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ABOUT COVER

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RESPONSIBLE EDITORS FOR THIS ISSUE

Associations with pancreatic exocrine insufficiency: An United Kingdom single-centre study

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Abstract

BACKGROUND

Pancreatic exocrine insufficiency (PEI) is said to be associated with numerous conditions both within and outside the gastrointestinal (GI) system. The majority of research has been concerned with conditions that reduce the volume of functioning pancreatic tissue or prevent adequate drainage to the small bowel, such as chronic pancreatitis, cystic fibrosis, pancreatic cancer and pancreatic resection. However, the evidence base supporting an association with extra-pancreatic conditions, such as coeliac disease, diabetes mellitus and congestive cardiac failure, is heterogeneous.

AIM

To strengthen the evidence base by studying all previously reported associations with PEI in a large cohort of outpatients.

METHODS

A single-centre retrospective study was performed. General gastroenterology outpatients tested for PEI with faecal elastase-1 (FE1) were identified and information retrieved from the electronic patient record. PEI was defined as FE1 < 200 µg/g. Patients already taking pancreatic enzyme replacement therapy were excluded. Multiple imputation was used to handle missing data. Univariable logistic regression was used to study which presenting symptoms predicted PEI. Multivariable logistic regression was used to explore the relationship between all previously reported associations and PEI.

RESULTS

Of 1027 patients were included. 182 patients (17.7%) were diagnosed with PEI. Steatorrhoea [odds ratios (OR): 2.51, 95% confidence intervals (CI): 1.58-3.98] and weight loss (OR: 1.49, 95%CI: 1.08-2.06) were the only presenting symptoms that predicted PEI. Chronic pancreatitis (OR: 7.98, 95%CI: 3.95-16.15), pancreatic

cancer (OR: 6.58, 95%CI: 1.67-25.98), upper GI surgery (OR: 2.62, 95%CI: 1.32-5.19), type 2 diabetes (OR: 1.84, 95%CI: 1.18-2.87), proton pump inhibitor therapy (OR: 1.87, 95%CI: 1.25-2.80) and Asian ethnicity (OR: 2.11, 95%CI: 1.30-3.42) were significantly associated with PEI in the multivariable analysis. None of the other historically reported associations with PEI were significant after adjustment for the other variables included in our multivariable analysis.

CONCLUSION
PEI is common in patients with chronic pancreatitis, pancreatic cancer, upper GI surgery and type 2 diabetes. Proton pump inhibitor therapy may also be associated with PEI or a false positive FE1.

Key Words: Exocrine pancreatic insufficiency; Chronic pancreatitis; Pancreatic elastase; Steatorrhoea; Proton pump inhibitors

Core Tip: Pancreatic exocrine insufficiency (PEI) is associated with chronic pancreatitis, pancreatic cancer, previous upper gastrointestinal surgery and type 2 diabetes. There should be a low threshold for testing for PEI in these patients. Proton pump inhibitor therapy may also be associated with PEI, or a false positive faecal elastase-1 (FE1). Until further evidence becomes available, we recommend repeat testing after a washout period. Steatorrhoea and weight loss were the only symptoms that predicted PEI in our cohort. Therefore, the diagnostic yield of FE1 testing in patients with non-specific presentations, such as bloating, is likely to be low.

INTRODUCTION

Pancreatic exocrine insufficiency (PEI) is defined by a reduction in the secretion or function of pancreatic enzymes or bicarbonate below the threshold required for normal digestion[1]. The resulting maldigestion can lead to substantial morbidity, including gastrointestinal (GI) symptoms, such as steatorrhoea, and nutritional deficiencies[1,2]. However, PEI remains under diagnosed and undertreated[3].

The majority of research into the aetiology of PEI has been concerned with conditions that reduce the volume of functioning pancreatic tissue or prevent adequate drainage to the small bowel, such as chronic pancreatitis, cystic fibrosis, pancreatic cancer and pancreatic resection[4]. However, multiple other conditions have been reported to be associated with PEI, in the absence of chronic pancreatitis, including previous acute pancreatitis[5,6], untreated or refractory coeliac disease[7], type 1 and type 2 diabetes[8], upper GI surgery[9], smoking[10], alcohol excess[11,12], human immunodeficiency virus (HIV) infection[13], chronic kidney disease (CKD)[14], hyperparathyroidism[15,16], haemochromatosis[17], congestive cardiac failure (CCF)[18,19], cirrhosis of the liver[20], and older age[21,22].

