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Exocrine pancreas insufficiency in chronic pancreatitis – Risk factors and associations with complications. A multicentre study of 1869 patients

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ABSTRACT

Background/objectives: There is scarce information about risk factors for exocrine pancreas insufficiency (EPI) in chronic pancreatitis (CP), and how it associates with other complications. The aim of the present study was to examine risk factors for EPI and associations to procedures and other CP related complications in a large, Northern European cohort.

Patients and methods: We retrieved cross-sectional data on demographics, status on EPI, aetiological risk factors for CP, CP related complications as well as surgical and endoscopic treatment from the Scandinavian Baltic Pancreatic Club Database. Associations were assessed by univariate and multivariate logistic regression analyses. Results are presented as odds ratios (OR) with 95% confidence intervals.

Results: We included 1869 patients with probable or definitive CP in the study. Exocrine pancreas insufficiency was present in 849 (45.4%) of patients. In multivariate analyses, EPI associated with smoking aetiology (OR 1.47 (1.20–1.79), $p < 0.001$), and nutritional/metabolic aetiology (OR 0.52 (0.31–0.87), $p = 0.01$) to CP. Pancreatic or common bile duct stenting procedure and pancreatic resection were both associated with EPI (ORs 1.44 (1.15–1.80), $p = 0.002$ and 1.54 (1.02–2.33), $p = 0.04$, respectively). The presence of diabetes mellitus (OR 2.45 (1.92–3.15), $p < 0.001$), bile duct stenosis (OR 1.48 (1.09

Abbreviations: CP, Chronic pancreatitis; EPI, Exocrine pancreas insufficiency; SPBC, Scandinavian Baltic Pancreatic Club; HaPanEU, Harmonizing diagnosis and treatment of chronic Pancreatitis across Europe; DM, Diabetes mellitus; BMI, Body mass index; SD, Standard deviation; OR, Odds ratio.

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−2.00), p = 0.02) and underweight (2.05 (OR 1.40−3.02), p < 0.001) were all associated with presence of EPI.
Conclusions: Smoking, bile duct stenosis, previous stenting and resection procedures are all associated with EPI in patients with CP. Presence of EPI were also associated with malnutrition and diabetes mellitus. Hence, intensive nutritional surveillance is needed in these patients.

1. Introduction

Chronic pancreatitis (CP) is a progressive disease caused by fibro-inflammatory changes in the pancreas [1,2]. Alcohol abuse and smoking are the most common aetiologic factors, but also genetic, autoimmune, obstructive, and nutritional/metabolic factors may cause or contribute to disease [3,4]. The aetiology is often complex and may be multifactorial. Although there is increasing knowledge on how aetiological factors affect the pathophysiology in CP [5], knowledge on how different aetiological factors contribute to disease development and eventual complications is scarce.

Exocrine pancreas insufficiency (EPI) is a common complication to CP caused by inadequate secretion of digestive enzymes and bicarbonate from the pancreas. In most CP cases, this is a condition resulting from loss of pancreatic parenchyma, but other factors, such as decreased secretion due to pancreatic duct obstruction may also contribute to EPI [6,7]. The prevalence of EPI in CP differs between cohorts [8,9]. Exocrine pancreas insufficiency causes maldigestion in affected individuals, and is associated with increased morbidity [10] and mortality in CP patients [11]. As EPI causes increased disease burden in CP patients, it is warranted to identify how aetiological risk factors for CP, treatment modalities and other CP related complications associate with EPI.

In the present cross-sectional study, we aimed to study how EPI associate with CP aetiology, treatment modalities and complications to CP in a large cohort from Northern Europe.

