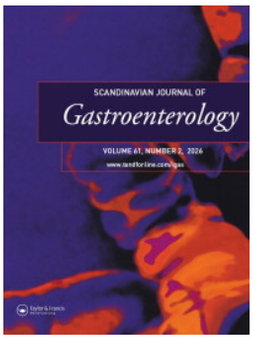

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A decade of collaborative research: insights from the Scandinavian Baltic Pancreatic Club database on chronic pancreatitis

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A decade of collaborative research: insights from the Scandinavian Baltic Pancreatic Club database on chronic pancreatitis

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ABSTRACT

Background: The clinical presentation of chronic pancreatitis (CP) is highly variable and determined by the presence of pancreatic and extrapancreatic complications that occur with varying prevalence and severity. The Scandinavian and Baltic Pancreatic Club (SBPC) Forum of Excellence is a forum for clinicians from the Nordic and Baltic countries with specific knowledge on pancreatic diseases. In 2016, the forum established a database for patients with CP, which became the largest database on this patient population.

Methods: This paper provides an insight into the 14 studies published from the SBPC database

Results: The cohort grew over the years, and finally, a total of 2608 patients were entered into the database. Smoking and alcohol were leading aetiologies and these are both associated with pain, pancreatic exocrine insufficiency and structural changes. Cluster analysis revealed distinct complication profiles. Imaging findings correlated with clinical outcomes, and enzyme therapy adherence was suboptimal. Chronic pancreatitis is associated with reduced quality of life compared to controls. Endoscopic procedures (EP) were common while surgery was rare and usually preceded by EPs.

Conclusion: The SBPC's research offers valuable insights into the aetiology, treatment and complications of CP, with significant implications for patient management. Future studies should aim to expand the evidence base for acute on chronic pancreatitis and explore the long-term outcomes of pancreatic enzyme replacement therapy adherence and invasive interventions in diverse populations. To address these problems, a new prospective register was started that is fully compliant with the current European Union legislation.

Abbreviations: CI: confidence interval; CP: chronic pancreatitis; CT: computed tomography; DM: diabetes mellitus; EP: endoscopic procedures; GDPR: general data protection regulations; IQR: interquartile range; MRI: magnetic resonance imaging; OR: odds ratio; PEI: pancreatic exocrine insufficiency; SBPC: Scandinavian and Baltic Pancreatic Club; QOL: quality of life.

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Introduction

Chronic pancreatitis (CP) is on the rise, and these patients are here to stay [1,2]. Subsequently, there are two direct functional deficits of the pancreas: exocrine insufficiency leading to maldigestion and endocrine insufficiency leading to diabetes mellitus. Both develop in most patients, as well as pain, which is the foremost complication of CP [3].

Scandinavian and Baltic Pancreatic Club Forum of Excellence is a forum for physicians from the Nordic and Baltic countries with specific scientific and empirical knowledge on pancreatic diseases. The forum was established in 2012 with the purpose of developing a scientific working group across borders, improving the understanding of the complex mechanisms underlying CP. The specialists in the working group come from Denmark, Norway, Sweden, Finland, Iceland, Lithuania, and Latvia. Russia and Northeast Germany (Lübeck) were later included as neighbor countries. The sites from these countries all represent highly scientifically active centres. The Nordic and Baltic countries, albeit small, have the advantage of developed healthcare systems and ethnically rather homogenous populations.

In 2016, the forum established a retrospective database for patients with CP, which became one of the largest databases on this patient population in the world. Since then, the active centres published a 14 of papers to describe the pathophysiology and natural history of CP. Here, we aimed to (1) characterise and describe the natural history of CP in the Nordic and Baltic countries and (2) provide a basis for future prospective, observational studies.

Methods

Representatives from the pancreatic centres of expertise (Figure 1) came together to define the parameters for the database. A retrospective database, with prospective follow ups annually from patients with CP was established with REDCap®. REDCap® was chosen as an academically based database [4], accessible *via* the internet and providing the necessary safety. Ethics approval was granted in all participating countries (participating countries and centres are presented in Figures 2 and 3). A clinical core module and an imaging module was agreed upon. Over time, initial visits of patients with CP were entered into the database, and curated. Furthermore, follow-up visits could be added. All participating centres are secondary or tertiary referral centres with special interest and expertise in CP. The Centre for Pancreatic Diseases at Aalborg University Hospital (Denmark) serves as the coordinating centre. Statistical methods and assesment variables

