ionized calcium, and low kidney function were considered risk factors for chronic pancreatitis.

All risk factors, except smoking, were firstly divided into four groups based on quartiles, and to ensure groups with extreme high values the top five percent (lowest five percent for kidney function) were secondly identified to form a separate fifth group. Smoking was also divided in five groups based on pack-years smoked; however, as almost 43% were never-smokers the lowest reference group included up to the 42nd percentile and the remaining individuals formed groups of approximately similar sizes with a fifth group including the top five percent. Waist-hip ratio was firstly split sex-specifically into quartiles and top five percent, and then both sexes were united to form the five groups used in analyses.

Laboratory analyses and other covariates

Blood samples were drawn nonfasting as endorsed by both European and American societies [20–22], and biochemical analyses were performed once at baseline on fresh samples. Plasma triglycerides, ionized calcium, and creatinine were measured using standard hospital assays. Age and sex corrected plasma creatinine was used to estimate glomerular filtration rate (eGFR) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. The following anthropometrics were measured by study staff: (i) body mass index (BMI) was measured weight divided by measured height squared (kg/m^2), (ii) waist, and (iii) hip circumference was measured to the nearest millimeter. Waist-hip ratio was measured waist circumference divided by measured hip circumference. Smoking status and quantity were self-reported and quantified as pack-years, where one pack-year equals 20 cigarettes or equivalent tobacco smoked per day for one year. Alcohol intake was self-reported in units per week; one unit = 12 g of alcohol. Diabetes mellitus was self-reported disease, use of anti-diabetic medication, nonfasting plasma glucose > 11 mmol/L (198 mg/dL), and/or a hospital diagnosis of diabetes prior to baseline from the national Danish Patient Registry (ICD8: 249-250; ICD10: E10, E11, E13, E14) from 1977 (outpatients included from 1995) and onwards. Diagnoses of acute pancreatitis (ICD-8 codes 577.00, 577.01, 577.08, and 577.09 and ICD-10 codes K85, K85.0, K85.1, K85.2, K85.2, K85.3, K85.8, and K85.9), gallstone disease (ICD-8:574-575; ICD-10: K80-K81), and non-alcoholic fatty liver disease (ICD-8: 571.11,

571.19; ICD-10: K75.9, K76.0, and K76.9 were likewise from the national Danish Patient Registry.

Chronic pancreatitis

Hospitalization or death due to chronic pancreatitis were based on diagnoses ascertained from the national Danish Patient Registry (from 1977) and the national Danish Causes of Death Registry (from 1973) using ICD-8 codes 577.10, 577.11, and 577.19 and ICD-10 codes K86.0 and K86.1. Chronic pancreatitis is typically diagnosed by the presence of relevant symptoms such as epigastric pain radiating to the back, jaundice, malabsorption, or weight loss in combination with findings compatible with chronic pancreatitis on cross-sectional imaging and/or endoscopic ultrasound, while pancreatic function tests sometimes is used additionally to look for exocrine and/or endocrine dysfunction [17, 18]. Using similar criteria, the positive predictive value of a diagnosis of chronic pancreatitis in the national Danish Patient Registry has previously been found to be 83% [23].

All individuals were followed from baseline until the occurrence of chronic pancreatitis (N = 313), death (N = 11,299), emigration (N = 457), or end of follow-up in December 2018, whichever came first. Follow-up was without losses due to the completeness of the Danish health registers.

Statistics

We used STATA version 15.1.

All 108,438 individuals had information on age, sex, diabetes, gallstone disease, acute pancreatitis, and non-alcoholic fatty liver disease from Danish nation-wide registries. Information on other covariates was 98.6% complete. Missing values were imputed based on age and sex using multivariable linear regression for continuous variables. When only including individuals with complete data, results were similar to those presented.

The associations of the six toxic risk factors as continuous variables with risk of chronic pancreatitis are shown by restricted cubic splines based on age and sex adjusted Cox proportional hazard regression models, with model fit according to Akaike's information criterion (lowest AIC indicate best model fit including number of knots used in the spline) [24]. Left truncation at study entry and age as the underlying time scale (automatically adjusting for age) were used. The top and bottom 0.5% of the six risk factors were removed from the splines to rule out outliers distorting the splines. To treat all six toxic risk factors similarly, the reference point for the splines were zero for smoking (43% were non-smokers) and median value of the lowest group (1st-24th percentile) for the five other risk factors. Non-alcohol drinkers were left out of all analyses as they also include former heavy-drinkers. Distribution of the six toxic risk factors are shown by Kernel density plots (y-axis unit 1/x) [25]. Similar analyses were performed for BMI and waist circumference grouped as the six toxic risk factors, and for current and former smokers only.

Associations of each of the six toxic risk factors categorized with risk of chronic pancreatitis were also examined using Cox proportional hazards regression. Hazard ratios (HR) were adjusted for potential confounders selected a priori, and included age (as time-scale), sex, smoking, alcohol intake, waist-hip ratio, plasma triglycerides, plasma ionized calcium, and eGFR, all as continuous variables; leaving out each risk factor as covariate when being the exposure. Diabetes mellitus, gallstone disease, acute pancreatitis, and non-alcoholic fatty liver disease were not considered confounders but on the causal pathway from one or more of the six toxic risk factors to chronic pancreatitis, and therefore not included in main regression analyses. Separate analyses for these diseases were done in models adjusted for (i) age and sex, and (ii) multivariable for the six toxic risk factors. Proportional hazard assumptions were not violated as assessed by Schoenfeld residuals. Trend was tested separately by entering each categorical risk factor as a continuous variable in Cox regression models. Prior to baseline, 198 individuals were diagnosed with chronic pancreatitis and were therefore excluded from prospective analyses. Similar analyses were performed for BMI and waist circumference grouped as the six toxic risk factors, and for current and former smokers only.

