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GASTRO-INTESTINAL EPIDEMIOLOGY

Low and high pancreatic amylase is associated with pancreatic cancer and chronic pancreatitis

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Abstract

Incidences of pancreatic cancer and acute and chronic pancreatitis are rising globally, and often no curative treatment is available at the time of diagnosis. We tested the hypothesis that low and high plasma concentrations of pancreatic amylase are associated with increased risk of pancreatic cancer, acute pancreatitis, and chronic pancreatitis in the general population. We included 101,765 individuals (55% women) aged 20–100 years from the Copenhagen General Population Study with baseline measurements of plasma pancreatic amylase. After recruitment in 2004–2015 during a median 9 years of follow-up (range 0–15), we collected information about diagnoses of pancreatic cancer, acute pancreatitis, and chronic pancreatitis from the national Danish Patient Registry, the national Danish Cancer Registry, and the national Danish Causes of Death Registry. The median age was 58 years (interquartile range: 48–67) and the median plasma pancreatic amylase 32 U/L (26–40). During follow-up, 442 individuals were diagnosed with pancreatic cancer, 282 with chronic pancreatitis, and 401 with acute pancreatitis. Compared to individuals with pancreatic amylase levels in the 41st–60th percentiles, those with extreme low (1st–2.5th percentiles) and extreme high (97.5th–100th percentiles) pancreatic amylase had hazard ratios of 2.4 (95% confidence interval; 1.6–3.6) and 2.2 (1.4–3.7) for pancreatic cancer, of 1.8 (1.1–3.3) and 3.2 (1.8–5.6) for chronic pancreatitis, and of 1.1 (0.6–1.8) and 1.5 (0.8–2.7) for acute pancreatitis, respectively. In apparently healthy individuals from the general population, extreme low and extreme high plasma pancreatic amylase were associated with 2–threefold higher risk of both pancreatic cancer and chronic pancreatitis.

Keywords Epidemiology · Gastroenterology · Pancreas · Biochemistry · Risk factor · General population study

Introduction

Pancreatic cancer and acute and chronic pancreatitis are dreaded diseases, where incidences are rising globally [1, 2]. At the time of diagnosis, often no curative treatment exists [3–5].

Acute and chronic pancreatitis can theoretically be viewed as a continuum of the same pathogenic processes, in which several episodes of acute inflammation lead to chronic inflammation and irreversible tissue damage [6, 7]. The diseases share common risk factors such as alcohol consumption, smoking, hypertriglyceridemia, obesity, and genetic predisposition [3, 4]. One-in-five with a single episode of acute pancreatitis, and one-in-three with recurrent acute pancreatitis develops chronic pancreatitis [8, 9], and half of individuals with chronic pancreatitis have had acute pancreatitis [10]. Both diseases are treated symptomatically, and are associated with low quality of life and reduced life

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expectancy [4, 7]. Pancreatic cancer shares the same risk factors as acute and chronic pancreatitis [2], and develops in 5% of individuals with chronic pancreatitis [11]. The mortality rate is high, as pancreatic cancer is mostly diagnosed in late stages where surgical treatment is often not curative due to local invasive growth and metastases. The five year survival rate is approximately 6% [12], and pancreatic cancer is one of the most lethal cancers worldwide [13].

Currently, plasma pancreatic amylase > 3 times above upper limit of normal is used as first line in diagnosing acute pancreatitis [14, 15], and in a Japanese guideline it is further suggested as a supplement to a probable diagnosis of chronic pancreatitis [16]. No current European or American guidelines include plasma pancreatic amylase as a diagnostic tool for chronic pancreatitis [17, 18] or pancreatic cancer [19, 20]. The use of low plasma pancreatic amylase has been suggested as an indirect test of pancreatic function supporting a diagnosis of chronic pancreatitis in a previous guideline [21], and findings from a Danish study of 121 individuals with chronic pancreatitis [22] supports this statement. Plasma pancreatic amylase is an inexpensive, well-known, and accessible biochemical analysis and more importantly, it is organ specific.

We tested the hypothesis that low and high plasma pancreatic amylase levels are associated with increased risk of pancreatic cancer, acute pancreatitis, and chronic pancreatitis in apparently healthy individuals in the general population; apparently healthy implies no knowledge of previous relevant pancreas disease.

Methods

Study population

In this retrospective study with endpoints collected prospectively, we studied 101,765 men and women aged 20–100 years with baseline measurement of plasma pancreatic amylase from the Copenhagen General Population Study, randomly selected from the Danish general population in 2004–2015. Individuals filled out a questionnaire, underwent a physical examination, and had blood samples drawn for biochemical analyses. 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). Written informed consent was obtained from all individuals.

Plasma pancreatic amylase

Plasma pancreatic amylase (U/L) was measured non-fasting (evidence suggest no oscillation in postprandial plasma amylase levels compared to fasting [23]) using standard hospital assay inhibiting salivary amylase by monoclonal antibodies. The same autoanalysers and assays were used for all measurements (KoneLab, Diasys kit). For statistical analyses, individuals were divided according to plasma pancreatic amylase quintiles, and to focus on extreme low and high values, into 1st–2.5th percentiles, 2.6th–20th percentiles, 21st–40th percentiles, 41st–60th percentiles (reference group), 61st–80th percentiles, 81st–97.4th percentiles, and 97.5th–100th percentiles.

Laboratory analyses and other covariates

Blood samples were drawn nonfasting as endorsed by both European and American societies [24–26], and biochemical analyses were performed once at baseline. Plasma triglycerides, high-sensitive C-reactive protein (CRP), pancreatic lipase (measured until July 2005), 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. Body mass index (BMI) was measured weight divided by measured height squared (kg/m^2). Smoking was quantified as pack-years, where 1 pack-year equals 20 cigarettes or equivalent smoked per day in one year. Alcohol intake was self-reported in units per week; 1 unit = 12 g of alcohol. Physical inactivity was < 4 h of light activity per week during leisure time. 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 cystic fibrosis (ICD-8: 273.0; ICD-10: E84; E84.0, E84.1, E84.8, E84.9) and non-alcoholic fatty lever disease (NAFLD) (ICD-8: 571.11, 571.19; ICD-10: K75.9, K76.0, and K76.9) were likewise from the national Danish Patient Registry.