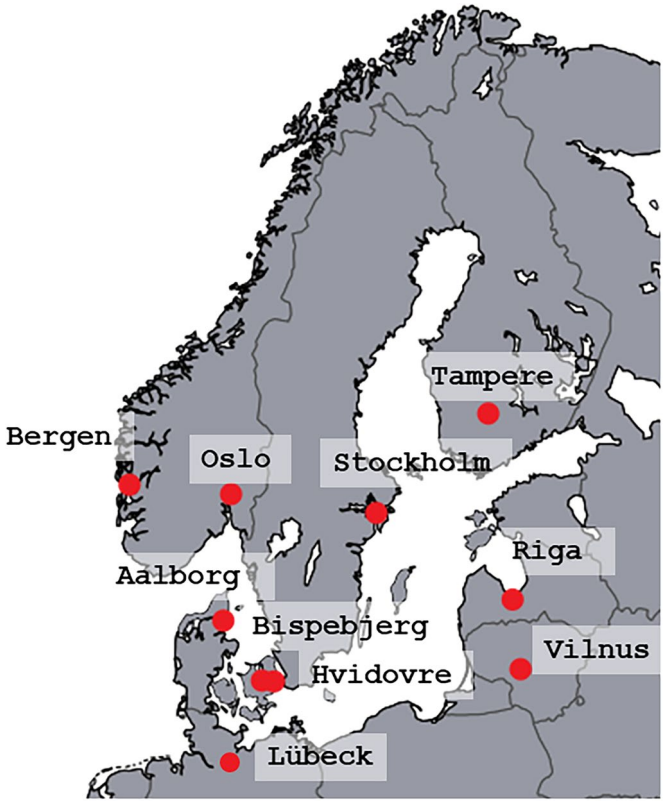

Figure 1. Centres participating in the Scandinavian Baltic Pancreatic Club database. Moscow and Reykjavik were included in the database but did not contribute data.

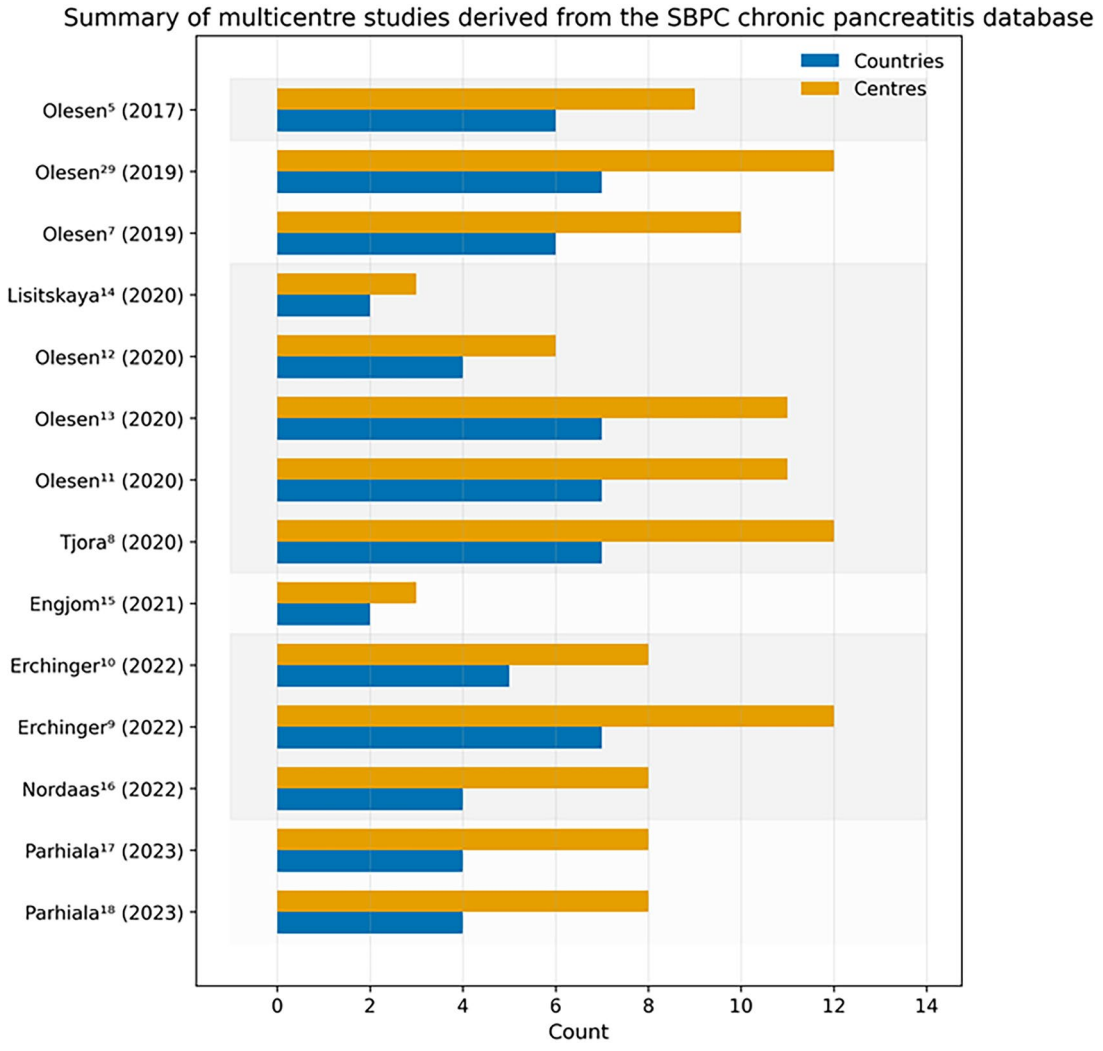

Figure 2. Number of countries and centres in each study.

are described in detail in manuscripts published by our group [5].