Incidence of chronic pancreatitis were estimated in three different age groups for (i) all individuals, (ii) women, and (iii) men. Also, the incidence ratio between men and women was estimated.

The population attributable fraction (PAF) was estimated separately for women and men for high levels of the risk factors found to be associated with high risk of chronic pancreatitis, that is, alcohol intake, plasma triglycerides, waist-hip ratio, and smoking. High-risk groups were set as individuals with ≥ 95th percentile of each continuous risk factor. We also estimated PAF in separate models for having a diagnosis of diabetes mellitus, gallstone disease, non-alcoholic fatty liver disease, or acute pancreatitis at baseline, respectively. PAF was estimated using the formula: $PAF = \frac{f(\mathrm{HR}-1)}{1+f(\mathrm{HR}-1)} x100\%$, where f is the frequency of individuals in high-risk groups and HR is the hazard ratio of chronic pancreatitis in the respective high-risk groups compared to the remaining individuals. Factors do not have additive PAF.

Multivariable adjusted Fine and Gray competing risk regression analyses with death as competing risk were also performed for all risk factors categorized as in Cox proportional hazard regression models, including BMI, waist circumference, and current and former smokers only.

Results

Baseline characteristics of all 108,438 individuals by sex are shown in Table 1. For 9 years (range: 0–15) of follow-up, 313 individuals developed chronic pancreatitis and the incidence of chronic pancreatitis was 3.1 per 10,000 person-years. Men had a higher incidence than women (3.5 vs. 2.8 per 10,000 person-years). The incidence of chronic pancreatitis was higher in individuals at older age for both women and men (Table 2).

Table 1 Baseline characteristics of 108,438 individuals from the Copenhagen General Population Study by sex

	Women	Men	All
Number (%)	59,718 (55)	48,720 (45)	108,438 (100)
Age, years	58 (48–67)	59 (49–68)	58 (48–67)
Smoking status, %			
Current	16	18	17
Former	39	43	41
Never	45	38	42
Smoking, pack-years[a]	1 (0–14)	6 (0–25)	3 (0–19)
Alcohol, units[b]/week	6 (3–11)	11 (6–20)	8 (4–15)
Waist-hip ratio	0.82 (0.78–0.87)	0.93 (0.89–0.98)	0.88 (0.81–0.94)
BMI, kg/m^2	25 (22–28)	26 (24–29)	26 (23–28)
Waist circumference, cm	83 (76–92)	96 (89–103)	90 (80–99)
Triglycerides, mmol/L	1.2 (0.9–1.8)	1.6 (1.1–2.4)	1.4 (1.0–2.0)
mg/dL	106 (80–159)	142 (97–213)	124 (89–177)
eGFR[c], mL/min/1.73 m^2	77 (67–88)	85 (74–94)	80 (70–91)
Ca^{2+}[d], mmol/L	1.21 (1.18–1.25)	1.20 (1.18–1.24)	1.21 (1.18–1.24)
Diabetes[e], %	3.3	5.4	4.2
Gallstone disease, %	5.4	2.5	4.1
Acute pancreatitis, %	0.4	0.5	0.4
NAFLD, %	0.4	0.3	0.3

Number of individuals varies slightly due to availability of covariates. Categorical variables are percent and continuous variables are median and interquartile range. [a]One pack-year equals 20 cigarettes or equals per day for one year. [b]One alcohol unit equals 12 g of alcohol. [c]Estimated glomerular filtration rates, estimated based on age and sex corrected plasma creatinine concentration. [d]Plasma ionized calcium. [e]Includes both diabetes type I and II. BMI = body mass index. eGFR = estimated glomerular filtration rate. NAFLD = non-alcoholic fatty lever disease

Table 2 Incidence of chronic pancreatitis in 108,438 individuals from the Copenhagen General Population Study by sex and age

	Age 20–50 years	Age 51–64 years	Age 65–100 years	All
All				
Number	32,284	42,148	34,006	108,438
Chronic pancreatitis events	38	124	151	313
Events/10,000 person-years	1.2	3.1	5.4	3.1
Women				
Number	18,438	23,301	17,979	59,718
Chronic pancreatitis events	19	57	81	157
Events/10,000 person-years	1.0	2.6	5.3	2.8
Men				
Number	13,846	18,847	16,027	48,720
Chronic pancreatitis events	19	67	70	156
Events/10,000 person-years	1.4	3.7	5.5	3.5
Men/women				
Incidence men/incidence women	1.4	1.4	1.0	1.3

Smoking

High smoking quantity, by pack-years, was associated with higher risk of chronic pancreatitis in an age and sex adjusted model (Fig. 1panel A). Compared to never-smokers (0 pack-years; 1st-42nd percentiles), multivariable adjusted HRs for chronic pancreatitis were 3.1 (95% confidence interval (CI): 2.1–4.5) for individuals who had smoked 45.1–296 pack-years (94–100th percentiles), 2.3 (1.6–3.2) for 24.1–45 pack-years (80th–93rd percentiles), 1.8 (1.3–2.5) for 9.1–24 pack-years (62nd-79th percentiles), and 1.1 (0.8–1.7) for 0.1–9 pack-years (43rd-61st percentiles) (p for trend $= 2 \times 10^{-11}$) (Fig. 2panel A). In an analysis excluding never-smokers, a similar stepwise higher risk of chronic pancreatitis with stepwise higher number of pack-years was seen (p for trend $= 2 \times 10^{-11}$) (Supplementary Fig. 1 panel A). Compared to never-smokers, former smokers had a HR