Pancreatic disease

Hospitalization or death due to pancreatic cancer, acute pancreatitis, and chronic pancreatitis were based on diagnoses ascertained from the national Danish Patient Registry, the national Danish Causes of Death Registry (from 1973), and the national Danish Cancer Registry (from 1943). Pancreatic cancer included ICD-8 codes 157.0, 157.8, and 157.9 and ICD-10 codes C25.3, acute pancreatitis included 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, and chronic pancreatitis included ICD-8 codes 577.10, 577.11, and 577.19 and ICD-10 codes K86.0 and K86.1. Details of diagnostic criteria are given in Supplementary Information methods

All individuals were followed prospectively until the occurrence of pancreatic cancer (N = 442), acute pancreatitis (N = 401), chronic pancreatitis (N = 282), death (N = 10,088), emigration (N = 438), or end of follow-up in December 2018, whichever came first. Due to the completeness of the Danish health registers, follow-up was without losses.

Statistics

We used STATA version 13. Comparison of baseline characteristics was conducted using Cuzick's nonparametric test for trend across ordered groups.

All 101,765 individuals had complete information from Danish nation-wide registries on age, sex, diabetes mellitus, cystic fibrosis, and NAFLD. Information on other covariates was 99% complete. Missing values were imputed based on age and sex using multivariable linear regression for continuous variables, and categorical variables were assigned a separate category. When only including individuals with complete data, results were similar to those presented.

The distribution of plasma pancreatic amylase in the population is shown using a Kernel-density plot. Trends in plasma pancreatic amylase by age and sex were estimated by Cuzick's nonparametric test for trend.

The associations between pancreatic amylase and risk of pancreatic cancer, acute pancreatitis, and chronic pancreatitis were examined using Cox proportional hazards regression with 95% confidence intervals (CI). Left truncation at study entry and age as the underlying time scale (automatically adjusting for age) were used. Hazard ratios were adjusted for potential confounders for all three pancreatic diseases, selected a priori, and included age (as time-scale), sex, smoking, alcohol intake, physical inactivity, BMI, plasma triglycerides, eGFR, diabetes mellitus, cystic fibrosis, and NAFLD. Proportional hazard assumptions were not violated as assessed by Schoenfeld residuals. Prior to baseline, 493 individuals were diagnosed with acute pancreatitis, 176 with chronic pancreatitis, and 24 with pancreatic cancer. These individuals were therefore excluded from the respective prospective analyses. Further adjustment for CRP was performed as a sensitivity analysis; CRP was not considered a confounder in precaution of over-adjustment.

Similar analyses were performed for plasma pancreatic lipase (available in a subgroup), divided into equivalent groups as pancreatic amylase.

Results

Of 101,765 individuals, 894 had acute pancreatitis (493 prevalent and 401 incident), 458 had chronic pancreatitis (176 prevalent and 282 incident), and 466 had pancreatic cancer (24 prevalent and 442 incident). Of these, 439 women and 455 men had acute pancreatitis, 224 women and 234 men had chronic pancreatitis, and 243 women and 223 men had pancreatic cancer.

Plasma pancreatic amylase

The distribution of plasma pancreatic amylase levels from 101,765 apparently healthy individuals from the general population is shown in Fig. 1. The distribution was slightly skewed towards higher levels with a median value of 32 U/L and an interquartile range (IQR) of 26–40 U/L. The reference range of 2.5th-97.5th percentiles corresponded to 16–63 U/L. Plasma pancreatic amylase levels were higher in women than in men in all age-groups (p-value: 8×10^{-132}), and levels were slightly higher with higher age for men (p for trend across age-groups: men 1×10^{-6}, women: 0.58) (Fig. 2).

Follow-up time and demographics

Median follow-up was 9 years (range 2 days–15 years), during which time 442 individuals experienced a first diagnosis of pancreatic cancer (through 919,316 person-years at risk), 401 developed acute pancreatitis (912,795 person-years at risk), and 282 developed chronic pancreatitis (916,052 person-years at risk). Median time from baseline to diagnosis was 5.5 years (IQR: 3.0–8.1) for pancreatic cancer, 5.3 years (3.0–7.7) for chronic pancreatitis, and 5.5 years (3.0–8.4) for acute pancreatitis. Baseline characteristics of all 101,765 individuals according to percentiles of plasma pancreatic amylase levels are shown in Table 1.

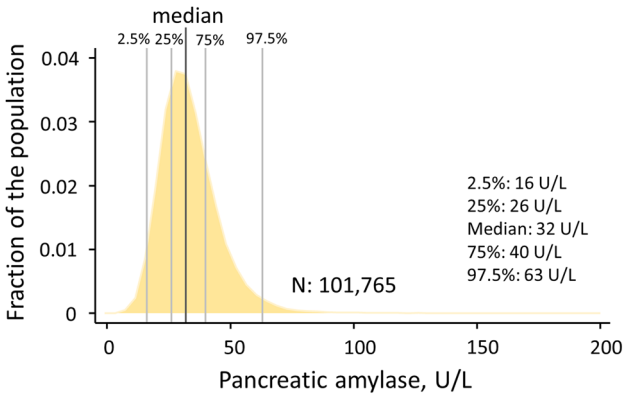


Fig. 1 Distribution of plasma pancreatic amylase in individuals from the general population. Vertical grey lines are the 2.5th, 25th, 50th, 75th, and 97.5th percentiles. Based on 101,765 individuals from the Copenhagen General Population Study