Results

All patients with probable or definitive CP according to the M-ANNHEIM diagnostic criteria [6] qualified for inclusion in the SBPC database. In the first study, the database had 910 patients: 608 men and 302 women; median age 58 [interquartile range (IQR): 48–67)] years, with definite 848 (93%) or probable CP 62 (7%) [5]. Smoking (70%) and alcohol (59%) were the most frequent aetiologies and were seen in combination in 44% of patients [5]. Idiopathic chronic pancreatitis accounted for 8% of patients in the cohort.

A history of recurrent acute pancreatitis (RAP) was seen in 49% prior to the development of CP. Pain (69%) and pancreatic exocrine insufficiency (PEI) (68%) were the most common complications, followed by diabetes mellitus (DM) (43%) [5]. Most patients (30%) were classified as clinical stage II (symptomatic CP with exocrine or endocrine insufficiency). Less than 10% of the patients had undergone pancreatic surgery [5].

The cohort grew over the years, and finally, a total of 2608 patients were entered into the database. Data were analysed as a cross-sectional study as the follow-up visits were not sufficiently regular. In the next sections, we will briefly review the knowledge learned from the SBPC database publications by analysing the large number of patients with CP. The most important findings are presented in Table 1.

Characterisation

Subtypes of chronic pancreatitis

In the cohort of 1070 patients, alcohol and smoking were the most common aetiological risk factors [7]. Cluster analysis identified three distinct complication clusters characterised by inflammation, fibrosis, and pancreatic insufficiencies. An independent association

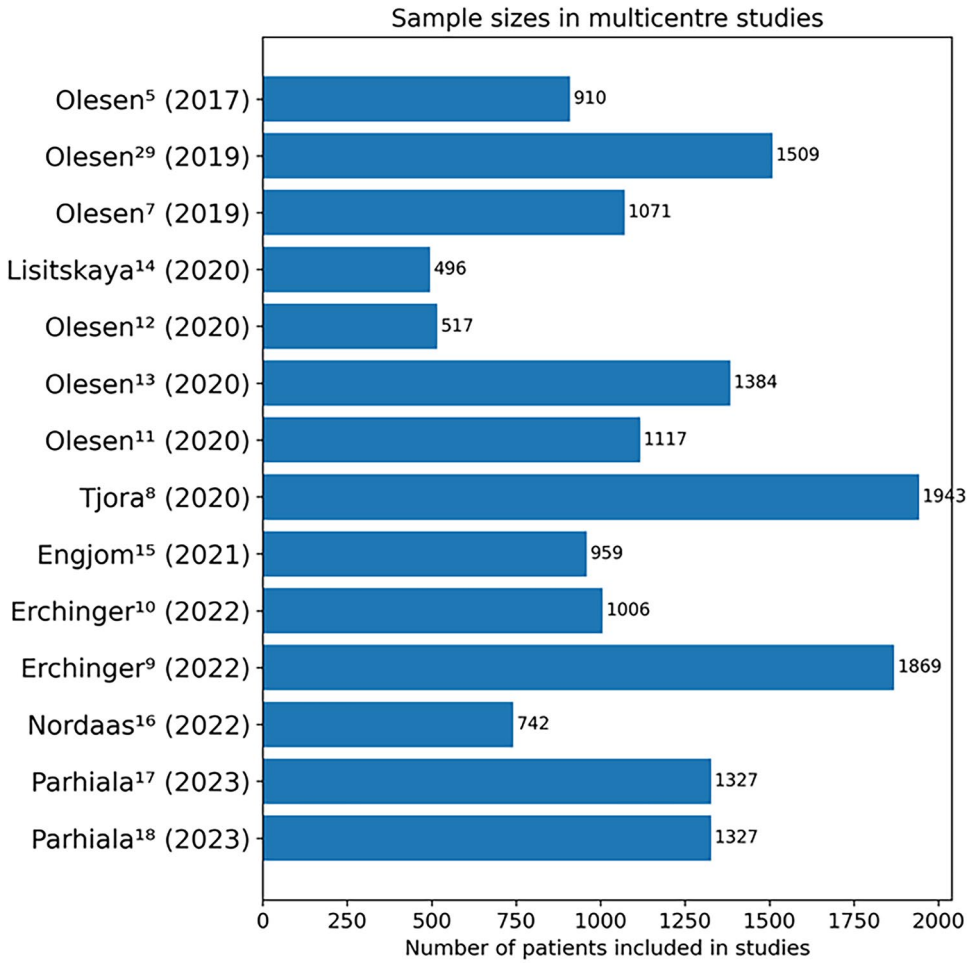

Figure 3. Number of patients included in each study.