2. Materials and methods

The Scandinavian Baltic Pancreatic Club (SPBC) database is a prospective database collecting data on patients with probable or definitive CP according to the M-ANNHEIM classification [4]. The data are collected from twelve centres, in Norway (Bergen, Oslo), Denmark (Aalborg, Bispebjerg, Herlev, Hvidovre), Finland (Tampere), Latvia (Riga), Lithuania (Kaunas), Russia (Moscow) and Sweden (Gothenburg, Stockholm) [12]. All centres use the Harmonizing diagnosis and treatment of chronic Pancreatitis across Europe (HaPanEU) guidelines in follow up and treatment of CP patients [13]. Local institutional ethical review boards and national data protection agencies have approved data collection and data storage at each of the participating centres. Centre for Pancreatic Diseases at Aalborg University Hospital (Denmark) serves as the coordinating centre.

2.1. Study design and data retrieval

This is a cross-sectional study based on inclusion registry data (i.e., baseline registrations) from the SBPC database. We retrieved data for the study on July 17th, 2019. We noted data on exocrine pancreatic function, age, gender, time since CP diagnosis at inclusion, physician assigned aetiology for CP, CP related complications according to M-ANNHEIM classification (see below), as well as clinical (patient height and body weight at inclusion), clinical chemistry (haemoglobin, albumin and 25-OH vitamin D).

Only subjects ≥18 years of age with definitive CP according to M-ANNHEIM criteria were included. Subjects with no data on exocrine pancreas function were excluded from the study.

2.2. Exocrine pancreas function

Exocrine pancreatic function was tested by treating physician at the individual centres and classified as sufficient or insufficient according to M-ANNHEIM classification. According to this classification, “proven EPI” requires pathological exocrine pancreas function test [4]. Methods available for testing exocrine pancreatic function were faecal elastase-1, faecal fat excretion and ^{13}C-MCT breath test [12]. Patients with gastrointestinal symptoms (e.g. intermittent diarrhoea), but normal exocrine pancreas function test and no need for pancreas enzyme replacement treatment were considered not to have EPI [4].

2.3. Aetiology

Aetiology of CP was classified according to M-ANNHEIM criteria [4] after judgement by treating physician [12]. We used the following aetiologies: smoking, alcohol abuse, efferent/obstructive, nutritional/metabolic, autoimmune, hereditary and miscellaneous/other, in the analyses. As CP aetiology may be multifactorial, patients could be classified with several aetiologies.

2.4. Surgical and endoscopic treatment modalities

Surgical treatment modalities were divided into drainage procedures, stenting procedures, and pancreatic resection. Drainage procedures comprise endoscopic or surgical drainage of localized fluid collections. Stenting procedures included stenting of pancreatic or common bile duct.

2.5. Chronic pancreatitis related complications

Chronic pancreatitis related complications were categorized according to the M-ANNHEIM classification [4]. Diabetes mellitus (DM) was diagnosed according to American Diabetes Association diagnostic criteria [14]. Osteoporosis was diagnosed demonstrating significantly reduced bone mineral density measured by dual energy X-ray absorptiometry or other imaging modalities [15]. Body mass index (BMI) was calculated as weight in kg divided by square of height in m. Body mass index <18.5 kg/m^2 was defined as underweight in agreement with guidelines from the European Society for Clinical Nutrition and Metabolism [16]. Hypoalbuminemia was defined by a serum albumin level of <35 mg/L [17], anaemia by serum haemoglobin levels <12 g/dL in women and 13 g/dL in men [18], and severe vitamin D deficiency as vitamin D levels <25 nmol/L [19].

2.6. Statistical methods

Values are expressed as numbers (%) or means (standard deviations (SD)) unless stated otherwise. Normal distribution was

tested by QQ plots and Shapiro Wilks tests. Groupwise comparisons of continuous data were performed by *t*-test or Mann-Whitney *U* test as appropriate. Categorical data were compared with Fisher's exact test. Trends for categorical data were tested with Mantel-Haenzel chi square for linear trend.