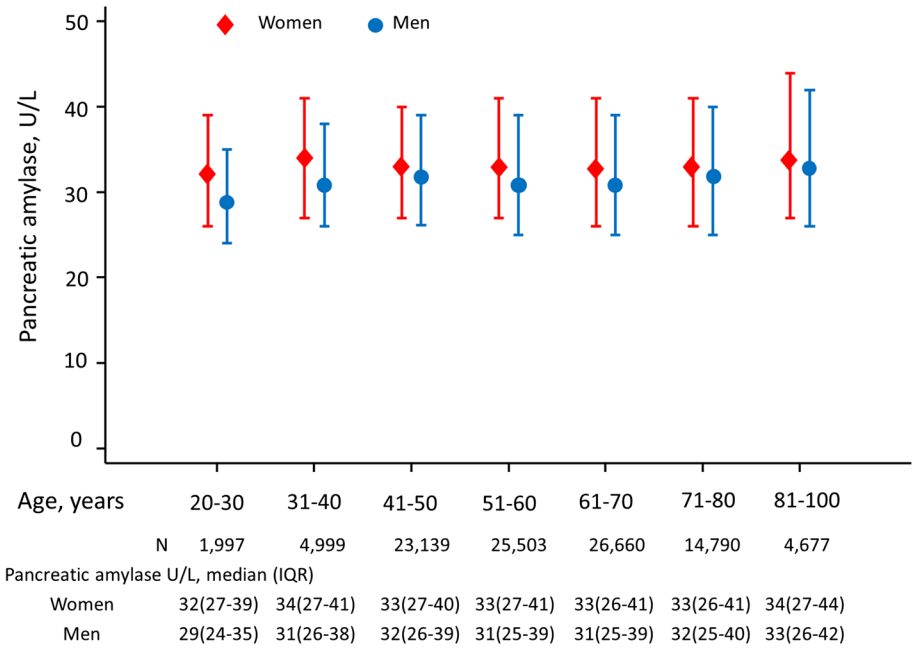


Fig. 2 Sex and age stratified distribution of plasma pancreatic amylase in individuals from the general population. (Plasma pancreatic amylase levels by 10-year age groups are shown as median and interquartile range. Diamond indicates women and circle indicates men. Based on 101,765 individuals from the Copenhagen General Population Study. N = number. IQR = interquartile range).

Table 1 Baseline characteristics of 101,765 individuals from the Copenhagen General Population Study by levels of plasma pancreatic amylase

Pancreatic amylase percentiles									
	1st–2.5th	2.6th–20th	21st–40th	41st–60th	61st–80th	81st–97.4th	97.5th–100th	*P* for trend	All
Number of individuals	3299	17,538	22,806	18,914	19,306	17,403	2499		101,765
Pancreatic amylase, U/L	14(12–16)	22(20–23)	28(26–29)	33(32–34)	39(37–40)	48(45–53)	72(67–85)		32(26–40)
Age, years	61(50–68)	59(49–68)	58(48–67)	57(48–67)	57(48–67)	59(49–68)	61(51–71)	0.80	58(48–67)
Men, %	50	51	47	44	42	39	44	1×10^{-123}	45
Smoking, pack-years[a]	7(0–28)	5(0–23)	2(0–19)	2(0–16)	1(0–15)	1(0–14)	3(0–20)	2×10^{-122}	2(0–18)
Alcohol intake, units[b]/week	10(4–19)	10(4–18)	9(4–16)	8(4–14)	7(3–14)	7(3–13)	7(3–14)	7×10^{-256}	8(4–15)
Physical inactivity[c], %	55	51	48	46	46	45	49	8×10^{-42}	47
Body mass index, kg/m^2	27(24–30)	27(24–30)	26(24–29)	25(23–28)	25(23–28)	25(23–27)	25(22–27)	$<1\times10^{-300}$	26(23–28)
Triglycerides, mmol/L	1.6(1.0–2.4)	1.5(1.0–2.2)	1.4(1.0–2.0)	1.4(0.9–2.0)	1.3(0.9–1.9)	1.3(0.9–1.9)	1.4(0.9–2.0)	3×10^{-136}	1.4(1.0–2.0)
mg/dL	142(89–213)	133(89–195)	124(89–178)	124(80–178)	115(80–169)	115(80–169)	124(80–178)	3×10^{-136}	124(89–178)
eGFR[d], ml/min/1,73 m^2	82(71–93)	82(71–92)	81(71–92)	81(70–91)	79(69–90)	77(66–88)	75(63–86)	7×10^{-243}	80(69–91)
Diabetes mellitus, %	11	6	4	3	3	3	5	7×10^{-92}	4
Cystic fibrosis, %	0.10	0.02	0.03	0.02	0.06	0.03	0.20	0.20	0.04
NAFLD, %									
For sensitivity analysis	0.4	0.4	0.3	0.3	0.4	0.2	0.5	0.002	0.3
CRP, mg/L	1.7(1.1–3.3)	1.5(1.0–2.7)	1.4(0.9–2.3)	1.4(0.9–2.1)	1.3(0.9–2.0)	1.3(0.9–2.0)	1.4(1.0–2.2)	2×10^{-119}	1.4(0.9–2.2)

Number of individuals varies slightly due to availability of data. Categorical variables are percent and continuous variables are median (interquartile range). P for trend were estimated by Cuzick non-parametric test for trend. [a] One pack-year equals twenty cigarettes or equivalent smoked per day in one year. [b] One alcohol unit equals 12 g of alcohol. [c] Physical inactivity was < 4 h light activity per week during leisure time. [d] Estimated glomerular filtration rate by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula based on age and sex corrected plasma creatinine levels. [e]Includes both diabetes mellitus type I and II. eGFR = estimated glomerular filtration rate. NAFLD = non-alcoholic fatty lever disease. CRP = high-sensitive C-reactive protein

Pancreatic amylase and pancreatic disease

In all comparisons, individuals with plasma amylase between the 41st-60th percentiles were used as the reference group.

Pancreatic cancer

Hazard ratios for pancreatic cancer were 1.4 (95%CI: 1.1–1.9) for individuals with pancreatic amylase levels in the 21st–40th percentiles, 1.0 (0.7–1.4) for the 2.6th–20th percentiles, and 2.4 (1.6–3.6) for individuals in the 1st–2.5th percentiles (Fig. 3, panel A). Further, the hazard ratios for pancreatic cancer were 1.2 (0.9–1.7) for individuals with pancreatic amylase levels in the 61st-80th percentiles, 1.0 (0.7–1.4) for the 81st–97.4th percentiles, and 2.2 (1.4–3.7) for individuals in the 97.5th–100th percentiles.