between inflammatory complications and alcoholic aetiology was seen (odds ratio [OR] 2.00, (95% CI [confidence interval), 1.38–2.90], $p < 0.001$), whereas smoking was associated with fibrosis-related complications (OR 2.23 (1.56–2.3.20), $p < 0.001$) and pancreatic insufficiencies (OR 1.42 (1.00–2.01), $p = 0.046$) [7].

Relationship between smoking and alcohol abuse and complications of chronic pancreatitis

A complete history of smoking and alcohol exposure was available for 932 patients [8]. In multivariate regression analyses, the presence of pain and PEI were both significantly associated with a history of smoking (OR 1.94 (1.40–2.68), $p < 0.001$ and OR 1.89 (1.36–2.62), $p < 0.001$, respectively) and alcohol abuse (ORs 1.66 (1.21–2.26), $p = 0.001$ and 1.55 (1.14–2.11), $p = 0.005$, respectively) [8]. Smoking was associated with calcifications (OR 2.89 (2.09–3.96), $p < 0.001$), moderate to severe ductal changes (OR 1.42 (1.05–1.92), $p = 0.02$), and underweight (OR 4.73 (2.23–10.02), $p < 0.001$). A history of alcohol abuse was associated with pseudocysts (OR 1.38 (1.00–1.90) $p = 0.05$) and diabetes mellitus (DM) (OR 1.44 (1.03–2.01), $p = 0.03$). There were significantly increased ORs for several complications with increasing exposure to smoking and alcohol abuse [8]. Smoking and alcohol abuse were both independently associated with the development of complications in patients with CP. Furthermore, there seems to be a dose-dependent relationship between smoking and alcohol abuse and complications in CP [8].

Pancreatic calcifications

The prevalence of calcifications was 60.4% in the overall patient cohort out of 1509 patients, but highly variable between patients with different aetiological risk factors (range: 2%–69%). On multivariate analysis, alcoholic aetiology (OR 1.76 (1.39–2.24), $p < 0.001$) and smoking aetiology (OR 1.77 (1.39–2.26), $p < 0.001$) were again positively associated with the presence of calcifications, while autoimmune aetiology was negatively associated with calcifications (OR 0.15 (0.08–0.27), $p < 0.001$) [20].

Table 1. The most important results from the Scandinavian Baltic Pancreatic Club expert group database.