The pathophysiological mechanisms underlying each association put forward in the literature generally fall into three categories: Reduced entero-hormonal stimulation of the exocrine pancreas; asynchronous digestion due to dysmotility or abnormal anatomy; and metabolic or toxic impairment of pancreatic function[23].

However, the quality of the evidence base for these purported associations varies widely. Although there are multiple observational studies reporting associations between PEI and diabetes, coeliac disease and HIV, some of the conditions, such as haemochromatosis, are suspected of causing PEI based only on small, historic case series or single case reports[15-17]. Yet these too are often included as established aetiological factors in modern review papers.

We aimed to strengthen the evidence base by studying all exposures previously reported to be associated with PEI in a large cohort of outpatients attending general gastroenterology clinics at a London teaching hospital. In addition, we planned to study three plausible aetiological factors whose associations with PEI have not been investigated previously: Cholecystectomy, bile acid malabsorption (BAM), and proton pump inhibitor (PPI) therapy. The first two conditions are anatomically and physiologically related to the exocrine pancreas, and can lead to similar symptoms[24-26], while a possible association between PPI therapy and PEI has been suggested recently by *in vitro* human and *in vivo* animal studies[27].

MATERIALS AND METHODS

A retrospective study was conducted at St George's University Hospitals NHS Foundation Trust. Outpatients aged > 18 years who were tested for PEI with faecal elastase-1 (FE1) between September 1, 2012 and August 31, 2018 were identified. There is no local protocol for PEI testing at our trust, and the decision to test is made on a case-by-case basis by each clinician. Demographic and clinical information were retrieved from the electronic patient record. Patients already taking pancreatic enzyme replacement therapy (PERT) were excluded.

The primary outcome was the diagnosis of PEI, defined as FE1 < 200 μg/g in accordance with most guidelines and the intended use label of the test[1]. FE1 was measured using a sandwich enzyme-linked immune-absorbent assay with two monoclonal antibodies highly specific for human pancreatic elastase-1 (ScheBo Biotech AG, Giessen, Germany). Where the test had been repeated, the most recent result was used for classification.

Potential associations, hereon referred to as exposure variables, and statistical methods were selected *a priori*. Exposure variables were selected based on previously published research, and included age, sex, and ethnicity (classified as white, Asian, black or other); and the following comorbidities, as documented at the time of FE1 testing: Type 1 and type 2 diabetes, inflammatory bowel disease (IBD), liver cirrhosis, previous acute pancreatitis (defined as one or more episodes of acute pancreatitis, with no radiological evidence of chronic pancreatitis), upper GI surgery, cholecystectomy, BAM (defined as seven-day SeHCAT retention ≤ 15%), biopsy-proven coeliac disease, CCF, CKD, hyperparathyroidism, HIV infection, PPI therapy, alcohol intake (classified as never-, ex- or current excess; with excess defined as > 14 units *per* week)[28], and smoking history (classified as never-, ex- or current smoker). The presence of chronic pancreatitis or pancreatic cancer was defined by documentation in the electronic patient record or a radiological diagnosis in the six months before or after FE1 testing. A radiological diagnosis of chronic pancreatitis was defined as two or more of the classical radiological findings of calcifications, atrophy, ductal stones, main pancreatic duct dilatation, pseudocyst or generalised cystic change[29]. We also noted presenting symptoms, as documented in the clinical letter that preceded FE1 testing, and the proportion of patients who underwent abdominal imaging, received PERT, and responded to PERT (defined by subjective improvement in clinical symptoms).

Multiple imputation (MI) was used to impute missing values for the three exposure variables with incomplete data [alcohol intake (27.1% missing), smoking history (24.4% missing), and PPI therapy (4.9% missing)], under the assumption that unobserved data were 'missing at random'. This allowed us to include exposure variables with missing data that otherwise merited inclusion in the multivariable model, and preserve a ratio of ten positive outcome events *per* exposure variable[30]. MI has been shown to reduce bias in logistic regression coefficients compared to complete case analysis or omitting variables with missing data[31]. Incomplete variables were imputed using a chained equations logistic regression model, including all exposure and outcome variables with complete data. Ten imputed datasets were used to account for sampling variability, and the results combined using Rubin's rules. The validity of the imputed datasets was verified (available in the online Supplementary Figure 1 and Supplementary Tables 1-7).