Chronic pancreatitis

Hazard ratios for chronic pancreatitis were 1.2 (95%CI: 0.8–1.9) for individuals with pancreatic amylase levels in the 21st–40th percentiles, 1.2 (0.8–1.9) for the 2.6–20th percentiles, and 1.8 (1.1–3.3) for the 1st–2.5th percentiles (Fig. 3, panel B). Further, hazard ratios of chronic pancreatitis were 1.4 (0.9–2.1) for individuals in the 61st–80th percentiles, 1.5 (1.1–2.4) for the 81st–97.4th percentiles, and 3.2 (1.8–5.6) for individuals in the 97.5th–100th percentiles.

Acute pancreatitis

Hazard ratios for acute pancreatitis were 1.0 (95%CI: 0.8–1.4) for individuals with pancreatic amylase levels in the 21st-40th percentiles, 0.9 (0.7–1.3) for the 2.6th-20th percentiles, and 1.1 (0.6–1.8) for the 1st–2.5th percentiles (Fig. 3, panel C). Further, hazard ratios for acute pancreatitis were 1.0 (0.7–1.4) for individuals in the 61st–80th percentiles, 1.3 (0.9–1.8) for the 81st–97.4th percentiles, and 1.5 (0.8–2.7) for individuals in the 97.5th–100th percentiles.

Extreme pancreatic amylase, CRP, and pancreatic disease

In all comparisons, individuals with plasma amylase between the 41st–60th percentiles were used as the reference group.

Individuals with extreme low levels of pancreatic amylase (1st–2.5th percentiles) had hazard ratios of 2.4 (95% CI: 1.6–3.6) for pancreatic cancer, 1.8 (1.1–3.3) for chronic pancreatitis, and 1.1 (0.6–1.8) for acute pancreatitis (Fig. 4a, top left panel). Similar estimates were seen with further adjustment for CRP (Fig. 4b, bottom left panel). In these individuals, median time from baseline to diagnosis was 5.4 years (IQR: 2.2–9.1) for pancreatic cancer, 3.9 years (2.6–6.4) for chronic pancreatitis, and 5.1 years (3.2–8.9) for acute pancreatitis.

Individuals with extreme high values of pancreatic amylase in the 97.5th–100th percentiles had hazard ratios of 2.2 (95%CI: 1.4–3.7) for pancreatic cancer, 3.2 (1.8–5.6) for chronic pancreatitis, and 1.5 (0.8–2.7) for acute pancreatitis (Fig. 4a, top right panel). Similar estimates were seen with further adjustment for CRP (Fig. 4b, bottom right panel). In these individuals, median time from baseline to diagnosis was 3.0 years (IQR: 0.9–6.3) for pancreatic cancer, 3.6 years (1.8–5.6) for chronic pancreatitis, and 5.1 years (1.2–6.5) for acute pancreatitis.

Pancreatic lipase and risk of pancreatic disease

The distribution of plasma pancreatic lipase levels from 10,071 apparently healthy individuals from the general population is shown in Supplementary Information Fig. 1, and sex and age differences are shown in Supplementary Information Fig. 2. During follow-up, 66 individuals experienced a first episode of pancreatic cancer (through 126,995 person-years at risk), 45 developed chronic pancreatitis (127,450 person-years at risk), and 63 developed acute pancreatitis (127,868 person-years at risk). No significant associations between plasma pancreatic lipase with any of the three pancreatic diseases were found (data not shown); however, the statistical power for these analyses were much less than for the analyses on pancreatic amylase.

Discussion

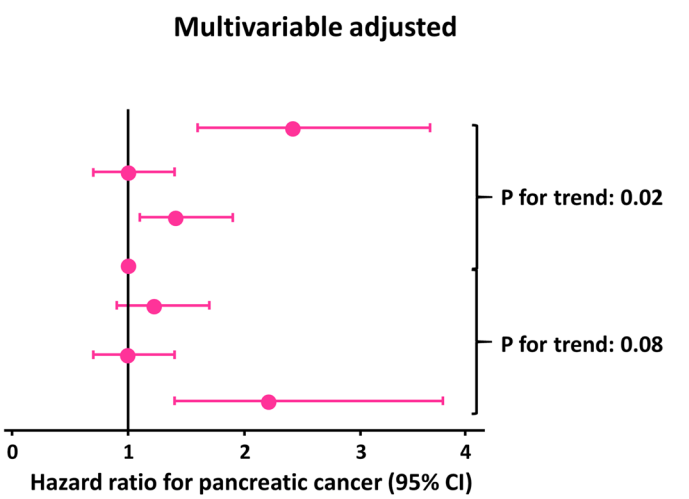
In this study of 101,765 apparently healthy individuals from the Danish general population, we found 2–threefold higher risk of pancreatic cancer and chronic pancreatitis in individuals with extreme low or extreme high levels of pancreatic amylase. In contrast, there was no association between pancreatic amylase and risk of acute pancreatitis These are novel findings.

Mechanistically, high plasma pancreatic amylase levels could reflect ongoing pancreatic tissue damage resulting in spillover of pancreatic enzymes into the circulation. Extremely high levels are usually seen in the setting of acute pancreatitis reaching peak-levels in 1–2 days and returning to normal within 7 days [27]. The present data suggest that even in the case of chronic pancreatitis and pancreatic cancer ongoing low-scale pancreatic tissue damage may occur. Low plasma pancreatic amylase levels could reflect modest, though, permanently compromised pancreatic tissue function with "lower than normal" production of pancreatic enzymes. This attenuation could be caused by obstructed ductal flow by tissue fibrosis and calcification in chronic