Reference	Results
Olesen [5]	• Smoking (70%) and alcohol (59%) were the most frequent aetiologies and seen in combination in 44% of patients. A history of recurrent acute pancreatitis was seen in 49% prior to the development of CP. • Pain (69%) and PEI (68%) were the most common complications followed by DM (43%). • Most patients (30%) were classified as clinical stage II (symptomatic CP with exocrine or endocrine insufficiency). • Less than 10% of the patients had undergone pancreatic surgery.
Olesen [7]	• Alcohol (55%) and smoking (53%) were the most common etiological risk factors and seen in combination in 36% of patients. • Cluster analysis identified 3 distinct complication clusters characterised by inflammation, fibrosis, and pancreatic insufficiencies. • An independent association between inflammatory complications and alcoholic aetiology was seen, whereas smoking was associated with fibrosis-related complications, and pancreatic insufficiencies.
Olesen [29]	• The prevalence of calcifications was 60.4% in the overall patient cohort, but highly variable between patients with different etiological risk factors (range: 2-69%). • Alcoholic aetiology and smoking aetiology were positively associated with the presence of calcifications, while an autoimmune aetiology was negatively associated with calcifications.
Tjora [8]	• The presence of pain and PEI were both significantly associated with history of smoking and alcohol abuse. • Smoking was associated with calcifications, moderate to severe ductal changes, and underweight. • History of alcohol abuse was associated with pseudocysts and DM. • There were significantly increased OR for several complications with increasing exposure to smoking and alcohol abuse.
Olesen [11]	• Parameters indicative of beta cell loss (pancreatic calcification, PEI, pancreatic resection) were confirmed as independent risk factors for DM. • In addition, type 2 DM-related risk factors (dyslipidemia and overweight/obesity) were associated with the presence of DM (all $p \leq 0.002$). • Patients with a history of pancreatic fluid collections (indicative of previous attacks of acute pancreatitis) had a marginally increased risk of DM.
Olesen [12]	• Patients with CP have significantly lower QoL compared to a population-based reference population. • Factors independently associated with a lowered QoL are constant pain, opioid based pain treatment and alcohol aetiology. • However, these factors only explain a fraction of QoL, and additional factors need identification.
Olesen [13]	• Active smoking and alcohol consumption were independently associated with the presence of pain. • In addition, patients' age at diagnosis, pancreatic duct pathology, and the presence of pseudocysts, duodenal stenosis, and PEI were confirmed as pain risk factors. • Constant pain, as opposed to intermittent pain, was more frequently reported by smokers, while alcohol consumption was associated with intermittent pain.
Lisitskaya [14]	• The presented system provides a feasible mean for systematic assessment of CP imaging features. • Imaging parameters based on quantitative assessment, as opposed to subjective assessments, have better reproducibility, and should be preferred in the development of new grading systems for understanding pathophysiology and disease progression in CP.
Engjom [15]	• Pancreatic structural changes were found in 94% of the subjects: 67% had calcifications, 59% main pancreatic duct dilatation, 33% pseudo-cysts and 22% pancreatic atrophy. • Alcohol abuse was independently associated with pancreatic calcifications and focal acute pancreatitis, whereas smoking was independently associated with more severe calcifications and involvement of the whole gland. • Disease duration was positively associated with calcifications and pancreatic atrophy and negatively associated with focal acute pancreatitis and pseudocysts.
Erchinger [9]	• Smoking, bile duct stenosis, previous stenting and resection procedures are all associated with PEI in patients with CP. • Presence of PEI were also associated with malnutrition and DM.
Erchinger [10]	• Sixty-four percent of PEI patients were correctly treated with PERT. • Twenty-five per cent of PEI patients were not taking enzymes at all, and 20% of PEI patients were undertreated with insufficient PERT doses according to the guidelines. • Fourteen percent of patients with sufficient pancreatic function were receiving enzymes despite normal exocrine pancreatic function. • Current smoking was associated with lack of treatment and alcohol abuse was associated with under-treatment. • In our CP expert centres, the adherence to guidelines for enzyme treatment is insufficient (both patient factors and centre differences have influence on treatment adherence).
Nordaas [16]	• This study shows independent associations between distinct structural changes on pancreatic imaging and clinical complications in chronic pancreatitis. • Pancreatic atrophy, severe calcifications and continuous organ involvement may be of particular clinical relevance, and these findings should motivate monitoring of pancreatic function and nutritional status.
Parhiala [17]	• One in five of the CP patients underwent endoscopic procedure. • These patients scored higher on QoL responses and had better symptom scores. • CP patients who had pancreatic stenting performed had the same pain patterns as the reference population.
Parhiala [18]	• Pancreatic surgery for CP is rare: surgical procedures were performed on only 7% of the CP patients in the SBPC database. • The indication for surgery was pain in half of the patients. • Endoscopic procedures were common before surgery. • Half of the patients reported being pain-free after surgery.

ACP: acute on-top-of chronic pancreatitis; CI: confidence interval; CP: chronic pancreatitis; DM: diabetes mellitus; GDPR: general data protection regulations; IQR: interquartile range; OR: odds ratio; PEI: pancreatic exocrine insufficiency; PERT: pancreatic enzyme replacement therapy; QOL: quality of life.

Pancreatic exocrine insufficiency and pancreatic enzyme replacement therapy

PEI was present in 849 (45.4%) out of 1869 patients. In multivariate analyses, PEI was associated with smoking (OR 1.47 (1.20–1.79), $p < 0.001$) and nutritional/metabolic aetiology (OR 0.52 (0.31–0.87), $p = 0.01$). Pancreatic or common bile duct stenting procedure and pancreatic resections were both associated with PEI (ORs 1.44 (1.15–1.80), $p = 0.002$ and 1.54 (1.02–2.33), $p = 0.04$, respectively). The presence of DM (OR 2.45 (1.92–3.15), $p < 0.001$), bile duct stenosis (OR 1.48 (1.09–2.00), $p = 0.02$) and underweight (OR 2.05 (1.40–3.02), $p < 0.001$) were also associated with the presence of PEI. Smoking (OR 1.47 (1.20–1.79), $p < 0.001$), bile duct stenosis, previous stenting (OR 1.44 (1.15–1.80), $p = 0.002$) and resection procedures (OR 1.54 (1.02–2.33), $p = 0.04$) are all associated with PEI in patients with CP in multivariate analysis. The presence of PEI was again associated with malnutrition (OR 2.05 (1.40–3.02), $p < 0.001$) and DM (OR 2.45 (1.92–3.15), $p < 0.001$) in a multivariate analysis [9].