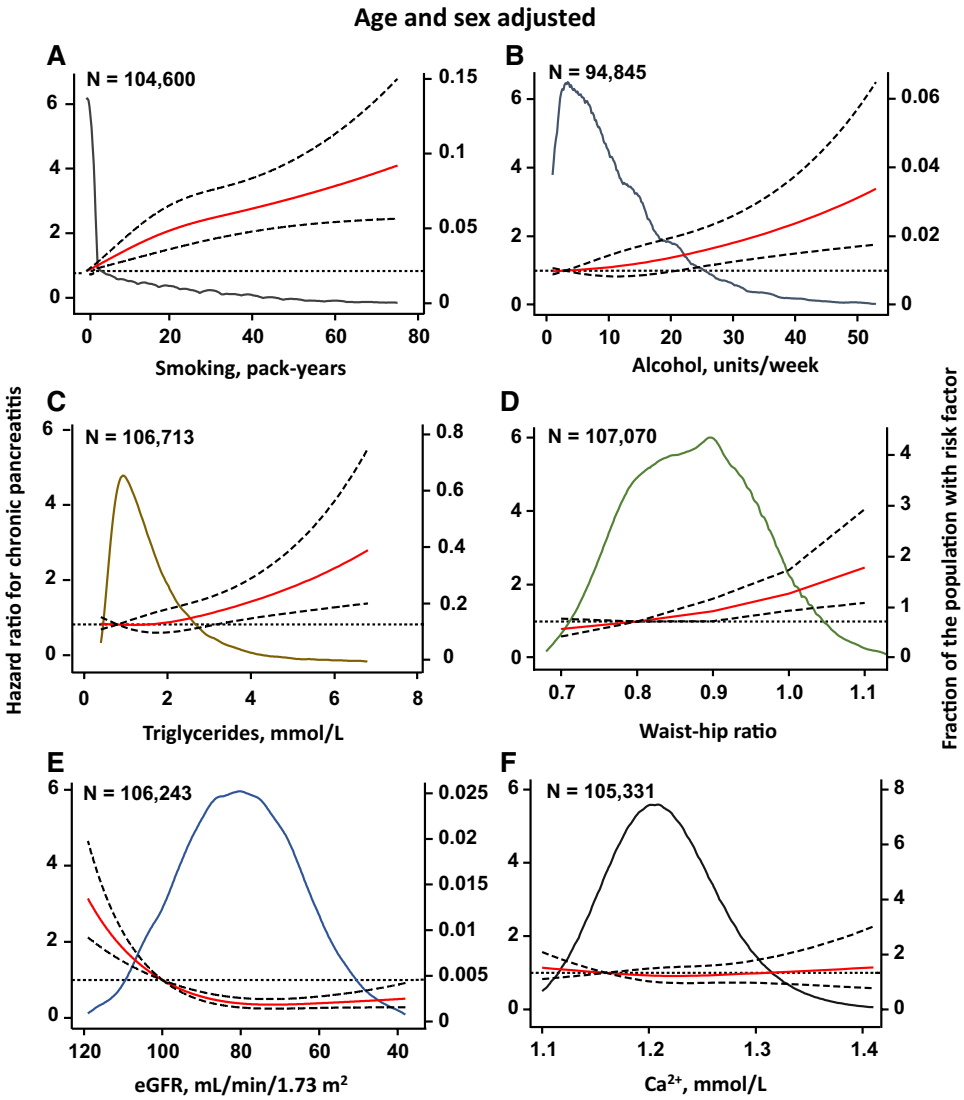

Fig. 1 Risk of chronic pancreatitis as function of six toxic risk factors on continuous scales. All six red curves are restricted cubic splines with 95% confidence interval (black doted lines) based on age and sex adjusted Cox proportional hazard regressions. Underlying distributions are kernel density plots of each of the six risk factors. Panel **A** smoking, pack-years, one pack-year equals 20 cigarettes or equivalent tobacco smoked per day for one year, panel **B** alcohol intake, units/week, one-unit equals = 12 g of alcohol, panel **C** plasma triglycerides, mmol/L (multiply by 88.6 to get mg/dL), panel **D** waist-hip ratio, panel **E** estimated glomerular filtration rate (eGFR, mL/min/1.73m^2) calculated based on age and sex corrected plasma creatinine using the Chronic Kidney Disease Epidemiology Collaboration formula. The x-axis is from high to low eGFR, and panel **F** plasma ionized calcium (Ca^{2+}), mmol/L. Horizontal line at hazard ratio = 1.0 indicates equal risk; when the 95% confidence interval for the hazard ratio no longer overlap 1.0, the hazard ratio is significant different from 1.0. Numbers of individuals varies slightly in each analysis due to availability in data. N = numbers. eGFR = estimate glomerular filtration rate. Based on individuals from the Copenhagen General Population Study

