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*A study of 959 cases from the Scandinavian Baltic Pancreatic Club (SBPC) imaging database*

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**Aetiological risk factors are associated with distinct imaging findings in patients with chronic pancreatitis:  
A study of 959 cases from the Scandinavian Baltic Pancreatic Club (SBPC) imaging database**

**Short title:** Aetiological risk factors and imaging findings in chronic pancreatitis

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**Abstract:**

**Objectives:** The relation between aetiology and structural changes of the pancreas in patients with chronic pancreatitis (CP) is not fully understood. Earlier studies are limited by focusing on selected factors in studies of limited sample size. We aimed to use a large dataset to explore associations between aetiology and pancreatic morphology in CP.

**Methods:** Subjects with definite or probable CP according to the M-ANNHEIM diagnostic criteria were included in this multicentre cross-sectional observational study and assessed using a standardized and validated CP imaging system. We performed multivariate logistic regression to analyse if aetiological factors adjusted for covariates were independently associated with morphological pancreatic features.

**Results:** We included 959 patients (66% males). Mean (SD) age was 55 (14) years. 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 (odds ratio (OR, [95 % CI]); 1.61, [1.09, 2.37]) and focal acute pancreatitis (OR; 2.13, [1.27, 3.56]), whereas smoking was independently associated with more severe calcifications (OR; 2.09, [1.34, 3.27]) and involvement of the whole gland (OR; 2.29, [1.61, 3.28]). Disease duration was positively associated with calcifications (OR; (per year) 1.05 [1.02, 1.08]) and pancreatic atrophy (OR; 1.05 [1.02, 1.08]) and negatively associated with focal acute pancreatitis (OR 0.91, [0.87, 0.95] and pseudo cysts (OR; 0.96, [0.93, 0.98]).

**Conclusion:** In this large-scale study, etiological risk factors and disease duration in CP were independently associated with specific structural pancreatic imaging changes.

**Key words:** Aetiology; Chronic pancreatitis; Imaging; Risk factor

**Abbreviations:**

CP: Chronic pancreatitis

RAP: Recurrent acute pancreatitis

CT: Computed tomography

MRI: Magnetic resonance imaging

EUS: Endoscopic ultrasound

US: Transabdominal ultrasound

FE: Faecal elastase

SD: Standard deviation

OR: Odds ratio

CI: Confidence interval

## Introduction

Chronic pancreatitis (CP) is a multifactorial and complex disease characterized by progressive pancreatic inflammation and fibrosis, which irreversibly damage the pancreatic parenchyma resulting in loss of exocrine and endocrine functions [1, 2]. The common clinical features of CP are abdominal pain, malnutrition and diabetes. Well known aetiological risk factors are smoking and alcohol, autoimmune-, hereditary-, and nutritional/metabolic factors, efferent duct factors and recurrent acute pancreatitis. These are incorporated into commonly used classification systems [3, 4, 5]. The M-ANNHEIM classification system [3], as used in the Scandinavian Baltic Pancreatic Club (SBPC) database, combines risk factors, clinical features and imaging findings into a comprehensive staging system of CP. A detailed understanding of associations between CP disease characteristics, including imaging features, and aetiological risk factors is still lacking.

Developments in computed tomography (CT) and magnetic resonance imaging (MRI) technologies [6, 7], and the detailed visualization provided by endoscopic ultrasound (EUS) [8], have enabled improved assessment of structural changes of the pancreas. The currently used imaging systems for CP focus on ductal changes, pancreatic calcifications, and irregularities and atrophy of the gland structure [3, 8, 9]. The recently updated guidelines for diagnostic, cross-sectional imaging in CP [6, 10, 11] share many common features, but a consensus is not yet reached. SBPC has collected a large, multicentre-database comprising subjects with CP [12, 13, 14, 15, 16]. Standards used in the SBPC imaging module was developed to adhere to the most commonly used imaging systems [3, 9]. Some continuous variables such as number of calcifications and two-dimensional measurements of pancreatic size and ductal diameter are also included. The inter-observer agreement for imaging features in the SBPC imaging module was recently published [17].

Lately, the traditional clinico-pathological definition for CP has been challenged by definitions focusing on the drivers of the pathogenic processes [18]. An updated international consensus guideline suggested a two-step mechanistic definition, where inclusion of etiological factors allows the CP diagnosis in the fibro-inflammatory stage before structural changes occur [19]. In this approach, knowledge of the relation between exposure to aetiological factors and the pattern of structural pancreatic changes in CP is crucial [18]. Existing studies in this field are limited by focusing on single or few etiological factors and structural features in studies with limited sample size [16, 20, 21, 22, 23, 24]. It is desirable to establish models linking multiple etiological factors to detailed imaging findings. Evaluation of such associations from larger databases may allow a more precise approach in the classification and prediction of clinical outcomes in CP.