In another study, we used data from the SBPC database to examine the use of pancreatic enzyme replacement therapy (PERT) in CP patients, and adherence to evidence-based guidelines from the United European Gastroenterology Guideline on treatment of CP [10]. We collected information on exposures, exocrine function, intake of pancreatic enzymes, and markers of nutrition in patients with CP. Faecal elastase <200 µg/g was defined as a marker for PEI. Enzyme replacement therapy of 100,000 lipase units or more per day was defined as adequate treatment. Our analysis showed that 64% of the patients were correctly treated. Twenty-five per cent of PEI patients were not taking enzymes at all, and 20% of PEI patients were under-treated with insufficient PERT doses according to the guidelines. Fourteen percent of patients with sufficient pancreatic function were receiving enzymes despite normal exocrine pancreatic function. There were centre differences. Current smoking was associated with lack of treatment, and alcohol abuse was associated with under-treatment. There were no associations between 'no treatment' or 'under-treatment' for underweight or vitamin D deficiency [10].

Diabetes mellitus

The study included 1117 patients, of whom 457 (40.9%) had DM [11]. The mean age was 52.8 ± 14.2 years, and 67% were men. On multivariate analysis, parameters indicative of beta cell loss (pancreatic calcification, exocrine insufficiency, pancreatic resections) were confirmed as independently associated with DM (all $p \leq 0.02$). In addition, type 2 DM-related risk factors (dyslipidemia and overweight/obesity) were associated with the presence of DM (all $p \leq 0.002$).

Patients with a history of pancreatic fluid collections (indicative of previous attacks of acute pancreatitis (AP)) had a trend toward increased risk of DM ($p = 0.07$) [11].

Quality of life and pain

The European organisation for research and treatment of cancer quality of life questionnaire (EORTC QLQ-C30) was used to evaluate quality of life in this study with scores ranging from 0 to 100 after linear transformation of the raw scores.

Compared to the separate reference population derived from the normative QOL-C30 criteria ($n = 11{,}343$), patients with CP ($n = 517$) had lower global health status (50.5 vs. 66.1; $p < 0.001$) as well as reduced scores for all functional scales (all $p < 0.001$) [12]. Additionally, CP patients reported a higher burden for all symptom items, with pain being the most prominent complaint (all $p < 0.001$). Constant pain ($p = 0.02$), opioid based pain treatment ($p < 0.001$) and alcoholic aetiology ($p = 0.03$) were independently associated with lowered global health status. The final multivariable model explained 18% of the variance in global health status [12].

In another study [13], active smoking (OR 1.6 (1.1–2.2), $p = 0.005$) and alcohol consumption (OR 1.8 (1.1–3.0), $p = 0.03$) were independently associated with the presence of pain. In addition, patients' age at diagnosis, pancreatic duct pathology, and the presence of pseudocysts, duodenal stenosis, and PEI were all associated with pain (all $p \leq 0.01$). Constant pain, as opposed to intermittent pain, was more frequently reported by smokers ($p = 0.03$), while alcohol consumption was associated with intermittent pain ($p = 0.006$) [13].

Imaging features of chronic pancreatitis

The feasibility study included pancreatic computed tomography (CT) or magnetic resonance imaging (MRI) from 496 patients with definitive CP in the SBPC database [14]. Images were assessed according to the new SBPC imaging system (quantitative assessments of ductal and parenchymal features). Inter-reader agreement of reported imaging parameters was investigated for 80 CT and 80 MRI examinations by two expert radiologists. Results showed that reporting the imaging features into the imaging system was deemed

feasible for >80% of CT and >90% of MRI examinations. Quantitative assessments of main pancreatic duct diameters, presence/number/diameter of calcifications, and gland diameters had high levels of inter-reader agreement with κ-values of 0.75–0.87 and intraclass correlation coefficients of 0.74–0.97. The more subjective assessments, e.g., irregular main pancreatic duct and dilated side-ducts, had poor to moderate agreement with κ-values of 0.03–0.4414.

In another study [15], 959 subjects with definite or probable CP according to the M-ANNHEIM diagnostic criteria were included in a multicentre cross-sectional observational study and assessed using a standardised and validated CP imaging system [14]. Multivariate logistic regression was used to analyse if aetiological factors adjusted for covariates were independently associated with morphological pancreatic features. Pancreatic structural changes were found in 94% of the subjects: 67% had calcifications, 59% main pancreatic duct dilatation, 33% pseudo-cysts and 22% pancreatic atrophy. Alcohol abuse was independently associated with pancreatic calcifications (OR 1.61 (1.09–2.37), $p=0.02$) and focal AP (OR 2.13 (1.27–3.56), $p=0.004$), whereas smoking was independently associated with more severe calcifications (OR 2.09 (1.34–3.27), $p=0.001$) and involvement of the whole gland (OR 2.29 (1.61–3.28), $p<0.001$). Disease duration was positively associated with calcifications (OR (per year) 1.05 (1.02–1.08), $p<0.001$) and pancreatic atrophy (OR 1.05 (1.02–1.08), $p>0.001$) but negatively associated with focal acute pancreatitis (OR 0.91 (0.87–0.95), $p<0.001$) and pseudocysts (OR 0.96 (0.93–0.98), $p<0.001$) [15].