We performed univariate and multivariate logistic regression analyses. In the multivariate models, predictors were removed using a backward conditional method, based on a significance level of $p < 0.10$ as threshold for inclusion in the final model. The final model was adjusted for age, gender, and duration of CP through forced entry. As there is an expected dependency between low vitamin D levels, osteoporosis, hypoalbuminemia and underweight, deficiency states detected through clinical chemistry were analysed separately, and not in the CP complications analysis. Results are presented as odds ratios (OR) with 95% confidence intervals in parentheses. We present number of patients included in each of the multivariate analyses as n. We used SPSS Statistics® statistical package (IBM®, Armonk, NY) for all statistical analyses. Analyses were performed and results are presented according to TRIPOD statement [20].

3. Results

At date of data retrieval, 1943 patients were included in the database, of whom 1869 (96%) were classified into whether EPI was present or not, and were included (Fig. 1). Mean age of included patients was 56.8 years and 1227 (66%) were men. The most common aetiology was smoking followed by alcohol abuse.

3.1. Characteristics of patients with exocrine pancreatic insufficiency

Exocrine pancreas insufficiency was present in 45.4% of the patients (Table 1). Mean age was significantly higher in the EPI patients ($p < 0.001$), as was median time since diagnosis ($p < 0.001$, Fig. 2). Even after disease duration >25 years, not all CP patients had developed EPI. Patients with EPI had significantly lower BMI than patients with normal exocrine pancreas function ($p < 0.001$). Furthermore, mean albumin was significantly lower in patients with EPI ($p < 0.001$), but there were no significant differences in vitamin D levels and haemoglobin levels.

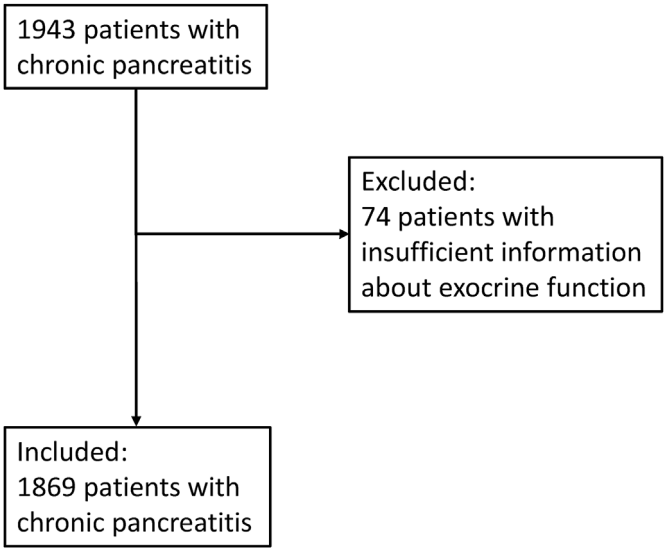

Fig. 1. Flow sheet showing exclusion and inclusion process, ending up with 1869 patients from twelve centres.

3.2. Associations between exocrine pancreas insufficiency and potential risk factors

In the multivariate regression model of associations between CP aetiology and EPI, smoking aetiology was strongly associated with EPI ($p < 0.001$), while nutritional/metabolic aetiology was negatively associated with EPI ($P = 0.01$, Table 2). Stenting of biliary or pancreatic duct and resection of pancreas were also associated with EPI in multivariate regression model ($p = 0.002$ and $p = 0.04$, respectively, Supplementary Table 1), associating surgical CP treatment modalities to EPI.

3.3. Associations between exocrine pancreas insufficiency and other complications to chronic pancreatitis

Exocrine pancreas insufficiency associated with DM ($p < 0.001$), bile duct stenosis ($p = 0.02$) and underweight ($p < 0.001$) in the multivariate model of associations between EPI and other complications to CP (Table 3).

Hypoalbuminemia was associated to EPI ($p = 0.003$, Supplementary Table 2), while anaemia and low vitamin D levels were not significantly associated to presence of EPI.

The proportion of CP patients with a combination of both DM and EPI increased with duration of CP (Fig. 3, $p < 0.001$).