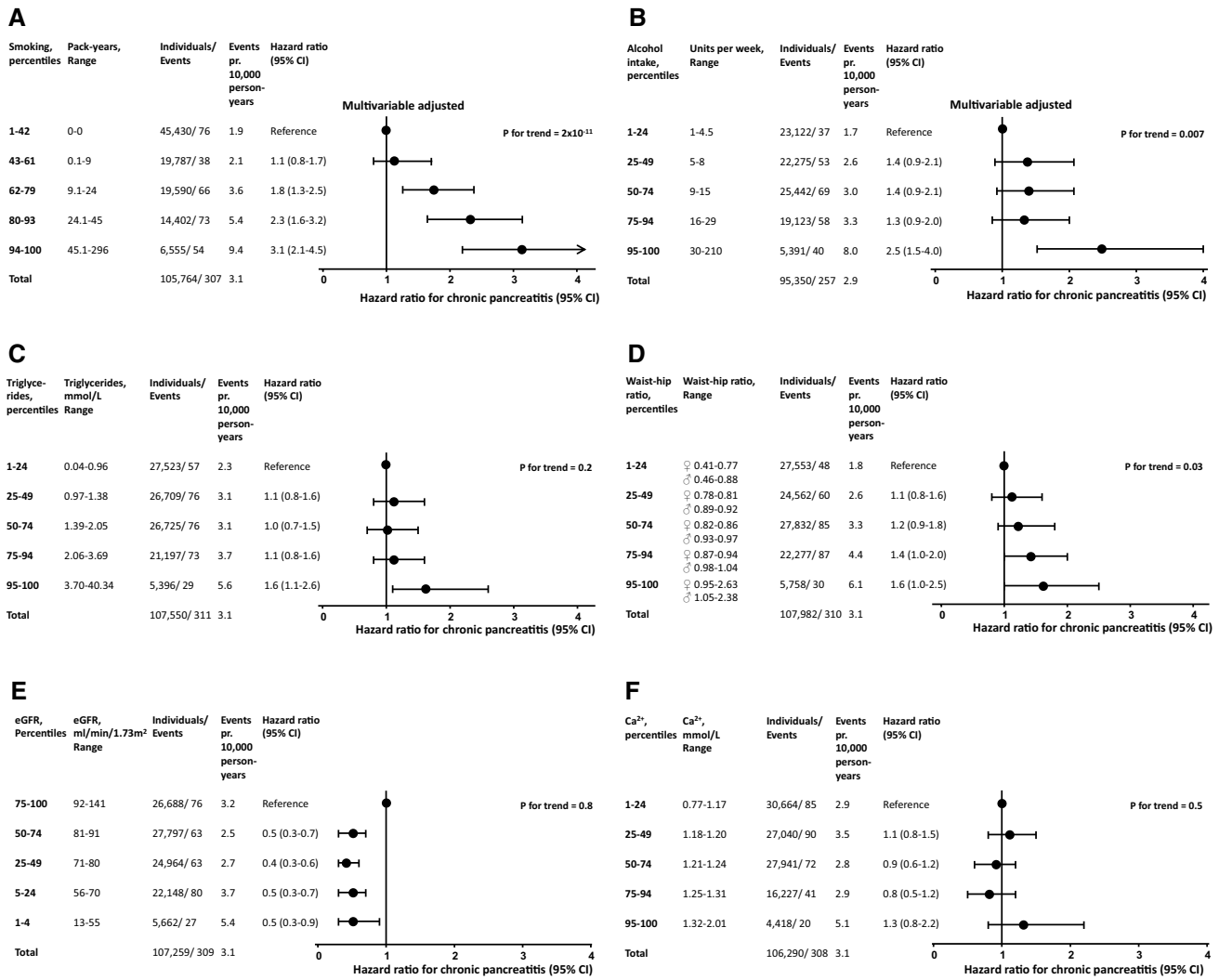

Fig. 2 Risk of chronic pancreatitis as a function of six toxic risk factors in categories. Forest plots showing risk of chronic pancreatitis are based on multivariable adjusted Cox proportional hazard regressions by each of the six risk factors categorized. Panel **A** smoking, pack-years, one pack-year equals 20 cigarettes or equivalent tobacco smoked per day in one year, panel **B** alcohol intake, units/week, one-unit equals = 12 g of alcohol, panel **C** plasma triglycerides, mmol/L (multiply by 88.6 to get mg/dL), **D** waist-hip ratio, panel **E** estimated glomerular filtration rate (eGFR, mL/min/1.73m^2) calculated based on age and sex corrected plasma creatinine using the Chronic Kidney Disease Epidemiology Collaboration formula, and panel **F** plasma ionized calcium (Ca^{2+}), mmol/L. Multivariable adjustment was for age (as time-scale), sex, smoking, alcohol intake, plasma triglycerides, plasma ionized calcium, waist-hip ratio, and eGFR, leaving out each risk factor as covariate when being the exposure. Number of individuals varies slightly in each analysis due to availability in data. CI = confidence interval. eGFR = estimated glomerular filtration rate. Based on individuals from the Copenhagen General Population Study

of 1.5 (1.1–1.9) and current smokers of 2.7 (2.0–3.7) for chronic pancreatitis (Supplementary Fig. 1 panel B).

Alcohol intake

High alcohol intake per week was associated with higher risk of chronic pancreatitis in an age and sex adjusted model (Fig. 1panel B). Compared to individuals drinking 1–4.5 units of alcohol per week (1st–24th percentiles), multivariable adjusted HRs for chronic pancreatitis were 2.5 (95% CI 1.5–4.0) for individuals drinking 30–210 units of alcohol per week (95–100th percentiles), 1.3 (0.9–2.0) for 16–29 units of alcohol (75–94th percentiles), 1.4 (0.9–2.1) for 9–15 units of alcohol (50–74th percentiles), and 1.4 (0.9–2.1) for 5–8 units of alcohol per week (25–49th percentiles) (p for trend = 0.007) (Fig. 2 panel B).

Plasma triglycerides

Individuals with high plasma triglycerides had higher risk of chronic pancreatitis in an age and sex adjusted model (Fig. 1panel C). Compared to individuals with

plasma triglycerides in the range of 0.04–0.96 mmol/L (3.5–85 mg/dL; 1st–24th percentiles), multivariable adjusted HRs for chronic pancreatitis were 1.6 (95% CI 1.1–2.6) for individuals with plasma triglycerides of 3.70–40 mmol/L (328–3547 mg/dL; 95–100th percentiles), 1.1 (0.8–1.6) for 2.06–3.69 mmol/L (183–327 mg/dL; 75–94th percentiles), 1.0 (0.7–1.5) for 1.39–2.05 mmol/L (123–182 mg/dL; 50–74th percentiles), and 1.1 (0.8–1.6) for 0.97–1.38 mmol/L (86–122 mg/dL; 25–49th percentiles) (p for trend = 0.2) (Fig. 2panel C).