This study, based on a large multi-centre CP cohort with detailed registrations in the SBPC imaging module, specifically aimed to 1) present pancreatic cross-sectional imaging findings, and 2) evaluate the associations between etiological factors and pancreatic morphology.

## Methods

### Study design

The baseline data collection in this cross-sectional observational study was performed from February 1st 2016 to July 1st 2019 at hospitals in the SBPC database collaboration. The study was conducted according to the Helsinki Declarations. Permissions for data collection and sharing were obtained from the institutional review board at each participating centre. Aalborg University Hospital is coordinating centre for the database (200858-0028, project ID

2018-19). Haukeland University Hospital, Bergen is coordinating the present study (Regional ethical committee, Western Norway: 2019/1037). The data are reported according to the TRIPOD statement [25].

## **Subjects**

The SBPC database includes adult patients with all-cause, definite or probable CP according to the M-ANNHEIM diagnostic criteria [3]. The participating centres are specialized pancreas referral centres. Filling in the comprehensive imaging module (as described below) was optional. To ensure high and consistent data quality of imaging registrations, we included only centres that reported imaging module data for the majority of their included patients. Patients without registered imaging data were excluded.

## **Patient characteristics**

**Patient/disease characteristics:** At the baseline visit we collected information on sex, age, body mass index (BMI) (anthropometric data), duration since first symptom of CP, past episodes of acute pancreatitis (anamnestic data), faecal elastase results and presence of diabetes [26] (clinical data).

**Aetiological risk factors:** We collected information on smoking history and alcohol consumption. The most probable aetiologies according to the M-ANNHEIM classification system [3] were registered by the physician at each centre. The evaluated aetiologies were alcohol, smoking, as well as hereditary, immunological, nutritional/metabolic and obstructive/efferent ductal factors. Subjects with no known aetiology were classified as idiopathic. We also included recurrent acute pancreatitis as an etiological factor. More than one factor could be registered. We did not include “miscellaneous and rare metabolic factors” or “idiopathic” for analysis due to etiological diversity in these groups. Factors registered in less than 5 % of the cases were not analysed. Some definitions are displayed in Table 1.

## **Pancreatic imaging data**

The SBPC database contains a comprehensive, structured module for reporting results from the available pancreatic imaging. Radiologists or clinicians with special experience in pancreatic imaging reviewed the imaging studies at each centre. Standardized definitions and instructions for reporting assessments into the imaging module of the SBPC database were provided [17]. Definitions are presented in Table 1. Illustrative examples are displayed in supplementary Figure s1. Measured variables (number of calcifications and anteroposterior diameter of the pancreatic head and body) were also obtained.

We registered pancreatic imaging parameters from CT, MRI, transabdominal ultrasound (US) and EUS examinations from the imaging examinations closest in time to the baseline data collection. To achieve a uniform dataset, we gave priority to the most frequently performed cross sectional modalities CT and MRI, but we chose not to exclude cases where only EUS or US were available. Thus, in cases where registrations from several modalities were available, we included one modality according to the following priority: CT > MRI > EUS > US. For measurement of pancreatic size, CT or MRI was used. For assessment of pancreatic calcifications, MRI was excluded.

## **Statistical analysis**

Continuous variables are presented as means and standard deviations (SD), unless stated otherwise. Evaluation for normality was performed by histograms and Q-Q plots. Comparisons of means were assessed by independent samples t-test or Mann-Whitney U-test as appropriate. Interactions between risk factors were evaluated by qualitative risk assessment. We analysed the quantitative factors “standard drinks per day” and “cumulative years of excessive ( $\geq 5$  units) alcohol use” in separate analyses. We considered the other factors as independent in the multivariate analysis. For the continuous imaging parameters, the univariate model was performed as simple comparisons of mean or medians. The multivariate model was performed as a three-step linear regression. In the first step, a backward conditional elimination analysis of associations was performed between the etiological factors, excluding the least relevant etiological factors stepwise until only factors with a probability of association  $\geq 90\%$  ( $p < 0.10$ ) were included. In the second step, we included the remaining etiological factors and the chosen covariates. Finally, factors considered to have general relevance (alcohol and smoking) were forced back into the final analysis. Results are expressed as linear regression coefficients ( $\beta$ ) with 95% confidence intervals (CI).