4. Discussion

In this this cross-sectional study, we demonstrate how different aetiologies, treatment modalities and complications associate with EPI in CP patients from a large, multinational cohort. We also demonstrate higher proportions of hypoalbuminemia and underweight in CP patients with EPI compared to CP patients with normal exocrine pancreas function.

4.1. Association between EPI and CP aetiology

We found a strong association between smoking and EPI, indicating that smoking is an independent risk factor for EPI in CP patients. On the other hand, we demonstrated no association between alcohol consumption and EPI. These findings are in line the study by Luaces-Regueira and co-workers [21]. In our earlier study from the SPBC, we demonstrated a strong association between smoking and EPI and a weaker association between alcohol abuse and EPI [22]. In that study, however, we based exposure on patients' self-reported history of smoking and alcohol abuse, and the multivariate model did not include other aetiological risk factors. Smoking was also associated with the “pancreatic insufficiency” (exocrine and endocrine) cluster in an earlier cluster analysis from the SPBC [23]. Hence, we argue that smoking may be a stronger risk factor for EPI than excessive alcohol consumption in patients with CP. This is to some degree supported by experimental data on cigarette smoke's direct effect on pancreatic stellate cells, promoting fibrosis in pancreatitis [24]. However, disease-causing mechanisms from smoking and alcohol abuse are multiple and complex [25], and there are few experimental studies on the isolated effects of tobacco-smoke in the development of CP.

Patients with a nutritional/metabolic aetiology of CP where less likely to have EPI at the time of inclusion. We do not have available data on subgroups of this category, but the largest proportion of this group is probably patients with hyperlipaemia and obesity [26]. The explanation may be that nutritional causes are treatable with diet intervention and medications, slowing the progress towards end-stage disease. However, we cannot exclude that patients with CP caused by nutritional/metabolic aetiology are less prone to develop EPI compared to other aetiologies. The associations

Table 1
Characteristics of patients with and without exocrine pancreas insufficiency (EPI). SD: Standard deviation. § Mean values for fecal elastase 1 are not compared, as this test is used for diagnosing EPI in most patients. *: Mann Whitney *U* test.

	Number (EPI)	EPI	Non-EPI	p-value
Number (males)		849 (566)	1020 (661)	0.4
Mean age, years (SD)		59.1 (13.2)	54.8 (15.1)	<0.001
Fecal elastase 1 (SD)	1083 (613)	52.6 (69.8)	273.7 (180.1)	N/A§
BMI kg/m^2 (SD)	1562 (705)	22.8 (4.2)	24.2 (4.6)	<0.001
Stool frequency (Median [Quartiles])	1091 (492)	2 [1–3]	1 [1–2]	<0.001*
Hemoglobin g/dL (SD)	1585 (744)	13.2 (1.8)	13.4 (2.3)	0.15
Albumin g/L (SD)	1411 (681)	37.2 (6.3)	38.6 (6.5)	<0.001
Vitamin D ng/L (SD)	940 (493)	64.6 (37.5)	66.7 (38.3)	0.4