Waist-hip ratio

Individuals with high waist-hip ratio had higher risk of chronic pancreatitis in an age and sex adjusted model (Fig. 1panel D). Compared to women and men having waist-hip ratio in the range 1st–24th percentiles, multivariable adjusted HRs for chronic pancreatitis were 1.6 (95%CI: 1.0–2.5) for 95–100th percentiles, 1.4 (1.0–2.0) for 75–94th percentiles, 1.2 (0.9–1.8) for 50–74th percentiles, and 1.1 (0.8–1.6) for 25–49th percentiles (p for trend = 0.03) (Fig. 2panel D). Corresponding results for BMI and waist circumference are shown in Supplementary Fig. 2 panels A and B.

Kidney function

Kidney function was associated with risk of chronic pancreatitis in a (horizontal) J-shaped manner, with higher risk for chronic pancreatitis when eGFR was > 100 mL/min/1.73m^2, and lower risk when eGFR was < 100 mL/min/1.73m^2 in an age and sex adjusted model (Fig. 1panel E). Compared to individuals with eGFR in the range of 92–141 mL/min/1.73m^2 (75–100th percentiles), multivariable adjusted HRs for chronic pancreatitis were 0.5 (95%CI: 0.3–0.9) for individuals with eGFR of 13–55 mL/min/1.73m^2 (1st–4th percentiles), 0.5 (0.3–0.7) for 56–70 mL/min/1.73m^2 (5–24th percentiles), 0.4 (0.3–0.6) for 71–80 mL/min/1.73m^2 (25–49th percentiles), and 0.5 (0.3–0.7) for 81–91 mL/min/1.73m^2 (50–74th percentiles) (p for trend = 0.8) (Fig. 2panel E).

Ionized calcium

No association was found between plasma Ca^{2+} and risk of chronic pancreatitis in an age and sex adjusted model (Fig. 1panel F). Compared to individuals with Ca^{2+} in the range of 0.77–1.17 mmol/L (1st–24th percentiles), multivariable adjusted HRs for chronic pancreatitis were 1.3 (95% CI 0.8–2.2) for individuals with Ca^{2+} of 1.32–2.01 mmol/L (95–100th percentiles), 0.8 (0.5–1.2) for 1.25–1.31 mmol/L (75–94th percentiles), 0.9 (0.6–1.2) for 1.21–1.24 mmol/L (50–75th percentiles), and 1.1 (0.8–1.5) for 1.18–1.20 mmol/L (25–49th percentiles) (p for trend = 0.5) (Fig. 2panel F).

Diseases on the causal pathway

Age and sex adjusted hazard ratios for chronic pancreatitis were 14.1 (95% CI 8.8–22.4) for individuals with baseline acute pancreatitis, 1.9 (1.3–2.9) for gallstone disease, 2.2 (1.5–3.1) for diabetes mellitus, and 0.8 (0.1–5.8) for individuals with baseline non-alcoholic fatty liver disease compared to individuals naive to the disease in question at baseline (Fig. 3A). Corresponding multivariable adjusted hazard ratios were 12.6 (7.9–20.2), 1.9 (1.2–2.8), 1.9 (1.3–2.7), and 0.7 (0.1–5.1), respectively (Fig. 3B).

The most important risk factors for chronic pancreatitis for individuals and society

In women ranked by HR, the three most important risk factors of chronic pancreatitis were (1) prior diagnosis of acute pancreatitis (HR: 8.7; 95%CI: 3.8–19.7), (2) high alcohol intake (2.9;1.4–6.2), and (3) a diagnosis of diabetes mellitus (2.3;1.4–4.0); and when ranked by population attributable fraction these were (1) being ever smoker (31%), (2) prior diagnosis of gallstone disease (5%), and (3) a diagnosis of diabetes mellitus (4%) (Table 3, top).

In men ranked by HR, the three most important risk factors of chronic pancreatitis were 1) prior diagnosis of acute pancreatitis (HR:16.2; 95% CI 9.1–28.9), 2) being ever smoker (2.0;1.3–3.1), and 3) high alcohol intake (1.7;1.1–2.5)/high plasma triglycerides (1.7;1.1–2.7); and when ranked by population attributable fraction these were (1) being ever smoker (38%), (2) prior diagnosis of acute pancreatitis (7%)/high alcohol intake (7%), and (3) high triglycerides (5%) (Table 3, bottom).

Competing risk analyses

Estimates were similar in Fine and Gray competing risk regression analyses with death as competing risk as in Cox regressions (data not shown). Corresponding cumulative incidence curves are shown in Fig. 4 for the six toxic risk factors and in Supplementary Fig. 3 for BMI, waist circumference, and current and former smokers only.

Discussion

In this study of 108,438 individuals from the Danish general population we found that smoking is the most important risk factor for chronic pancreatitis in both women and men, with population attributable fractions of 31% for women and 38% for men. This were far more than for high alcohol intake with