For the binary imaging parameters, we used univariate and multivariate logistic regression in the same three-step model as described above was performed to assess the associations between risk factors, covariates and imaging features. Results were expressed as odds ratio (OR) with 95% CI. We performed the statistical analyses in SPSS® statistics package version 25 (IBM®, Armonk, NY).

## **Results**

### **Patient inclusion**

Seven centres performed good quality registrations in the SBPC imaging module: Aalborg, Bispebjerg, Hvidovre and Herlev (Denmark), Bergen and Oslo (Norway), Kaunas (Lithuania), and Moscow (Russia). By July 2019, these centres included 1290 subjects. We excluded 331 subjects due to lack of reported imaging data. Imaging data were complete for 959 patients (633 males) and these were included for further analyses. Demographic and clinical characteristics are reported in Table 2. Mean time (SD) between inclusion in the database and date of imaging examination was 1.0 (1.6) years. Only 3 % were evaluated to have immunological aetiology. This factor was not further analysed.

### **Imaging data**

The imaging modalities reported were CT ( $n=742$ , 77%), MRI ( $n=131$ , 14%), endoscopic ultrasound ( $n=50$ , 5%) and transabdominal ultrasound ( $n=36$ , 5%).

### **Frequencies of CP related imaging features**

The frequencies of CP related imaging findings are presented in Table 3. Structural changes of the pancreas were observed in 94% ( $n=904$ ) of the subjects. The entire gland was affected in 41% ( $n=380$ ). Pancreatic calcification was the most frequent finding and was observed in 67% ( $n=548$ ), whereas MPD dilatation was observed in 59% ( $n=539$ ) and pseudo-cysts in 33% ( $n=308$ ).

### **Associations of aetiological risk factors and patient characteristics to number of calcifications and pancreatic size**

The association between aetiological risk factors and covariates to the quantitative measures pancreatic size and calcifications are presented in Table 4. The distributions stratified by intervals of age and disease duration are presented in Figure 1 a-d. Male gender ( $\beta$ ; 3.66, [95 % CI, 1.10, 6.23],  $p=0.005$ ) and recurrent acute pancreatitis ( $\beta$ ; 4.02, [95 % CI, 1.55, 6.49],  $p=0.001$ ) were associated with larger pancreatic size. Longer disease duration ( $\beta$ ; -0.24, [95 % CI, -0.40, -0.08],  $p=0.003$ ) and older age ( $\beta$ ; -0.15, [95 % CI, -0.24, -0.05],  $p=0.002$ ) were associated with smaller pancreatic size.

Smoking aetiology ( $\beta$ ; 2.31, [95 % CI, 1.09, 3.54],  $p<0.001$ ) and disease duration (Per year) ( $\beta$ ; 0.14, [95 % CI, 0.07, 0.20],  $p<0.001$ ) were associated with increased number of pancreatic calcifications. Patients with a history of recurrent acute pancreatitis ( $\beta$ ; -1.21, [95 % CI, -2.37, -0.05],  $p=0.04$ ) or nutritional aetiology ( $\beta$ ; -4.48, [95 % CI, -6.75, -2.21],  $p<0.001$ ) had less calcifications. When we replaced the physician aetiology estimates with patient reported numbers of smoked pack years or years of excessive alcohol intake, there were no independent associations of quantitative doses of smoking or alcohol with pancreatic size or numbers of calcifications.

### **Gender-adjusted definition of pancreatic atrophy**

Due to the clear association between gender and pancreatic size, we derived a gender-adjusted definition of pancreatic atrophy. The gender-adjusted percentiles for the anteroposterior diameters of the pancreatic head and body, and the sum of both diameters are presented in Table s1. Pancreatic atrophy was defined as a sum of diameters less than the 25-percentile: <37 mm for males and <32 mm for females; these sex specific cut-offs were used for further analysis.

### **Associations between risk factors and imaging parameters**

We present the results of the uni- and multivariate analyses of associations between aetiological risk factors, covariates and morphological pancreatic changes in Table 5. We also present restacked Forrest plots illustrating the morphological changes independently associated with smoking, alcohol and disease duration (Figures 2 A-C)

#### *Smoking aetiology (Figure 2, panel A)*

Smoking aetiology was independently associated with the presence of calcifications (OR; 1.67, [95 % CI 1.16, 2.42],  $p<0.006$ ) and severe calcifications (OR; 2.09, [95 % CI, 1.34, 3.27],  $p=0.001$ ). Smoking was also associated to structural involvement of the entire pancreas (OR; 2.29, [95 % CI, 1.61, 3.28],  $p<0.001$ ). The association of smoking to MPD changes in the univariate analysis was lost in the multivariate analysis.