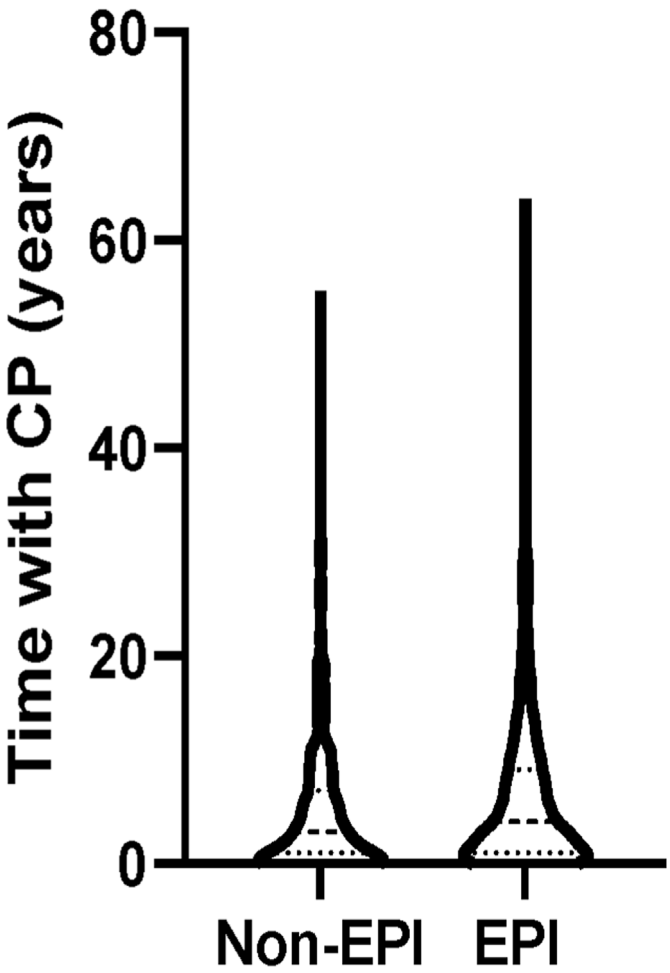

Fig. 2. Violin plots of time with chronic pancreatitis (CP) in patients with (n = 826) and without (n = 984) exocrine pancreas insufficiency (EPI). Dashes symbolize medians, and dots symbolize quartiles. The patients with EPI had significantly longer time with CP than patients without (medians (quartiles) 4 [1-9] years and 3 [1-7] years respectively, p < 0.001 (Mann Whitney *U* test)).

between aetiological risk factors and EPI are to some degree supported by imaging findings by another study from the SPBC material [27]. In this study, smoking aetiology was associated with global structural changes of the pancreas and severe calcifications, indicating severe involvement of the whole gland. On the other hand, nutritional/metabolic aetiology was associated with less extensive, focal structural changes of the pancreas, and negatively associated with calcifications.

4.2. Associations between EPI and surgical procedures

Stenting of bile- or pancreatic duct was associated with EPI in our material. Stenting may be performed to treat an obstructive aetiology or complication to CP [28]. Stenting of the pancreatic duct has earlier been associated with slowing of the progression of EPI in CP patients [29]. Hence, our demonstrated association between stenting procedure and EPI may rather be an effect of selection of patients needing treatment for efferent ductal obstruction hindering pancreatic secretions, rather than an effect of stenting itself. We also found an association between pancreatic resection in CP patients and EPI, which is earlier demonstrated to be a common complication to pancreatic resection surgery [30].

4.3. Associations between EPI and other CP complications

As expected, there were clear associations between markers of malnutrition and presence of EPI in our material. Hence, the mean value of BMI in CP patients with EPI was lower than in patients with preserved exocrine pancreatic function, and there was a larger proportion of patients with underweight in the EPI group. Malabsorption due to lack of digestive enzymes is probably the most important cause of underweight in CP patients, but pain, systemic inflammation and small intestinal overgrowth also mediate poor nutritional status in this context [31]. This may explain why malnutrition is prevalent in CP, even after adequate treatment with enzyme supplementation [32,33], and supports the need for additional measures and a multidisciplinary setup to improve nutritional status in these patients.

We also observed a lower mean albumin level and more prevalent hypoalbuminemia in the EPI group of CP patients. Hypoalbuminemia is associated with increased morbidity in CP patients [34], and is not a specific biomarker for poor nutrition [35]. Due to the link to generally more severe morbidity and presence of inflammation, low albumin level is generally a marker for poor prognosis in patients [35,36].