Descriptive statistics were used to describe the study population. Univariable logistic regression was used to explore the dependence of PEI on exposure variables and presenting symptoms. All exposure variables significant at alpha < 0.1 in univariable analysis were selected for inclusion into a multivariable logistic regression model. The multivariable model's discrimination was tested using the c-statistic, specification with the link test, calibration with the Hosmer-Lemeshow goodness-of-fit test, and multicollinearity with the variance inflation factor. The presence of

interactions was checked using the link test, and by including an interaction term for alcohol and smoking into the model. The assumption of linearity of continuous exposure variables was examined using exploratory plots and including transformed terms in test models. Outliers were detected by inspecting index plots of Pearson residuals, deviance residuals and leverage. The influence of any detected outliers was checked by removing them and repeating the analysis.

Sensitivity analyses were performed using complete case analysis (n = 674) and two models that assumed unobserved data were 'missing not at random' (MNAR). MNAR Model 1 assumed that missing data were in the reference group for each variable, and therefore may have been more likely to be omitted from clinical documentation. MNAR Model 2 assumed that data were missing as patients may have been less likely to disclose current smoking or alcohol excess to healthcare providers. For MNAR Model 2, any patients with missing data for PPI therapy were considered to be on PPI therapy.

All statistical analyses were performed using Stata version 13.1 (StataCorp, College Station, Texas, United States). As this work was a retrospective study analysing previously collected data, patients were not involved in the design or conduct of this study. This study was approved by the Health Research Authority (HRA) and Health and Care Research Wales (HCRW) (reference number: 20/LO/0433).

RESULTS

Cohort description and univariable analysis

1034 outpatients were tested for PEI using FE1 during the study period. Seven were already on PERT and were excluded. 1027 patients were included in the final analysis; the mean age was 53 years (mean ± SD 17.2) and 436 (42.5%) were male. 182 patients (17.7%) were diagnosed with PEI; 7.0% with mild-moderate PEI (FE1 100-199 µg/g) and 10.7% with severe PEI (FE1 < 100 µg/g).

The demographic and clinical characteristics of the cohort are presented in Table 1, in the whole cohort and separated by FE1 result (≥ 200 µg/g and < 200 µg/g). The results from the univariable analysis, presented as odds ratios (OR), 95% confidence intervals (CI) and *P* values, are also shown in Table 1. The association with haemochro -matosis could not be assessed by logistic regression due to complete separation.

Presenting symptoms

The distribution of presenting symptoms in the cohort and the results of the univariable logistic regression analysis of the association between symptoms and PEI are displayed in Table 2. The only presenting symptoms that were statistically significant predictors of PEI in our cohort were steatorrhoea (OR: 2.51, 95%CI: 1.58-3.98) and weight loss (OR: 1.49, 95%CI: 1.08-2.06). There was a non-significant trend towards abdominal pain, bloating, flatulence and fatigue predicting against a diagnosis of PEI.

Pancreatic imaging

In total, 718 patients (69.9%) underwent abdominal imaging in the 6 mo before or after FE1 testing; 81.9% of patients with PEI and 67.3% of those with no PEI. Pancreatic abnormalities were detected in 161 imaged patients (23.1%): 46.9% of patients with PEI and 17.0% of patients without. Of the 48 patients with chronic pancreatitis, 12 (25%) were classified from previous medical documentation, 22 (45.8%) from imaging prior to FE1 testing and 14 (29.2%) from imaging after FE1 testing. Of the patients with pancreatic cancer, one (9.1%) was diagnosed radiologically after FE1 testing.

Treatment

Of 103 patients (56.6%) with PEI were treated with PERT, at a median starting dose of 50000 IU/meal. 67 patients responded to treatment (82.7% of patients whose response was documented).