A

Pancreatic cancer

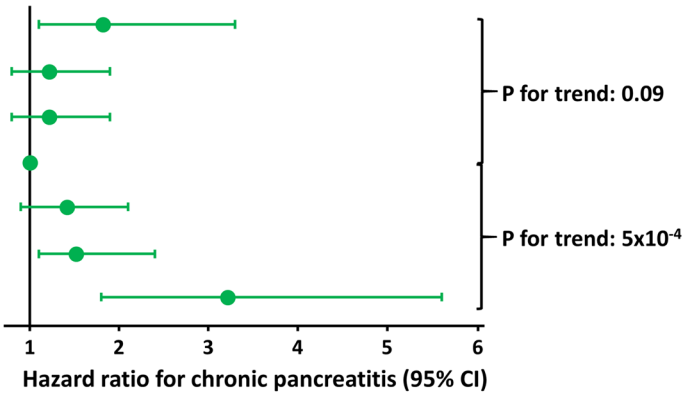
Amylase groups, %	Amylase median, U/L	Individuals/ Events	Events pr. 10,000 person-years	Hazard ratio (95% CI)
1-2.5	14	3,293/ 34	11.4	2.4 (1.6-3.6)
2.6-20	22	17,531/ 69	4.4	1.0 (0.7-1.4)
21-40	28	22,800/ 114	5.6	1.4 (1.1-1.9)
41-60	33	18,914/ 64	3.7	Reference
61-80	39	19,302/ 79	4.5	1.2 (0.9-1.7)
81-97.4	48	17,401/ 61	3.8	1.0 (0.7-1.4)
97.5-100	71	2,497/ 21	9.4	2.2 (1.4-3.7)
Total	32	101,738/ 442	4.8	



B

Chronic pancreatitis

Amylase groups, %	Amylase median, U/L	Individuals/ Events	Events pr. 10,000 person-years	Hazard ratio (95% CI)
1-2.5	14	3,271/ 17	5.8	1.8 (1.1-3.3)
2.6-20	22	17,503/ 51	3.3	1.2 (0.8-1.9)
21-40	28	22,782/ 59	2.9	1.2 (0.8-1.9)
41-60	33	18,897/ 37	2.2	Reference
61-80	39	19,282/ 50	2.8	1.4 (0.9-2.1)
81-97.4	48	17,366/ 51	3.2	1.5 (1.1-2.4)
97.5-100	71	2,485/ 17	7.7	3.2 (1.8-5.6)
Total	32	101,586/ 282	3.1	



C

Acute pancreatitis

Amylase groups, %	Amylase median, U/L	Individuals/ Events	Events pr. 10,000 person-years	Hazard ratio (95% CI)
1-2.5	14	3,256/ 16	5.4	1.1 (0.6-1.8)
2.6-20	22	17,444/ 68	4.4	0.9 (0.7-1.3)
21-40	28	22,710/ 89	4.4	1.0 (0.8-1.4)
41-60	33	18,840/ 67	3.9	Reference
61-80	39	19,232/ 69	3.9	1.0 (0.7-1.4)
81-97.4	48	17,320/ 78	4.9	1.3 (0.9-1.8)
97.5-100	71	2,467/ 14	6.4	1.5 (0.8-2.7)
Total	32	101,269/ 401	4.4	

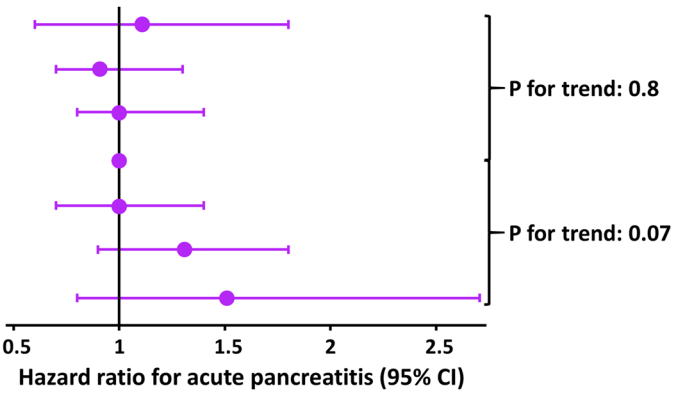


Fig. 3 Plasma pancreatic amylase and risk of pancreatic cancer, chronic pancreatitis and acute pancreatitis in individuals from the general population. (Hazard ratios are for pancreatic cancer, chronic pancreatitis, and acute pancreatitis with 95% confidence intervals. Only individuals naïve to the respective diseases at baseline were included in the prospective analyses for **a** pancreatic cancer (top), **b** chronic pancreatitis (middle), and **c** acute pancreatitis (bottom). Therefore, the number of individuals differs slightly. All analyses were multivariable adjusted for age (as timescale), sex, smoking, alcohol intake, physical activity, body mass index, plasma triglycerides, kidney function, diabetes mellitus, cystic fibrosis, and non-alcoholic fatty lever disease. Based on 101,765 individuals from the Copenhagen General Population Study. CI = confidence interval)