There were no significant differences in vitamin D levels or proportions of low vitamin D between the two groups. Low vitamin D levels have been reported to be prevalent in CP patients, but also in healthy controls [37]. Levels of vitamin D must be used with caution as a nutritional marker, as differences between laboratories, genetic differences in different populations and differences in skin exposure to the sun will confound the results [38]. In the Nordic countries, huge seasonal differences in sun exposure and vitamin D levels is also a potential bias [39]. Vitamins A and E would possibly be better indicators of fat-soluble vitamin malabsorption in CP patients [40], but were not available in this study. There was an increased proportion of patients with osteoporosis in the EPI group, but this did not reach significance in the multivariate

Table 2
Associations between presence of exocrine pancreatic insufficiency (EPI) and aetiology for chronic pancreatitis (CP). Adjusted model includes age, gender and time with CP. n: number of patients included in the analysis, OR: Odds ratio, CI: Confidence interval.

n = 1746		Univariate model		Multivariate model	
	Number (EPI)	OR (95% CI)	p-value	OR (95% CI)	p-value
Alcohol	1002 (472)	1.14 (0.95–1.37)	0.2		
Smoking	1083 (538)	1.53 (1.26–1.85)	<0.001	1.47 (1.20–1.79)	<0.001
Nutritional/metabolic	81 (23)	0.46 (0.28–0.76)	0.002	0.52 (0.31–0.87)	0.01
Hereditary	149 (64)	0.88 (0.63–1.23)	0.4		
Efferent duct	169 (69)	0.81 (0.59–1.11)	0.2		
Immunological	126 (53)	0.85 (0.59–1.23)	0.4		
Miscellaneous	157 (67)	0.88 (0.63–1.22)	0.4		

Table 3
Associations between complications to CP and EPI. Multivariate model is adjusted for age, gender and time with CP. n: number of patients included in the analysis, *: BMI <18,5 kg/m^2, OR: Odds ratio, CI: Confidence interval.

n = 1258		Univariate		Multivariate	
	Number (EPI)	OR (95% CI)	p-value	OR (95% CI)	p-value
Calcifications	1134 (528)	1.15 (0.95–1.39)	0.2	1.13 (0.89–1.45)	0.3
Pseudocysts	670 (285)	0.83 (0.68–1.00)	0.05	0.81 (0.63–1.03)	0.09
Diabetes mellitus	657 (413)	2.80 (2.29–3.41)	<0.001	2.45(1.92–3.15)	<0.001
Bile duct stenosis	288 (157)	1.55 (1.29–1.99)	0.001	1.48 (1.09–2.00)	0.02
Underweight*	172 (101)	1.85 (1.34–2.55)	0.001	2.05 (1.40–3.02)	<0.001
Osteoporosis	151 (86)	1.71 (1.22–2.39)	0.002		
Ascites	111 (49)	0.95 (0.64–1.39)	0.8		
Bleeding	79 (39)	0.73 (0.46–1.16)	0.2		
Pleural effusion	76 (29)	0.73 (0.45–1.17)	0.2		
Portal vein thrombosis	75 (38)	1.24 (0.78–1.97)	0.4		
Duodenal stenosis	75 (35)	1.06 (0.66–1.68)	0.8		
Splenic vein thrombosis	72 (30)	0.85 (0.53–1.37)	0.5		
Pancreatic fistula	36 (17)	1.08 (0.56–2.09)	0.8		
Pseudoaneurysm	32 (10)	0.54 (0.25–1.15)	0.1		
Pancreatic cancer	16 (8)	1.20 (0.45–3.21)	0.7		

model. This probably reflects that the mechanism for development of metabolic bone disease in CP is more complex than just malabsorption of vitamin D, including other factors associated with CP e.g., systemic inflammation, smoking and alcohol abuse [41,42].

Low haemoglobin levels can reflect both malabsorption and chronic inflammation in CP [43], and has been associated with EPI in CP patients in another study [44]. However, we do not demonstrate significant differences in haemoglobin levels or proportions of subjects with anaemia between the two patient groups in our material.