Multivariable analysis

Estimates of the ORs, 95%CIs and *P* values from the MI multivariable logistic regression analysis are displayed in Table 3. Holding all other variables constant, chronic pancreatitis (OR: 7.98, 95%CI: 3.95-16.15) and pancreatic cancer (OR: 6.58, 95%CI: 1.67-25.98) had the strongest associations with PEI, followed by type 2 diabetes (OR: 1.84, 95%CI: 1.18-2.87), upper GI surgery (OR: 2.62, 95%CI: 1.32-5.19) and PPI

Table 1 Distribution of exposure variables in total cohort and by faecal elastase-1 result, and result from the univariable logistic regression analysis

Variable	Total cohort, *n* (%)	FE1 ≥ 200 µg/g, *n* (%)	FE1 < 200 µg/g, *n* (%)	OR (95%CI)	*P* value
Total	1027 (100)	845 (82.3)	182 (17.7)		
Demographics					
Age (yr) (mean ± SD)	53.01 (17.2)	52.29 (17.4)	56.42 (16.0)	1.01 (1.01-1.02)	0.003
Sex					
Male	436 (42.5)	343 (40.6)	93 (51.1)	1.53 (1.11-2.11)	0.010
Ethnicity					
Asian	159 (15.5)	116 (13.7)	43 (23.6)	2.02 (1.33-3.06)	0.001
Black	105 (10.2)	85 (10.1)	20 (11.0)	1.28 (0.75-2.19)	0.370
Other	203 (19.8)	171 (20.2)	32 (17.6)	1.02 (0.65-1.58)	0.939
Comorbidities					
Type 1 diabetes	25 (2.4)	18 (2.1)	7 (3.9)	1.84 (0.76-4.46)	0.180
Type 2 diabetes	182 (17.7)	125 (14.8)	57 (31.3)	2.62 (1.82-3.78)	< 0.001
IBD	42 (4.1)	36 (4.3)	6 (3.3)	0.77 (0.32-1.84)	0.551
Liver cirrhosis	57 (5.6)	40 (4.7)	17 (9.3)	2.07 (1.15-3.74)	0.016
Chronic pancreatitis	48 (4.7)	15 (1.8)	33 (18.1)	12.26 (6.50-23.12)	< 0.001
Pancreatic cancer	11 (1.1)	4 (0.5)	7 (3.9)	8.41 (2.44-29.04)	0.001
Previous acute pancreatitis	23 (2.2)	17 (2.0)	6 (3.3)	1.66 (0.65-4.27)	0.293
Upper GI surgery	49 (4.8)	33 (3.9)	16 (8.8)	2.37 (1.27-4.40)	0.006
Cholecystectomy	57 (5.6)	47 (5.6)	10 (5.5)	0.99 (0.49-1.99)	0.968
Bile acid malabsorption	111 (10.8)	94 (11.1)	17 (9.3)	1.03 (0.52-2.04)	0.938
Coeliac disease	15 (1.5)	13 (1.5)	2 (1.1)	0.71 (0.16-3.17)	0.654
CCF	13 (1.3)	8 (1.0)	5 (2.8)	2.95 (0.95-9.13)	0.060
CKD	38 (3.7)	25 (3.0)	13 (7.1)	2.52 (1.26-5.03)	0.009
Hyperparathyroidism	9 (0.9)	8 (1.0)	1 (0.6)	0.58 (0.07-4.64)	0.606
HIV	9 (0.9)	6 (0.7)	3 (1.7)	2.34 (0.58-9.45)	0.232
Haemochromatosis	3 (0.3)	3 (0.4)	0 (0)	-	-
PPI therapy[1]	425 (41.4)	316 (37.4)	109 (59.9)	2.50 (1.78-3.52)	< 0.001
Alcohol excess[1]					
Ex-excess	108 (10.5)	70 (8.3)	38 (20.9)	3.24 (1.68-6.22)	0.001
Current excess	114 (11.1)	87 (10.3)	27 (14.8)	1.83 (1.13-2.97)	0.014
Smoking history[1]					
Ex-smoker	261 (25.4)	207 (24.5)	54 (29.7)	1.55 (0.98-2.46)	0.061
Current smoker	176 (17.1)	132 (15.6)	44 (24.2)	2.00 (1.31-3.04)	0.001

[1]Proportions and odds ratios derived from the pooled multiple imputation datasets. Ethnicity reference group is white ethnicity; Alcohol excess reference group is never excess; Smoking history reference group is never-smoker. IBD: Inflammatory bowel disease; GI: Gastrointestinal; CCF: Congestive heart failure; CKD: Chronic kidney disease; HIV: Human immunodeficiency virus; PPI: Proton pump inhibitor; FE1: Faecal elastase-1.

therapy (OR: 1.87, 95%CI: 1.25-2.80), each of which approximately doubled the odds of being diagnosed with PEI. Individuals of Asian ethnicity had double the risk of PEI of patients of white ethnicity (OR: 2.11, 95%CI: 1.30-3.42).