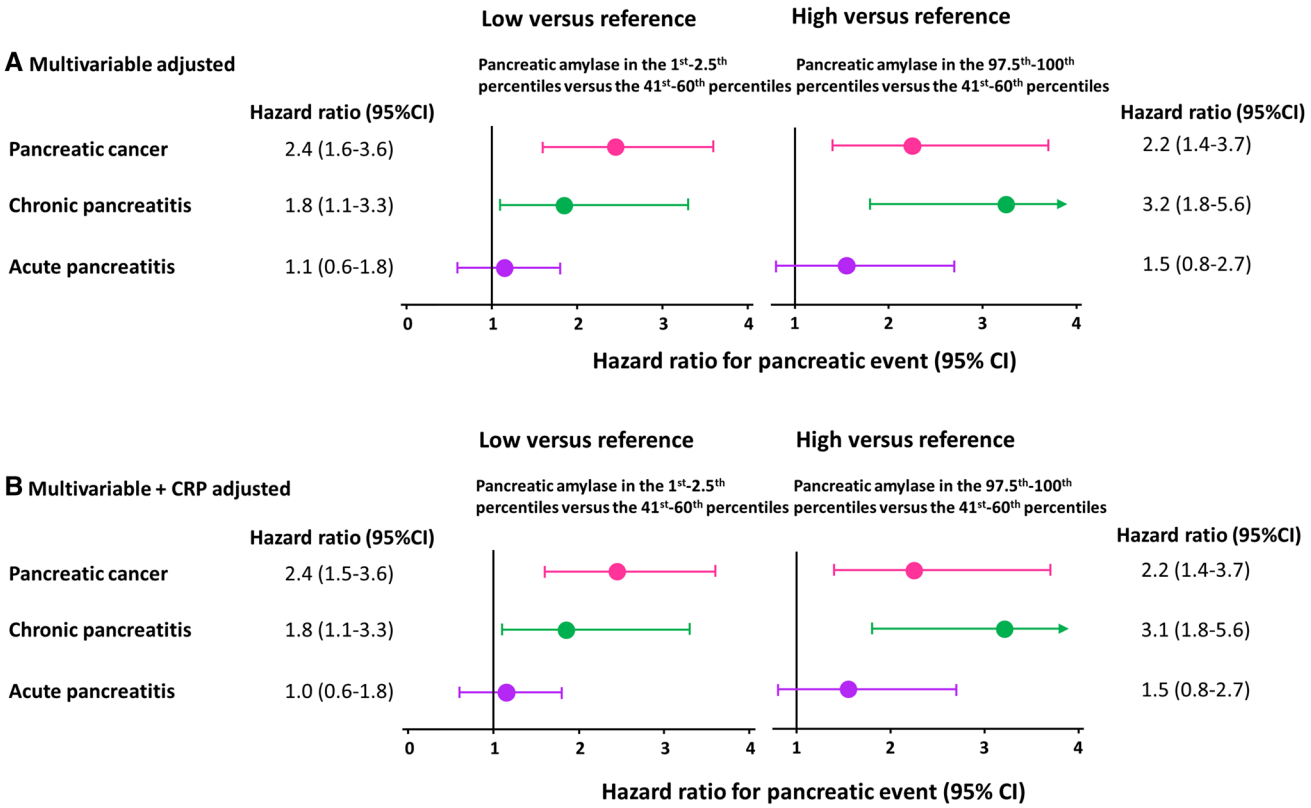


Fig. 4 Extreme low and extreme high plasma pancreatic amylase, C-reactive protein, and risk of pancreatic disease in individuals from the general population. (Hazard ratios are for pancreatic cancer (top), chronic pancreatitis (middle), and acute pancreatitis (bottom) with 95% confidence intervals. Left figures: extreme low pancreatic amylase levels (1st–2.5th percentiles) versus the reference group (41st–60th percentiles). Right figures: extreme high pancreatic amylase levels (97.5th–100th percentiles) versus the reference group (41st–60th percentiles). **a** Multivariable adjusted for age (timescale), sex, smoking, alcohol intake, physical activity, body mass index, plasma triglycerides, kidney function, diabetes mellitus, cystic fibrosis, and non-alcoholic fatty lever disease. **b** Multivariable adjusted also including high-sensitive C-reactive protein. Based on individuals from the Copenhagen General Population Study. CI = confidence interval. CRP = high-sensitive C-reactive protein)

pancreatitis [4], or by tumor cell invasion in pancreatic cancer [12] in both cases causing upstream atrophy of pancreatic tissue. Our findings support this concept, as we found that increased risk of pancreatic cancer and chronic pancreatitis was associated with extremely low pancreatic amylase levels. Surprisingly, extremely high pancreatic amylase levels were also associated with high risk of pancreatic cancer and chronic pancreatitis in the present study. We speculate that this could be due to intermittent episodes of localized low-scale acute inflammation/destruction of acinar cell integrity during tissue invasion by tumor cells in pancreatic cancer and by progressing fibrosis in chronic pancreatitis. Acharya et al [28] found that fibrotic pancreatic tissue limits or even encases pancreatic inflammation resulting in minor systemic involvement when acute-on-chronic pancreatitis is ongoing, compared to the cause of acute pancreatitis in a non-fibrotic pancreas. Extremely low or high pancreatic amylase could in this study, however, not distinguish between whether individuals were in risk of pancreatic cancer or chronic pancreatitis. We found no association between baseline pancreatic amylase values and risk of future episodes of acute pancreatitis in apparently healthy individuals without signs of acute pancreatic disease at baseline. This supports the idea of acute pancreatitis as a non-chronic condition[3], which nevertheless potentially could be different in individuals with recurrent episodes of acute pancreatitis [9, 27]. All our findings were robust despite further adjustment for CRP, an important finding as all three pancreatic diseases observationally are associated with inflammation [29–31].

As plasma pancreatic lipase like pancreatic amylase is used to assess pancreatic function, we ran similar analyses as done for amylase. We found, however, no associations between pancreatic lipase and risk of pancreatic cancer, acute or chronic pancreatitis. This is probably due to lack of statistical power as only 10,071 participants had lipase measurements (compared to 101,765 with amylase measurements) and therefore very few events of all three pancreatic diseases were seen in this subgroup.

No current guidelines for the diagnosis of pancreatic cancer [19, 20] or chronic pancreatitis [17, 18] mention plasma pancreatic amylase as a diagnostic or screening tool, and previous guidelines are even conflicting regarding whether a measurement of low [21] or high [16] pancreatic amylase supports a probable diagnosis of chronic pancreatitis. An explanation for previous unclear results could be that many individuals experience episodes of acute pancreatitis preceding a diagnosis of pancreatic cancer or chronic pancreatitis, which would mask both low and high values as normal, due to the combination of low pancreatic function (resulting in low levels) and acute tissue damage (resulting in high levels). In support of this idea, an American population-based study of 50,080 individuals with pancreatic cancer found that 15% of individuals with pancreatic cancer had a previous diagnosis of idiopathic pancreatitis, 81% had pancreatitis within 3 months of their pancreatic cancer diagnosis, and 99% within 3 years [32]. Together with the present study, this emphasizes the possibility that plasma pancreatic amylase could be used as a supplement in the diagnostic workup of chronic pancreatitis and pancreatic cancer.

Early detection of both pancreatic cancer and chronic pancreatitis are difficult as symptoms are only present with advanced disease [4, 33]. Today, pancreatic cancer screening with imaging modalities is solely recommended for high-risk individuals, that is, for individuals above 45 years with a genetic predisposition (having a causal germ line mutation or > 2 blood relatives with pancreatic cancer) [34], and in individuals with mucinous cystic lesions of the pancreas [33]. No biomarkers are used as screening tools [33]. Evidence suggests that individuals with chronic pancreatitis should be surveilled for pancreatic cancer years after diagnosis [35], or if diabetes mellitus occurs [4]; however, screening for chronic pancreatitis is not recommended. Based on our data, we suggest further research into the use of plasma pancreatic amylase as a supplementary tool in screening for pancreatic cancer in high-risk individuals, and in screening for chronic pancreatitis in individuals with recurrent acute pancreatitis. Plasma pancreatic amylase is an inexpensive and well-established biochemical analysis already used in most laboratories, it is organ specific, and clinicians are familiar with it. Changes in plasma pancreatic amylase, both increases and decreases, could be used in combination with lifestyle risk factors and current symptomatology to establish recommendation of whom and when to screen.