Diabetes mellitus was strongly associated with EPI in this material, probably reflecting that both complications often represent end-stage CP. Not surprisingly, the proportion of patients with both EPI and DM increase with increasing disease duration, but it is worth noting that even after <5 years of disease duration, 19% have developed this combination of organ dysfunctions. We have earlier demonstrated that a rather large proportion of CP patients with diabetes had known disease for less than five years [45]. As CP diagnosis is often delayed, and our study is not designed to differ between pancreatic diabetes and other types of diabetes, these findings must be considered with some caution. Still these findings may indicate that for a sizeable proportion of CP patients, organ dysfunctions occur before the commonly described 5–10 years since diagnosis [46]. On the other hand, there is a small proportion of patients in our cohort with >25 years of CP without EPI, demonstrating the heterogeneity of this disease.

4.4. Strengths and limitations

Major strengths of this study are the high number of patients, and the relatively low number of excluded subjects from the study. However, missing data in the each of the multivariate analyses may still introduce some selection bias in the results.

Diagnosing EPI may be challenging in CP, and symptoms may not be obvious. To counteract such classification bias, we have classified patients as EPI only when there is a pathological test for exocrine function. Intermittent diarrhoea and other non-specific abdominal symptoms with a normal test may have many different causes besides EPI. Hence, we have classified the “mild exocrine insufficiency, not needing medication” group from the M-ANNHEIM criteria [4] as exocrine pancreas sufficient. As exocrine pancreas function has been evaluated using the fecal elastase 1 test in most patients in this material, this approach may cause some classification bias. The sensitivity of fecal elastase 1 is rather low in patients with mild to moderate exocrine insufficiency, classifying them as normal exocrine pancreas function, even though some of them may benefit from pancreas enzyme treatment. In addition, the specificity of fecal elastase 1 is only moderate [47]. Furthermore, there is no consensus of the cut-off value of fecal elastase 1 test in the HaPanEU guidelines [13]. Still, in a CP cohort with an expected large proportion of patients with EPI, the diagnostic value of fecal elastase-1 is probably rather high.

We have not collected data on time from last exocrine pancreas function test to registration. Hence, there is a possibility that patients classified as exocrine sufficient may have developed EPI at time of registration. As it is recommended in the HaPanEU guidelines to test CP patients annually for exocrine pancreas function, this does probably not constitute a strong bias [13].

Classification bias may also apply to aetiological factors, especially smoking and alcohol aetiology, based on physicians’ classifications, rather than patient reported exposure [22].