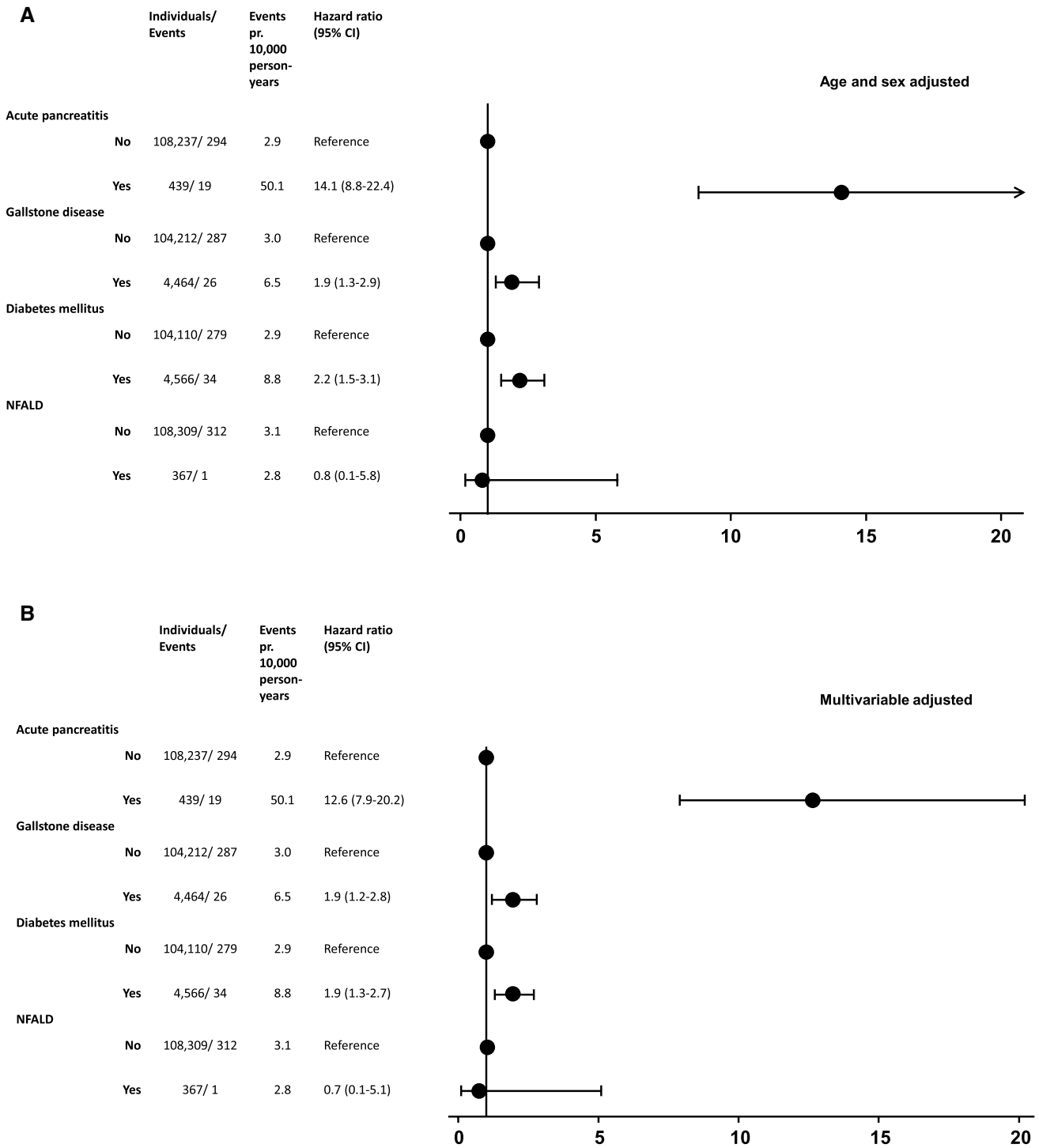

Fig. 3 Risk of chronic pancreatitis by disease considered on the causal pathway. Hazard ratios for chronic pancreatitis in individuals with baseline prevalence of acute pancreatitis, gallstone disease, diabetes mellitus, or non-alcoholic fatty lever disease shown in age and sex adjusted (Panel **A**) and multivariable adjusted (Panel **B**) models. Multivariable adjusted were for age, sex, smoking, alcohol intake, plasma triglycerides, plasma ionized calcium, waist-hip ratio, and eGFR. CI = confidence interval. NFALD = non-alcoholic fatty liver disease. Based on individuals from the Copenhagen General Population Study

corresponding fraction of 3% for women and 7% for men. These findings for six toxic risk factors evaluated back-to-back in the same individuals are novel.

Chronic pancreatitis has a complex nature including potentially different gene-environment interactions in individual patients [12]. Acute and chronic pancreatitis share

Table 3 Ranking of risk factors for chronic pancreatitis by hazard ratio and population attributable fraction in women and men from the Copenhagen General Population Study

Ranking by hazard ratio				Ranking by population attributable fraction (PAF)		
Women		Prevalence[a], %	HR (95% CI)			PAF, %
1	Acute pancreatitis	0.4	8.7 (3.8–19.7)	1	Smoker	31
2	High alcohol intake	1.6	2.9 (1.4–6.2)	2	Gallstone disease	5
3	Diabetes mellitus	3.3	2.3 (1.4–4.0)	3	Diabetes mellitus	4
4	Gallstone disease	5.4	1.9 (1.2–3.1)	4	Acute pancreatitis	3
5	Smoker	55.1	1.8 (1.2–2.5)	5	High alcohol intake	3
6	High waist-hip ratio	5.2	1.1 (0.6–2.0)	6	High waist-hip ratio	NA
7	High triglycerides	2.6	1.0 (0.5–2.4)	7	High triglycerides	NA
Ranking by hazard ratio				Ranking by population attributable fraction (PAF)		
Men		Prevalence[a], %	HR (95% CI)			PAF, %
1	Acute pancreatitis	0.5	16.2 (9.1–28.9)	1	Smoker	38
2	Smoker	61.6	2.0 (1.3–3.1)	2	Acute pancreatitis	7
3	High alcohol intake	10.1	1.7 (1.1–2.5)	3	High alcohol intake	7
4	High triglycerides	8.0	1.7 (1.1–2.7)	4	High triglycerides	5
5	Gallstone disease	2.5	1.8 (0.9–3.7)	5	Diabetes mellitus	NA
6	Diabetes mellitus	5.4	1.6 (0.9–2.6)	6	Gallstone disease	NA
7	High waist-hip ratio	5.5	1.4 (0.9–2.4)	7	High waist-hip ratio	NA

[a]Occurrence of risk factor at baseline. Incident cases after baseline of acute pancreatitis, gallstone disease, and diabetes mellitus were not included. Diabetes mellitus include both type I and II. Smoker included both current and former smokers. Non-alcoholic fatty lever disease is not mentioned in this table, as only one individual with non-alcoholic fatty lever disease at baseline developed chronic pancreatitis during follow-up. HR = Hazard ratio. CI = Confidence interval. NA = Not available, as we chose not to list PAF for factors where the hazard ratio for chronic pancreatitis was not statistically significant

common risk factors and are considered a continuum of progressing pancreatic damage [12], with development of pancreatic cancer as the theoretical end-stage. We found that being a smoker, both current and former, smoking in a dose-dependent manner, drinking > 35 units of alcohol per week, having plasma triglycerides > 4.5 mmol/L (399 mg/dL), and having a baseline diagnosis of acute pancreatitis, gallstone disease, or diabetes mellitus were each associated with high risk of chronic pancreatitis in individuals from the general population.