Table 2 Distribution of symptoms in the total cohort and by faecal elastase-1 result, and results from the univariable logistic regression analysis.

Symptom	Total cohort, *n* (%)	FE1 ≥ 200 µg/g, *n* (%)	FE1 < 200 µg/g, *n* (%)	OR (95%CI)	*P* value
Abdominal pain	567 (55.2)	476 (56.3)	91 (50.0)	0.77 (0.56-1.06)	0.112
Diarrhoea	671 (65.3)	545 (64.5)	126 (69.2)	1.23 (0.87-1.74)	0.231
Weight loss	392 (38.2)	308 (36.4)	84 (46.2)	1.49 (1.08-2.06)	0.015
Bloating	263 (25.6)	226 (26.7)	37 (20.3)	0.70 (0.47-1.03)	0.072
Nausea and vomiting	129 (12.6)	106 (12.5)	23 (12.6)	1.01 (0.62-1.63)	0.973
Steatorrhoea	95 (9.3)	64 (7.6)	31 (17.0)	2.51 (1.58-3.98)	< 0.001
Dyspepsia	86 (8.4)	71 (8.4)	15 (8.2)	0.98 (0.55-1.75)	0.943
Flatulence	61 (5.9)	55 (6.5)	6 (3.3)	0.49 (0.21-1.16)	0.103
Fatigue	21 (2.0)	19 (2.3)	2 (1.1)	0.48 (0.11-2.09)	0.331

FE1: Faecal elastase-1.

Age, sex, liver cirrhosis, CCF, CKD, alcohol excess and smoking history did not have statistically significant associations with PEI after adjusting for all other exposures in the model. However, a trend towards increased risk of PEI in patients reporting historic alcohol excess was noted (OR: 2.06, 95%CI: 0.94-4.51).

Overall, 81.6% of incident PEI could be explained by the significant exposure variables: 18.1% by chronic pancreatitis; 3.2% by pancreatic cancer; 7.2% by upper GI surgery; 23.1% by type 2 diabetes; 23.7% by PPI therapy; and 6.3% by Asian ethnicity.

Model diagnostics

The model diagnostics indicated adequate model discrimination and calibration; that the included exposure variables were meaningful; and that the model was free from significant interactions or multicollinearity. The relevant statistical assumptions were met, and no influential outliers were identified. The complete model diagnostics are available in the online supplementary materials.

Sensitivity analyses

The complete case analysis model (*n* = 674) found that Asian or other ethnicity, chronic pancreatitis and PPI therapy had statistically significant positive associations with PEI. MNAR Models 1 and 2 (both *n* = 1027) detected the same associations as the primary analysis; however, ex-alcohol excess was also a significant predictor of PEI in both MNAR analyses. The full results of the sensitivity analyses are available in the online supplementary materials.

DISCUSSION

This is one of the larger studies of the factors associated with PEI to date, and the first to use a multivariable model to adjust for all previously described associations. We have shown, after adjusting for all other covariates, that chronic pancreatitis, pancreatic cancer, type 2 diabetes, upper GI surgery, PPI therapy and Asian ethnicity have significant positive associations with PEI in our cohort.

Pre-existing pancreatic conditions were the strongest predictors of PEI. The largest effect sizes were seen for chronic pancreatitis and pancreatic cancer, and 21.4% of the cases of PEI could be explained by these conditions alone. We diagnosed PEI in 68.8% of patients with known chronic pancreatitis who were investigated with FE1. This is in keeping with previous observational data showing a prevalence of 20%-85% in chronic pancreatitis[23,32], and a longitudinal study demonstrating a median time to development of PEI of 13 years in patients with alcohol-related chronic pancreatitis [11]. PEI was diagnosed in two thirds of patients with pancreatic cancer who were investigated with FE1, supporting previous estimates of a 50%-90% prevalence in inoperable pancreatic cancer and 20%-63% in operable disease[33-35].