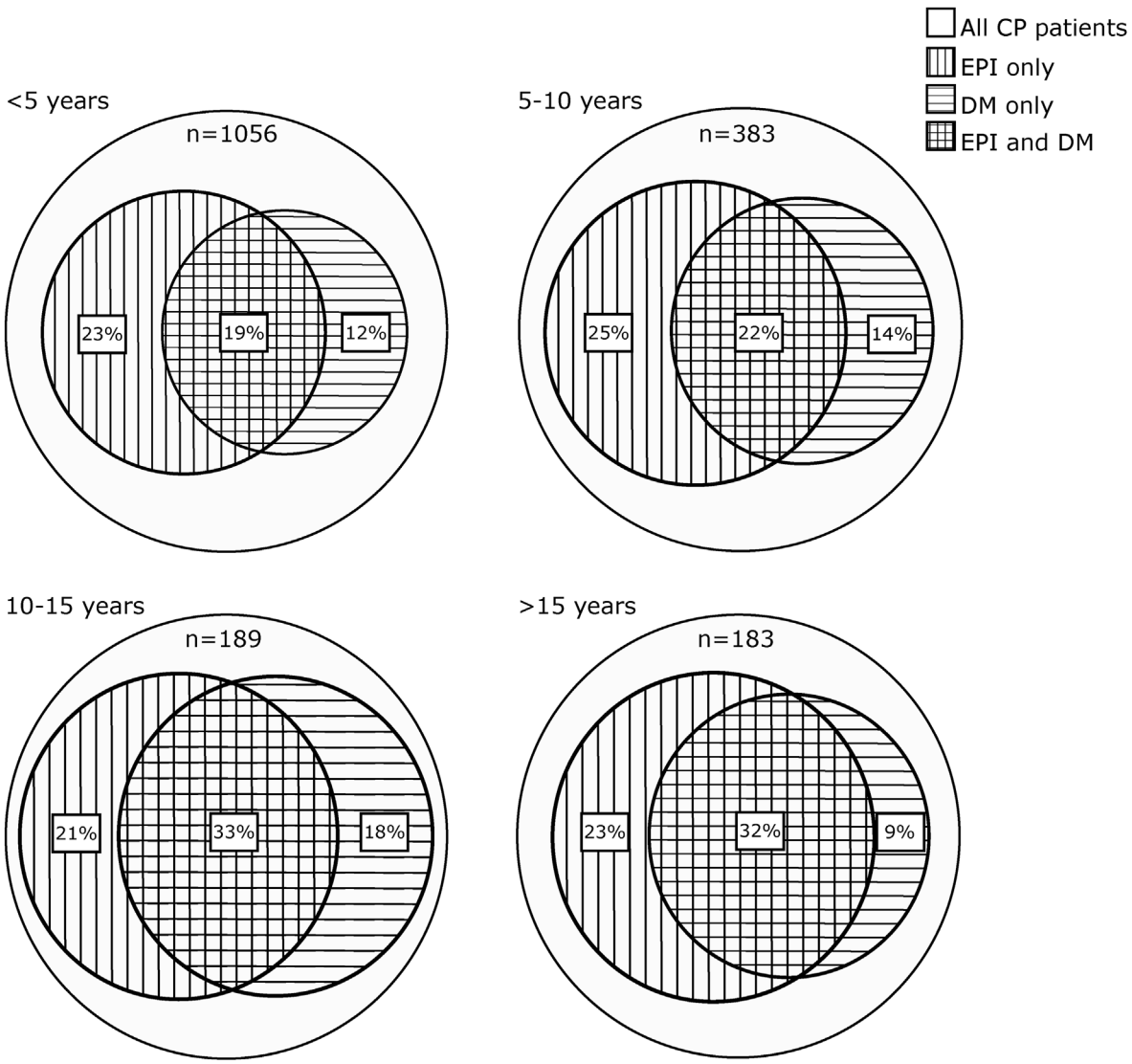

Fig. 3. Venn diagrams showing proportions with exocrine pancreatic insufficiency, diabetes mellitus and the combination of these diagnoses. Diagrams are stratified into time since diagnosis of chronic pancreatitis. There was an increasing trend towards combination of exocrine pancreatic insufficiency and diabetes with increasing time since diagnosis (n = 1811, p for trend <0.001). EPI: Exocrine pancreatic insufficiency; CP: Chronic pancreatitis.

The multicentre approach may introduce confounding bias due to possible heterogeneity in diagnostic and treatment traditions between the different centres. Common guidelines recommended in diagnostics and treatment of CP will partly counteract this bias [13]. Ethnic differences between the populations from the countries taking part in this study may also contribute to confounding bias. We have not collected data on ethnicities from the participants in this study.

Finally, the cross-sectional design of the study will preclude inference of causal relations of the associations observed.

5. Conclusions

In this study, we demonstrate that smoking is a strong risk factor for EPI in patients with CP. Surgical and endoscopic interventions associate with presence of EPI. We further demonstrated that EPI was associated with signs of malnutrition and other late-onset complications to CP.

Our findings support that CP patients should be encouraged to quit smoking. Furthermore, patients with EPI need active treatment with pancreas enzyme replacement therapy, but also other measures of nutritional support as well as active surveillance for complications. Confirmation of causality of the observed associations warrant future, longitudinal studies.

Declaration of competing interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2022.02.003.

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