#### *Alcohol aetiology (figure 2, panel B)*

Alcohol aetiology was independently associated with the presence of calcifications (OR; 1.61, [95 % CI 1.09, 2.37],  $p=0.02$ ) and focal acute pancreatitis (OR; 2.13, [95 % CI, 1.27, 3.56],  $p=0.004$ ). The association of alcohol to pseudo-cysts in the univariate analysis was lost in the multivariate analysis.

To assess the implications of current and cumulated alcohol abuse we performed separate analyses replacing the physician assessed alcohol aetiology classifications with groupings from quantitative, patient reported cumulative or current alcohol use (definitions in Table 1). Current heavy alcohol abuse  $\geq 5$  units per day was positively associated with the presence of pseudo-cysts (OR; 1.83 [95 % CI, 1.08, 3.11],  $p=0.03$ ). There were no independent associations of cumulative heavy alcohol abuse with any of the imaging factors.

### *Hereditary-, nutritional- and efferent/ obstructive aetiology*

These diverse etiological groups all over demonstrated a negative association to pancreatic changes.

A significant independent negative association after the multivariate analysis was seen between nutritional/metabolic pancreatitis and calcifications (OR; 0.45, [95 % CI, 0.25, 0.82],  $p=0.009$ ), focal acute pancreatitis (OR; 0.18 [95 % CI, 0.04, 0.77],  $p=0.02$ ) MPD obstruction (OR; 0.41, [95 % CI, 0.19, 0.90],  $p=0.03$ ) and involvement of the entire gland (OR; 0.21, [95 % CI, 0.09, 0.48],  $p<0.001$ ).

### *Recurrent acute pancreatitis*

A history of recurrent acute pancreatitis was positively associated with imaging features indicating focal acute pancreatitis (OR; 3.69, [95 % CI, 2.31, 5.89],  $p<0.001$ ), and negatively associated with pancreatic calcifications (OR; 0.64, [95 % CI, 0.45, 0.92]  $p=0.008$ ) and pancreatic atrophy (OR; 0.58, [95 % CI, 0.37, 0.91],  $p=0.02$ ).

### *The covariates disease duration (figure 2, panel c), age and sex*

Disease duration (per year of disease) was positively and independently associated with pancreatic calcifications (OR; 1.05, [95 % CI, 1.02, 1.08],  $p<0.001$ ), severe calcifications (OR; 1.04, [95 % CI, 1.01, 1.06],  $p=0.001$ ), MPD dilatation (OR; 1.02, [95 % CI 1.00, 1.04],  $p=0.03$ ) and atrophy (OR; 1.05, [95 % CI, 1.02, 1.08],  $p<0.001$ ). Disease duration was negatively associated with focal acute pancreatitis (OR; 0.91, [95 % CI, 0.87, 0.95],  $p<0.001$ ) and presence of pseudo-cysts (OR; 0.96, [95 % CI, 0.93, 0.98],  $p<0.001$ ). Age at inclusion (per year) was positively and independently associated with MPD dilatation (OR; 1.02, [95 % CI, 1.00, 1.03],  $p=0.007$ ), MPD obstruction (OR; 1.01, [95 % CI, 1.00, 1.03],  $p=0.04$ ), pancreatic atrophy (OR; 1.03, [95 % CI, 1.01, 1.05],  $p=0.001$ ) and involvement of the entire gland (OR; 1.02; [95 % CI, 1.01, 1.03],  $p=0.002$ )

Sex was not specially associated with any of the imaging features.

## **Discussion**

The different drivers of the disease development toward the multifaceted appearance of CP needs further exploration. Studies using multivariate models in large CP populations with detailed imaging evaluations are to date lacking. In order to identify the complex associations between aetiological risk factors and pancreatic morphology in CP, we present a multivariate analysis from a large Scandinavian-Baltic cohort of CP patients with complete characterization of aetiology according to the M-ANNHEIM system [3]. In this comprehensive study we demonstrate independent associations between the aetiological factors and corresponding pancreatic morphologic changes in CP.