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 [4]. Insufficient adjustment for confounders is another possible limitation of our study; however, we were able to adjust for the majority of known potentially confounding factors. These include factors associated with high levels of plasma amylase and/or pancreatic amylase like physical activity, reduced kidney function, and some medications, particularly anti-diabetics [36], while factors associated with low pancreatic amylase levels are diabetes mellitus (insulin is essential for production of pancreatic amylase [37]), obesity, hypertriglyceridemia, smoking, excess alcohol intake, cystic fibrosis, and NAFLD [36]. Therefore, our results support that plasma pancreatic amylase levels mostly reflect pancreatic function in the present study. That said, we naturally cannot exclude yet unknown confounders/residual confounding which could still bias our results, or negligent potential amylase production in other tissues or by occult tumors [38]. Unfortunately, due to a considerable lower amount of pancreatic lipase measurements we could not use results from these analyses to further substantiate our main findings. Finally, this study was limited by having solely baseline measurements, and no information on whether pancreatic amylase or other risk factors for pancreatic disease changed during study time were available.

A strength of our study is the large homogeneous sample size of apparently healthy individuals from the general population. Furthermore, there were no losses to follow-up. Finally, endpoints were collected unbiased based on the nationwide Danish health registries, that is, without knowledge of plasma pancreatic amylase, and plasma pancreatic amylase was measured without knowledge of pancreas disease.

Conclusion

In apparently healthy individuals from the general population, extreme low and high pancreatic amylase levels are associated with 2–threefold higher risk of both pancreatic cancer and chronic pancreatitis.

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Author contribution SEJH, AL, and BGN 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, AL, and BGN. Acquisition, analyses and interpretation of data: SEJH, AL, and BGN. Drafting of manuscript: SEJH. Critical revision of the manuscript for important intellectual content: AL, AV, CMM, ATH, and BGN. Statistical analyses: SEJH and AL. Study supervision: AL, AV, CMM, ATH, and BGN.

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Availability of data and material Data will be made available upon reasonable request to corresponding author.

Declarations

Conflict of Interest BGN reports consultancies or talks sponsored by AstraZeneca, Sanofi, Regeneron, Akcea, Amgen, Kowa, Denka, Amarin, Novartis, Novo Nordisk, Esperion, and Silence Therapeutics. ATH reports consultancies for AstraZeneca, Silence Therapeutics, Novartis, Sanofi, Akcea, and Draupnir Bio. AV and CMM are currently employed at Novo Nordisk. SEJH and AL have no conflicts of interest.

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

Ethical 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.

References

1. Xiao AY, Tan ML, Wu LM, et al. Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. Lancet Gastroenterol Hepatol. 2016;1(1):45–55. https://doi.org/10.1016/s2468-1253(16)30004-8.
2. Rawla P, Sunkara T, Gaduputi V. Epidemiology of pancreatic cancer: global trends, etiology and risk factors. World J Oncol. 2019;10(1):10–27. https://doi.org/10.14740/wjon1166.
3. Boxhoorn L, Voermans RP, Bouwense SA, et al. Acute pancreatitis. Lancet (London, England). 2020;396(10252):726–34. https://doi.org/10.1016/s0140-6736(20)31310-6.
4. Beyer G, Habtezion A, Werner J, Lerch MM, Mayerle J. Chronic pancreatitis. Lancet (London, England). 2020;396(10249):499–512. https://doi.org/10.1016/s0140-6736(20)31318-0.
5. Khalaf N, El-Serag HB, Abrams HR, Thrift AP. Burden of Pancreatic Cancer: From Epidemiology to Practice. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2020; https://doi.org/10.1016/j.cgh.2020.02.054
6. Habtezion A. Inflammation in acute and chronic pancreatitis. Curr Opin Gastroenterol. 2015;31(5):395–9. https://doi.org/10.1097/mog.0000000000000195.
7. Machicado JD, Yadav D. Epidemiology of recurrent acute and chronic pancreatitis: similarities and differences. Dig Dis Sci. 2017;62(7):1683–91. https://doi.org/10.1007/s10620-017-4510-5.
8. Ahmed Ali U, Issa Y, Hagenaars JC, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. Clinical gastroenterol hepatol: Off Clin Pract J Am Gastroenterol Assoc. 2016;14(5):738–46. https://doi.org/10.1016/j.cgh.2015.12.040.
9. Sankaran SJ, Xiao AY, Wu LM, Windsor JA, Forsmark CE, Petrov MS. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. Gastroenterology. 2015;149(6):1490-1500.e1. https://doi.org/10.1053/j.gastro.2015.07.066.
10. Hori Y, Vege SS, Chari ST, et al. Classic chronic pancreatitis is associated with prior acute pancreatitis in only 50% of patients in a large single-institution study. *Pancreatology : official journal of the International Association of Pancreatology (IAP) [et al]*. Mar 2019;19(2):224–229. doi:https://doi.org/10.1016/j.pan.2019.02.004
11. Raimondi S, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract Res Clin Gastroenterol. 2010;24(3):349–58. https://doi.org/10.1016/j.bpg.2010.02.007.
12. McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol. 2018;24(43):4846–61. https://doi.org/10.3748/wjg.v24.i43.4846.
13. https://gco.iarc.fr/today/online-analysis-multi-bars?v=2020&mode=cancer&mode_population=countries&population=900&populations=900&key=total&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=14&nb_items=10&group_cancer=1&include_nmsc=1&include_nmsc_other=1&type_multiple=%257B%2522inc%2522%253Afalse%252C%2522mort%2522%253Atrue%252C%2522prev%2522%253Afalse%257D&orientation=horizontal&type_sort=0&type_nb_items=%257B%2522top%2522%253Atrue%252C%2522bottom%2522%253Afalse%257D. Accessed 14.07.2021,
14. Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN. American gastroenterological association institute guideline on initial management of acute pancreatitis. Gastroenterology. 2018;154(4):1096–101. https://doi.org/10.1053/j.gastro.2018.01.032.
15. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology : official journal of the International Association of Pancreatology (IAP) [et al]*. 2013;13(4 Suppl 2):e1–15. doi:https://doi.org/10.1016/j.pan.2013.07.063
16. Ito T, Ishiguro H, Ohara H, et al. Evidence-based clinical practice guidelines for chronic pancreatitis 2015. J Gastroenterol. 2016;51(2):85–92. https://doi.org/10.1007/s00535-015-1149-x.
17. Gardner TB, Adler DG, Forsmark CE, Sauer BG, Taylor JR, Whitcomb DC. ACG Clinical Guideline: Chronic Pancreatitis. *Official journal of the American College of Gastroenterology | ACG*. 2020;115(3):322–339. doi:https://doi.org/10.14309/ajg.0000000000000535
18. Löhr JM, Dominguez-Munoz E, Rosendahl J, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United Eur gastroenterol J. 2017;5(2):153–99. https://doi.org/10.1177/2050640616684695.
19. Sohal DPS, Kennedy EB, Cinar P, et al. Metastatic Pancreatic Cancer: ASCO Guideline Update. J Clin Oncol. 2020:Jco2001364. doi:https://doi.org/10.1200/jco.20.01364
20. Ducreux M, Cuhna AS, Caramella C, et al. Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v56-68. https://doi.org/10.1093/annonc/mdv295.
21. Conwell DL, Lee LS, Yadav D, et al. American pancreatic association practice guidelines in chronic pancreatitis: evidence-based report on diagnostic guidelines. Pancreas. 2014;43(8):1143–62. https://doi.org/10.1097/mpa.0000000000000237.
22. Olesen SS, Krarup H, Poulsen JL, et al. Pancreas-specific plasma amylase for assessment and diagnosis of chronic pancreatitis: New insights on an old topic. United Eur gastroenterol J. 2019;7(7):955–64. https://doi.org/10.1177/2050640619846011.
23. Sonne DP, Vilsbøll T, Knop FK. Pancreatic amylase and lipase plasma concentrations are unaffected by increments in