Mechanistically, smoking is found to cause pancreatic inflammation and fibrosis in rodent models [26–28] and combined with alcohol also in human pancreatic stellate cells [27]. Alcohol is metabolized in pancreatic cells promoting inflammation and fibrosis, and make pancreatic cells more susceptible to autodigestion [29]. Hypertriglyceridemia is observationally [30] and genetically [31] associated with acute pancreatitis and w severe hypertriglyceridemia is believed to obstruct blood-flow due to hyperviscosity causing hypoxia-induced inflammation [32]. However, the mechanisms for mild-to-moderate hypertriglyceridemia are not fully understood but could involve liberation of tissue toxic free fatty acids in pancreatic tissue during triglyceride hydrolysis by pancreatic lipase. Diabetes mellitus (type 3C) is a frequent complication to chronic pancreatitis [1], and seems to succeed the pancreatic damage caused by acute pancreatitis [33]. Also, diabetes mellitus is associated with higher risk of acute pancreatitis [33].

In line with our findings, a previous Mendelian randomization study used genetic variants to examine association of gallstone disease, diabetes, plasma total calcium, plasma triglycerides, smoking, and alcohol consumption with risk of chronic pancreatitis in the UK Biobank and the FinnGenn consortium [34]. They found that gallstone disease, smoking, alcohol consumption (FinnGenn consortium only), elevated plasma total calcium (UK Biobank only), and elevated plasma triglycerides were associated with risk of chronic pancreatitis. However, we were not able to find an association between elevated plasma ionized calcium and chronic pancreatitis, which could be explained by the difference in measured calcium component; plasma total versus ionized calcium, the latter being the biologically active part. Another explanation for the different findings could be that plasma ionized calcium perhaps needs to be substantially elevated beyond 3 mmol/L to be observationally associated with pancreatitis [19], which very few in our study population had.