In detail, smoking was independently associated with the presence of calcifications and severe calcifications with involvement of the entire gland. Alcohol aetiology was associated with the presence of spread calcifications and focal acute pancreatitis. A complementary analysis of current or cumulative drinking demonstrated that current drinking was associated with pseudo-cysts, whereas cumulative high alcohol intake did not reveal independent association to specific structural changes. Recurrent acute pancreatitis as an etiological risk factor was frequently associated with focal acute pancreatitis, but less frequently associated with calcifications and pancreatic atrophy. Among the other etiological groups, nutritional/ metabolic pancreatitis revealed a structural pattern with all-over less morphological pancreatic changes.



The covariate disease duration was highly relevant for the presence of structural changes. Disease duration was positively associated with calcifications, MPD changes and reduced pancreatic size (pancreatic atrophy) and negatively associated with pseudo-cysts and focal acute pancreatitis. Age at inclusion also demonstrated some independent associations, but all over less convincing. We conclude that duration of the disease is the key time-related factor in the development of structural changes. The state of disease progression must be taken into account when evaluating morphological changes in CP.

The increased risk for developing chronic pancreatitis in smokers and subjects with alcohol abuse is established in several studies [23, 27, 28]. Smoking and alcohol have been firmly linked to the development of calcifications [22, 29, 30]. Alcohol is considered to be an important cause of both single and recurrent acute inflammatory episodes in the pancreas [27, 31] and the development of pseudo-cysts [32, 33]. Patterns of structural changes in hereditary pancreatitis [34] and autoimmune pancreatitis [35] are also reported. Finally, decreasing pancreatic size following disease progression has been demonstrated [36]. Reports exploring independent associations between aetiological risk factors and patterns of structural changes using multivariate analyses in large CP cohorts are scarce. The North American Pancreatitis Study (NAPS) group reported imaging changes from a cohort of more than 500 patients with CP [37]. They reported similar frequencies of calcifications (55%) and pseudo-cysts (32 %), but higher frequencies of MPD dilatation (68%) and atrophy (57 %) [37]. This study found no clear individual associations between aetiologies of CP and structural changes.

The SBPC study group has recently published several works exploring etiological factors and associations with clinical outcomes [12, 13, 14, 15]. Findings from the present study are in line with earlier reports from the same cohort. The data obtained from the comprehensive SBPC imaging module add a more detailed image analysis compared to the previous publications from SBPC. A cluster analysis from the database linked smoking aetiology to fibrotic complications and alcohol to inflammatory complications [15]. If we consider acute pancreatitis and pseudo-cysts to be structural changes related to inflammation, we found the same associations in our study. In line with Tjora et al [16] a supplementary analysis using quantitative assessment of alcohol abuse did not reveal strong associations to structural changes.

The complex mechanisms linking alcohol and smoking to different patterns of inflammatory and fibrotic changes are discussed earlier by Olesen et al [15]. A recent review of the literature promotes the synergistic effects of alcohol and smoking [38]. Alcohol alone has in animal models not demonstrated the ability to cause pancreatitis, but alcohol is suggested to sensitize the pancreas to other injuries, and thus induce damage through repeated inflammatory episodes [39]. The pathophysiology of smoking as a causative factor for CP, and the mechanism of synergy with alcohol is less clear. Recently it has been demonstrated that smoking may induce acinar cell death of alcohol sensitized cells through endoplasmic reticulum stress pathways [40]. Animal studies have also linked smoking to mechanisms promoting fibrosis through interleukin-22 effects and activation of pancreatic stellate cells [41]. Our finding of inflammatory changes associated with alcohol but not with smoking aetiology is explained by these suggested mechanism. We postulate that fibrotic transformation is a general process in the whole gland in opposition to repeated inflammatory episodes with focal affection. This may explain that smoking, but not alcohol, is independently associated to entire gland involvement and more severe calcifications. The present imaging model do not contain robust modalities for assessment of fibrosis. Such associations may be explored in the future by adequate supplementary imaging modalities or studies of pathological specimens.

Olesen et al. found that disease duration and age at inclusion was independently associated with the presence of pancreatic calcifications [14]. We concluded that disease duration was the dominating, time-related factor. This fits well into a “time x exposure” model. Our analyses suggest that associations between age and structural changes are more related time of exposure than to specific structural characteristics related to high age.