endogenous GLP-1 levels following liquid meal tests. Diabetes Care. 2015;38(5):e71–2. https://doi.org/10.2337/dc14-2751.
24. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: a report of the American college of cardiology/american heart association task force on clinical practice guidelines. J Am Coll Cardiol. 2019;73(24):e285–350. https://doi.org/10.1016/j.jacc.2018.11.003.
25. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–88. https://doi.org/10.1093/eurheartj/ehz455.
26. Nordestgaard BG, Langsted A, Mora S, et al. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points-a joint consensus statement from the European atherosclerosis society and european federation of clinical chemistry and laboratory medicine. Eur Heart J. 2016;37(25):1944–58. https://doi.org/10.1093/eurheartj/ehw152.
27. Kim YS, Chang JH, Kim TH, Kim CW, Kim JK, Han SW. Prolonged hyperamylasemia in patients with acute pancreatitis is associated with recurrence of acute pancreatitis. Medicine (Baltimore). 2020;99(3): e18861. https://doi.org/10.1097/md.0000000000018861.
28. Acharya C, Cline RA, Jaligama D, et al. Fibrosis reduces severity of acute-on-chronic pancreatitis in humans. Gastroenterology. 2013;145(2):466–75. https://doi.org/10.1053/j.gastro.2013.05.012.
29. Sollie S, Michaud DS, Sarker D, et al. Chronic inflammation markers are associated with risk of pancreatic cancer in the Swedish AMORIS cohort study. BMC Cancer. 2019;19(1):858. https://doi.org/10.1186/s12885-019-6082-6.
30. S Rasch I Valantiene A Mickevicius et al 2016 Chronic pancreatitis: Do serum biomarkers provide an association with an inflammageing phenotype? Pancreatology : official journal of the International Association of Pancreatology (IAP) [et al] Sep-Oct 16 5 708 714 https://doi.org/10.1016/j.pan.2016.08.004
31. Hansen SEJ, Madsen CM, Varbo A, Nordestgaard BRG. Low-grade inflammation in the association between mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis: a study of more than 115000 individuals from the general population. Clin Chem. 2018. https://doi.org/10.1373/clinchem.2018.294926.
32. Syed A, Babich O, Thakkar P, et al. Defining pancreatitis as a risk factor for pancreatic cancer: the role, incidence, and timeline of development. Pancreas. 2019;48(8):1098–101. https://doi.org/10.1097/mpa.0000000000001367.
33. Pereira SP, Oldfield L, Ney A, et al. Early detection of pancreatic cancer. Lancet Gastroenterol Hepatol. 2020;5(7):698–710. https://doi.org/10.1016/s2468-1253(19)30416-9.
34. Goggins M, Overbeek KA, Brand R, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the international cancer of the pancreas screening (CAPS) consortium. Gut. 2020;69(1):7–17. https://doi.org/10.1136/gutjnl-2019-319352.
35. Kirkegård J, Mortensen FV, Cronin-Fenton D. chronic pancreatitis and pancreatic cancer risk: a systematic review and meta-analysis. Am J Gastroenterol. 2017;112(9):1366–72. https://doi.org/10.1038/ajg.2017.218.
36. Nakajima K. Low serum amylase and obesity, diabetes and metabolic syndrome: a novel interpretation. World J Diabetes. 2016;7(6):112–21. https://doi.org/10.4239/wjd.v7.i6.112.
37. Mössner J, Logsdon CD, Williams JA, Goldfine ID. Insulin, via its own receptor, regulates growth and amylase synthesis in pancreatic acinar AR42J cells. Diabetes. 1985;34(9):891–7. https://doi.org/10.2337/diab.34.9.891.
38. Seyama K, Nukiwa T, Takahashi K, Takahashi H, Kira S. Amylase mRNA transcripts in normal tissues and neoplasms: the implication of different expressions of amylase isogenes. J Cancer Res Clin Oncol. 1994;120(4):213–20. https://doi.org/10.1007/bf01372559.