In another study [16], we aimed to explore the associations between pancreatic morphology and clinical complications in our CP cohort. In this cross-sectional study, we used multivariate logistic regression analyses to evaluate whether imaging-based structural pancreatic changes were associated with common clinical complications. Main pancreatic duct obstruction (OR 2.9 (1.3–6.7), $p=0.010$), severe calcifications (OR 2.9 (1.3–6.5), $p=0.012$), pancreatic atrophy (OR 4.6 (1.8–11.3), $p=0.001$), and parenchymal changes throughout the entire pancreas (continuous organ involvement) (OR 2.1 (1.1–4.0), $p=0.021$) were positively associated with PEI. Continuous organ involvement (OR 1.5 (1.0–2.3), $p=0.038$) and pseudocysts (OR 0.6 (0.4–1.0), $p=0.037$) were positively and negatively associated with DM, respectively. Pancreatic atrophy (OR 2.48(1.19–5.13), $p=0.015$) and severe calcifications (OR 2.02 (1.01–3.83), $p=0.030$) were positively associated with underweight, and severe calcifications (OR 0.53 (0.33–0.84), $p=0.006$) were negatively associated with pain [16].

Endoscopic treatment

This study aimed to determine the frequency of endoscopic procedures (EP) in CP patients and to analyse pain and quality of life (QoL) in these patients after their EP [17]. Patients undergoing EPs and gathered information on the procedure, pancreatic function, pain, disease, and duration were analysed. We prospectively gather the EORTC C-30 QoL questionnaire. The CP reference population from the database had no interventions ($n=870$). Out of 1327 patients, up to 260 CP patients (22%) underwent EPs, median one year (range 0–39 years) after CP diagnosis. The most prevalent aetiological factors were alcohol (65%) and smoking (71%). Extracorporeal shock wave lithotripsy was used in 6% of the CP population and in 21% of the EP group. Biliary duct stenting was performed on 37% and pancreatic stenting was performed on 56% of the patients.

Following their procedures, the EP group demonstrated moderately better QoL ($p=0.047$), functioning, and fewer symptoms compared with the reference population, who had not undergone any invasive interventions. Smoking, alcohol, hereditary factors, efferent duct aetiology, gender, age, and disease duration showed no significant interaction effects on QoL between the EP and reference groups (all $p>0.12$). The only notable interaction was observed in patients with painless pancreatitis, who showed a positive interaction with QoL in the reference population (+4.5%, $p=0.001$).

There was no difference in the QoL and pain in the pancreatic stent group and the reference group. The patients who had EPs and then later surgery (23%) had more pain ($p=0.043$) and fatigue ($p=0.021$) [17].

Surgical treatment

This study aimed to determine the surgical treatment strategies for the treatment of CP [18]. Patients who had pancreatic surgery were analysed, and the baseline CP population from the eight centres was used as a reference. We included information on comorbidities, pancreatic function, previous interventions, time and type of surgery, and the EORTC-30 QoL questionnaire. On the whole, 95 out of 1327 (7%) patients underwent pancreatic surgery.

The final study group comprised 51 patients (54%) who underwent pancreatic surgery for chronic pain, excluding those who had surgery for complications or suspected malignancy. Most patients (75%) had undergone endoscopic procedures before surgery; however, information on the technical or clinical success of these procedures was not available. The median

follow-up time was two years (range 0–8) after surgery and seven years (range 1–46) after diagnosis. CP patients who underwent surgery had a higher proportion of idiopathic pancreatitis than those with known causes (30% vs 7%, $p < 0.001$). Pancreatic resection combined with drainage (54%) was the most common surgical procedure, followed by pancreatic resections (32%) and drainage procedures (14%). Pain patterns did not differ from the reference population: postoperatively, 47% of the patients were pain-free with or without pain medication, while 16% had chronic pain episodes. Patients experiencing constant pain had a significantly longer duration of disease prior to surgery compared with those without constant pain (median 11 years, range 1–28, vs. 3 years, range 1–23; $p = 0.034$). Patients who underwent pancreatic surgery for pain reported the same QoL, but worse social functioning and more symptoms compared to the control CP population [18].

Discussion

The CP database from the Scandinavian and Baltic Pancreatic Club is one of the largest registries of patients with CP worldwide. Our results have contributed significantly to our understanding of CP, highlighting the aetiological complexity and the multifaceted nature of CP, with alcohol consumption and smoking emerging as the predominant risk factors.