A few previous studies have explored the normal size of the pancreas using one dimensional anterior-posterior measurements [42, 43]. Comprehensive measurements of pancreatic volume are not feasible for multicentre studies [11]. A consented definition of pancreatic atrophy does not exist [6]. Recently, two separate groups suggested using measurement of the pancreatic body at the level of the left margin of the vertebral body with AP diameters of 21 mm, 14 mm, and 7 mm as thresholds for varying degrees of atrophy [10, 11]. We performed measurements using the same standardized positions for the pancreatic body, and added a standardized measurement of the pancreatic head. These standards are simple and have demonstrated good inter-observer reproducibility [17]. The 25-percentile cut-off for the measures of the body of pancreas in males in our cohort was largely corresponding to the cut-offs for moderate atrophy in the two studies mentioned above, but indicate a somewhat lower cut-off for females. Due to gender differences in pancreatic size, we constructed a gender-adjusted definition based on the sum of AP diameters. Further studies exploring the associations between this definition and disease outcomes is warranted to validate this strategy.

### *Limitations*

Database studies have several limitations, where missing data may result in biased analyses. We excluded datasets from centres not delivering adequate reporting of imaging data. This may have introduced selection biases from centre related differences. Furthermore, the excluded subjects without available imaging registrations from were older and had more exocrine and endocrine failure. This selection bias may reduce the number of subjects with severe structural changes in the cohort.

Biased reporting of risk exposures is a main limitation of the dataset. Firstly, the aetiology assessment is based on expert opinion. Conclusions may be biased from earlier established assumptions. Patient reported exposures are also prone to biased reporting. Subjects who made changes in their consumption habits due to debilitating disease or advice from their physicians, may underreport their exposures. Systematic conclusions based on earlier experience and underreporting and recall biases may weaken the conclusions regarding the risk factors smoking and alcohol [44].

The assessment of the imaging data may be subject to centre-related differences in standards. Differences in experience of the readers may have influenced the conclusions. By distributing instructions to the centres before the registrations, we attempted to reduce such differences. In a recent study we found good inter-observer reproducibility for the applied standards [17].

The use of different imaging modalities was challenging. We applied modalities relevant for each structural change. Information on the reason for performing the imaging or symptoms on the day of imaging is lacking. Imaging obtained under suspicion of a CP related complication may increase the prevalence of structural complications such as acute pancreatitis, duct obstruction or pseudo-cysts. Most structural complications of CP are long-lasting and we consider the effect of this bias less important.

Using a database of CP patients in the absence of matched, healthy subjects limits the conclusions regarding consequences of exposures in a general population. The conclusions from this study cannot easily be translated to the consequences of risk exposures in a non-CP population.

Multivariate analyses are highly dependent of a correct and transparent selection of factors included. Selection process and analysis in the present study were reported according to the instructions in the TRIPOD statement [25] and all steps in the analysis are displayed in table s2.

### *Clinical relevance and future directions*

This study improves the understanding of how aetiological risk factors and covariates impact on the patterns of structural changes in CP. Increased knowledge on the influence of etiological factors for the development of structural changes in CP support the further development of the proposed mechanistic model for definition of early CP [19] by pointing out the most relevant factors to include. This knowledge may also be crucial in improved models integrating predictors, imaging data and disease outcomes into diagnostic and prognostic tools for CP. Longitudinal studies within this field are highly warranted.

### *Conclusions*

We found clear associations between etiological risk factors and specific pancreatic morphological changes in CP. Structural pancreatic changes in CP also seem to be highly related to disease duration. Our findings from this large scale study, provide a more complete exploration of the independent associations between aetiology and structural changes as compared to previous studies [37]. Better understanding of the link between etiological risk factors and differences in structural disease development may improve understanding and aid in development of definitions, diagnostics and preventive strategies for this highly variable and multifaceted disease.

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**Figure texts:****Figure 1**

Panels A and B display sum of mean antero-posterior diameters (columns) with standard deviations (error bars) in the head and body of the pancreas stratified by 10 year age-groups and 5-year groups of disease duration. Panels C and D display median numbers of calcifications (columns) in the pancreas stratified by 10 year age-groups and 5-year groups of disease duration.

**Figure 2**

The restacked Forrest Plots display the Odds ratios (Circle) with 95 % CI from the multivariate analysis of each factor analysed (smoke aetiology (Panel A), alcohol aetiology (Panel B) and disease duration (Panel C)).

**Figure s1**

Computer tomography scans illustrating relevant structural changes.

Panel A displays a dilated ( $\geq 3$  mm) and severely calibre variated ( $> 2$ mm) main pancreatic duct in the body of an atrophic pancreas. Panel B displays a ductal obstruction from a large ductal stone (Arrow). Panel C displays a severely calcified and atrophic pancreas. Panel D illustrates the AP diameter in the head of pancreas. Panel E illustrates the AP diameter in the body of pancreas