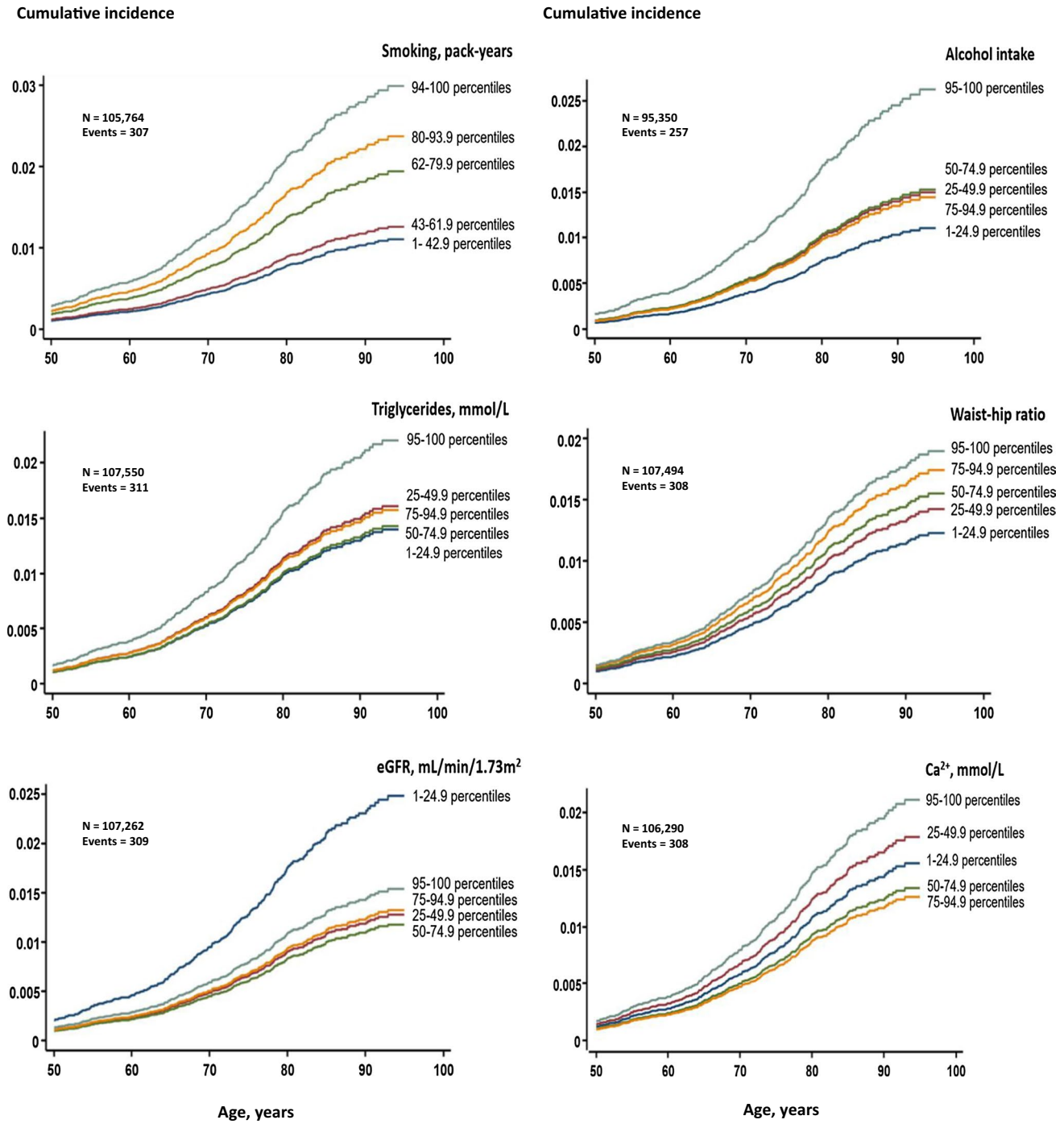

Fig. 4 Cumulative incidence of chronic pancreatitis as a function of six toxic risk factors allowing for death as competing risk. Cumulative incidence curves are based on multivariable adjusted Fine and Gray competing risk regression models with death as competing risk. Multivariable adjustment was for age (as time-scale), sex, smoking, alcohol intake, plasma triglycerides, plasma ionized calcium, waist-hip ratio, and eGFR, leaving out each risk factor as covariate when being the exposure. N = numbers. eGFR = estimate glomerular filtration rate. Based on individuals from the Copenhagen General Population Study

Looking at event rates, individuals with the highest plasma ionized calcium in the present study did indeed have the highest event rate of chronic pancreatitis.

Further, supporting the present findings on smoking, smoking was found to be a dose-dependent risk factor for chronic pancreatitis in a meta-analysis from 2019 including data from four prospective studies [35]. First, a study from

2009 of 17,905 Danish individuals by Tolstrup et al. [36] with 97 chronic pancreatitis events, second, a study from 2015 of 36,436 elderly North American women by Prizment et al. [37] with 149 cases of recurrent acute pancreatitis and/or chronic pancreatitis combined, third, a multiethnic study from 2016 by Setiawan et al. [38] of 145,886 individuals with 523 cases of recurrent acute pancreatitis and/or chronic pancreatitis combined, and forth, a study from 2018 by Pang et al. [39] including 512,891 Chinese individuals with 113 chronic pancreatitis events (findings for chronic pancreatitis were not statistically significant in this study alone). Our results support the finding of the meta-analysis, and even strengthens its conclusion as our endpoint was solely chronic pancreatitis events and not a composite of both recurrent acute pancreatitis and chronic pancreatitis (as 2/4 of the studies in the meta-analysis). Tolstrup et al. [36] found smoking to attribute by 46% to risk of both acute (160 events) and chronic (97 events) pancreatitis events combined, which is in accordance with our finding of 31% for women and 38% for men of chronic pancreatitis events. Smoking pattern has changed markedly over the past 50 years in Denmark; while 62% were current smokers and 17% former smokers in the 1976–1978 baseline visit for Tolstrup et al. [36]. The prevalence has changed to 17% for current smokers and 41% for former smokers in the 2003–2015 baseline visit in our study. Despite this substantial drop in current smokers, smoking still seems to be the most important risk factor for chronic pancreatitis in the general population today, as although smoking cessation might attenuate it seems not to eliminate the risk of chronic pancreatitis.

Alcohol consumption has historically been accepted as the main reason for development of chronic pancreatitis [10, 40], and it is still the most common etiology chosen by physicians when doing work-up of patients with chronic pancreatitis, especially in men [41]. The quantity of alcohol consumed to be associated with chronic pancreatitis has been shown to be substantial [42–44]. This was confirmed in our study, as individuals should consume > 35 units/week to be at high risk of chronic pancreatitis compared to light drinkers, and furthermore, just 3% and 7% of chronic pancreatitis cases could potentially be prevented in women and men, respectively, if they had not been drinking high quantities of alcohol. Taken together, this indicate that alcohol consumption alone should not be the main topic of concern when thinking prevention of chronic pancreatitis in the general population.

Low kidney function has been suggested as a risk factor for chronic pancreatitis, as renal failure was associated with chronic pancreatitis in the NAPS2-CV study [16]. Conversely, we found high kidney function, that is high eGFR, was associated with high risk of chronic pancreatitis. This discrepancy is not easy to explain and therefore needs further examination in other studies.

One strength of our study is the large homogeneous sample size of individuals from the general population with no losses to follow-up. Also, the relatively large amount of previously validated [23] endpoints collected unbiased based on the nationwide Danish health registries is a strength.

The present study is limited by including only white individuals of Danish descent; however, we are not aware of data to suggest that the present results should not apply to other ethnicities. That said, being non-white is an independent risk factor of pancreatic disease, whether this is due to genetics or a skewed distribution of risk factors is unknown [45]. In all analyses on alcohol consumption zero-drinkers were excluded to limit the bias from former heavy-drinkers, meaning that results found cannot be generalized to populations predominantly consisting of never-drinkers. Finally, as this is an observational study, residual and unknown/unmeasured confounding could potentially bias our results.

Conclusion

Smoking is the most important risk factor for chronic pancreatitis in the general population.

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Authors contribution SEJH, BGN, and AL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. Study concept and design: SEJH, BGN, and AL. Acquisition, analyses and interpretation of data: SEJH, BGN, and AL. Drafting of manuscript: SEJH. Critical revision of the manuscript for important intellectual content: BGN and AL. Statistical analyses: SEJH and AL. Study supervision: BGN and AL.

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Availability of data and material Data and further analyses will be made available upon reasonable request to corresponding author. The Danish Data Protection Agency does not allow open access to our data.

Code availability Coding will be made available upon reasonable request to corresponding author.

Declarations

Conflict of interest None.

Ethics approval The study was conducted in accordance with the Declaration of Helsinki and approved by local institutional reviews boards and Danish ethical committees (H-KF-01–144/01).

Consent to participate Written informed consent was obtained from all individuals.

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