There are several others CP registries such as the Dutch CARE [19], the North American NAPS2 [20] and PROCEED studies [21]. In the CARE study the patients ($n = 1218$) recruited had RAPs along with CP unlike in the SBPC database which focused only on the patients with probable or definitive CP according to M-ANNHEIM. The PROCEED ($n = 350$) studies are more focused on the progression and phenotyping of CP with specimen samples [21]. They also include patients with AP and abdominal pain without pancreatitis. The NAPS2 study includes controls and CP patients who give blood samples for further study of genetics and biomarkers of pancreatitis [22]. An Italian research team has just started a multicentre registry called ITARECIPE focused on understanding the progression of CP [23]. All of the studies above have different approaches to studying CP but to this date the SBPC database is the largest and most prosperous with 14 studies.

The cluster analysis conducted by the SBPC delineated three distinct complication clusters: inflammation, fibrosis, and pancreatic insufficiencies. The analysis demonstrated an independent association between inflammatory complications and alcoholic aetiology, while smoking was linked to fibrosis-related complications and pancreatic insufficiencies. These findings are instrumental in tailoring patient-specific management strategies.

The SBPC's work also contributed to a better understanding of acute on chronic pancreatitis (ACP) a condition that has been challenging to characterise due to its overlapping features with acute and CP [13]. Although the evidence base is currently limited, the SBPC's position statement lays a foundation for future research and clinical management. Spin-offs of the database also resulted in other studies, among them the first definition of ACP [13]. Although the evidence base is poor, this position statement provides a foundation from which to advance the management of ACP [24].

In terms of treatment adherence, the SBPC's examination of PERT revealed that only 64% of patients were correctly treated according to the United European Gastroenterology guidelines. A concerning 25% of PEI patients were not taking enzymes at all, and 20% were undertreated. An earlier study was performed with the CARE cohort with focus on the diagnosis of PEI, they found that only half of the patients had PEI screened at the time of diagnosis and 60% in case of symptoms [25]. This underscores the need for improved patient education and adherence to treatment protocols to optimise clinical outcomes.

The SBPC also focused on the multiple procedures CP patients need. Not only due to pain but also other CP-related complications. In our database, up to 20% of CP patients underwent endoscopic procedures, and 7% had surgery, with half being performed for pain and the other for complications or suspected malignancy. Although limited by the observational design, we found that patients who had surgery before prior endoscopic procedures had better QOL and less pain. The ECAPE trial had similar findings, where early surgery performed better results [26]. In a nationwide Dutch cohort study, they found an increase in surgery for CP-related symptoms with good outcomes [27]. Still, results are inconclusive as a sham arm was never used. On that note, a recent sham-controlled study compared litotripsy and endoscopy versus sham for painful CP. The pain relief in the active arm was only marginally superior compared with sham after 12 weeks, and after 24 weeks, there were no differences between groups [28]. Future SBPC studies should aim to systematically collect pre- and post-intervention data on symptoms and quality of life in order to evaluate the effectiveness of endoscopic and surgical treatments and to identify patient subgroups most likely to benefit from specific interventions.

Although alcohol and smoking were the predominant aetiological factors in our CP cohort, genetic and idiopathic cases were present but uncommon and

therefore not analysed as separate groups. Future SBPC studies should seek to characterise these subgroups more comprehensively, as they may exhibit distinct clinical trajectories and management needs.

The strengths of the SBPC publications lie in its large patient cohort and the robust statistical analyses employed. Also the Nordic and Baltic countries in the study population have a similar cultural risk factors and healthcare structures. The findings provide a nuanced understanding of the risk factors and complications associated with CP, which can inform both clinical practice and future research directions.

However, the studies based on our database are not without limitations. It must emphasised that each article in this review are from the same database, they used data at different time points and from different centres, thus resulting in slight epidemiological differences. Also, the retrospective nature of the data collection nature may introduce biases as well as the fact that longitudinal follow-up data were available for selected patients. The European General Data Protection Regulation (GDPR) legislation prevented us from carrying on the way we started. While the database taught us a lot about CP, it is not comparable to conducting prospective (randomised) controlled trials. We therefore, had to close this database and have started a new prospective register fully compliant with the current European Union legislation. We are now enrolling patients into a new 2.0 SBPC database where all data will be prospective with yearly follow-ups. Future collaboration with other chronic pancreatitis registries may offer valuable opportunities to compare patient subgroups across populations and work towards harmonised international data collection.

Conclusion

The SBPC based research publications offer valuable insights into the aetiology and complications of CP, with significant implications for patient management. Future studies should aim to expand the evidence base for CP by exploring the long-term outcomes of PERT adherence and invasive interventions in diverse populations, and also explore associations between the clinical and para-clinical development of the disease including the development of ductal, calcification and parenchymal imaging features over time.

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Author contributions

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