Table 3 Multiple imputation multivariable logistic regression analysis showing associations between exposure variables and pancreatic exocrine insufficiency

Variable	OR (95%CI)	*P* value
Demographics		
Age	1.00 (0.99-1.01)	0.597
Sex		
Male	1.18 (0.80-1.74)	0.399
Ethnicity		
Asian	2.11 (1.30-3.42)	0.002
Black	1.22 (0.66-2.27)	0.524
Other	1.45 (0.88-2.38)	0.144
Comorbidities		
Type 2 diabetes	1.84 (1.18-2.87)	0.007
Liver cirrhosis	0.96 (0.45-2.06)	0.924
Chronic pancreatitis	7.98 (3.95-16.15)	< 0.001
Pancreatic cancer	6.58 (1.67-25.98)	0.007
Upper GI surgery	2.62 (1.32-5.19)	0.006
CCF	1.67 (0.42-6.65)	0.466
CKD	1.71 (0.74-3.97)	0.212
PPI	1.87 (1.25-2.80)	0.002
Alcohol excess		
Ex-excess	2.06 (0.94-4.51)	0.07
Current excess	1.56 (0.85-2.87)	0.152
Smoking history		
Ex-smoker	1.02 (0.57-1.84)	0.949
Current smoker	1.33 (0.79-2.25)	0.287

Ethnicity reference group is white ethnicity; Alcohol excess reference group is never excess; Smoking history reference group is never-smoker. GI: Gastrointestinal; CCF: Congestive heart failure; CKD: Chronic kidney disease; PPI: Proton pump inhibitor.

Our study adds to the growing body of literature supporting an association between diabetes and PEI[8]. We found that type 1 and type 2 diabetes were twice as common in patients with PEI than those without. Type 2 diabetes was present in one third of patients with PEI, and was a significant exposure in the univariable and multivariable analysis. Type 1 diabetes did not achieve statistical significance, likely due to the relatively small number of cases.

Previous upper GI surgery was twice as prevalent in patients with PEI than in those without, and one third of previously operated patients who were investigated with FE1 were diagnosed with PEI. Five patients had undergone pancreatic surgery (80% diagnosed with PEI); 28 had undergone gastro-duodenal surgery (35.7% diagnosed with PEI); and 16 had undergone gastro-oesophageal surgery (12.5% diagnosed with PEI). These findings are in keeping with the prevalence of PEI in post-surgical patients reported in the literature. Depending on the indication and specific procedure, PEI has been reported in 11.9%-100% of patients following pancreatic surgery, and in 47%-100% of total gastrectomy patients[8,9]. The reported prevalence of PEI following bariatric surgery is 9.1%-31%[36,37], and it has been suggested that PEI may account for post-surgical symptoms and malabsorption in a proportion of these patients[37].

This is the first study to explore the hypothesised association between PPI therapy and PEI in humans. 59.9% of patients diagnosed with PEI were taking PPI therapy at the time of FE1 testing, compared to 37.4% of patients without PEI. PPI therapy doubled the odds of PEI after adjustment for all other covariates in the model, and had a statistically significant association with PEI in the primary analysis and each

sensitivity analysis.

The mechanism by which this association could be mediated is currently unknown. An *in vitro* study of human pancreatic cell lines has demonstrated that proton pumps are present on the luminal membrane of pancreatic ducts, and may play a role in protecting the pancreatic epithelium from the high duodenal pH[27]. In addition, *in vivo* animal experiments have demonstrated that both short- and long-term PPI therapy reduces the volume of pancreatic secretions in rats, and alters its electrolyte composition[27].

Although PPI therapy is recommended as an adjunct in the treatment of PEI when symptoms are refractory to PERT, no patients included in the analysis had commenced PERT at the time of FE1 testing. The potential association of PPI therapy with PEI has important implications, given the frequency with which PPIs are prescribed, and their association with a number of GI side effects and nutritional deficiencies[38]. A previously unknown association with PEI may account for some of these adverse reactions. Alternatively, it may be that PPI therapy can yield falsely positive FE1 results. Further investigation of this finding is warranted, ideally with an interventional study. In the interim, where it is feasible to discontinue PPI therapy, we recommend repeating FE1 after a washout period.

Ethnic variations in the incidence and clinical course of acute and chronic pancreatitis have been reported previously[39,40], however this is the first study to suggest such a variation may exist in PEI. Patients of Asian ethnicity who underwent FE1 testing had double the risk of PEI compared to white patients. The elevated risk persisted after adjustment for other exposure variables that might explain the association, such as ethnic variations in type 2 diabetes, smoking and alcohol intake. We suggest this finding be researched further before firm conclusions are drawn.

We found no meaningful association between PEI and IBD, coeliac disease, previous acute pancreatitis (in the absence of chronic pancreatitis), BAM, cholecystectomy, HIV infection or hyperparathyroidism. Absolute patient numbers were small for some exposure variables, notably coeliac disease and HIV, which may have led to the failure to detect statistically significant associations.

Although they were significant exposures in univariable analysis, we did not detect significant associations between PEI and CCF, CKD, liver cirrhosis, alcohol excess, smoking history, sex or age, after adjustment for the other exposures in the multivariable model. CCF, CKD and liver cirrhosis, in the absence of coexisting alcohol excess, have not been linked convincingly with PEI. The estimated prevalence of PEI in these conditions in the published literature is 6.9%-11.1%[14,18-20], which is comparable to the prevalence of low FE1 found in healthy older adults[21,22].

Alcohol is implicated in the development and progression of chronic pancreatitis [11]. In patients with alcohol excess without known chronic pancreatitis, a prevalence of PEI of 64.4% has been reported[12], and similar findings have been reported in patients with alcohol-related chronic liver disease[41]. Compared to patients without a significant alcohol intake history, the risk of PEI was elevated in patients reporting ex- or current alcohol excess in the univariable analysis. The increased risk did not persist once adjusted for other exposures in the multivariable model, although ex-alcohol excess did approach statistical significance. Current smoking status was also significant in univariable, but not multivariable, analysis. Multiple studies have found that smoking is a risk factor for chronic pancreatitis, both alone and in synergy with alcohol[42,43]. Our results suggest that the majority of PEI in smokers and patients reporting alcohol excess occurs only once chronic pancreatitis has developed, and not before.

Differences in the prevalence of PEI have been observed between older and younger individuals, and studies have estimated that 16.6%-21.7% of adults aged > 50 years old have FE1 < 200 μg/g[21,22]. We found that age was a significant predictor of PEI in univariable analysis, however the association disappeared in the multivariable analysis. It may be that age mediates its previously reported association with PEI *via* the accumulation of other, more relevant, risk factors over time.

Steatorrhoea is acknowledged to be the most specific symptoms of PEI, but tends to occur only in advanced disease[44]. However, there has been a recent trend towards testing for PEI in patients with non-specific presentations, such as diarrhoea, abdominal pain or bloating[25,45]. We found that steatorrhoea and weight loss were the only symptoms associated with PEI, and that less specific presenting symptoms favoured an alternative diagnosis. Whether this is due to the high prevalence of non-specific symptoms in patients with functional GI disease or the reduced sensitivity of the FE1 assay in mild-moderate PEI of 49%-67% is unknown[46], but it does suggest that the diagnostic yield of widespread FE1 testing may be low.

Strengths and limitations

This study benefits from a large cohort of outpatients attending gastroenterology clinics in an ethnically diverse region of the United Kingdom, with a wide variety of clinical symptoms and comorbidities. We included consecutive patients tested for PEI with the FE1 assay over a 6-year period, only excluding patients already prescribed PERT. As such, the study does reflect everyday clinical practice, which should reduce selection bias. However, the cohort inclusion criterion (outpatients selected for FE1 testing) precludes commenting on the prevalence of PEI in patients with each comorbidity.

We included all previously reported associations with PEI into our multivariable model, thereby reducing confounding. The statistical methods were robust and the relevant statistical assumptions met. Whilst our dataset did contain missing values, MI was used to reduce the bias associated with complete case analysis, and the findings were similar across the sensitivity analyses.

We acknowledge limitations to this study. This was a retrospective analysis, albeit of prospectively recorded data, which is commonly associated with misclassification bias. We tried to reduce this risk by defining exposure variables and statistical methods *a priori*. External validity has not been conducted, and it is conceivable that local trends in ethnic variation, comorbidities and clinical practice may limit the generalisability of our findings. However, our results were generally in keeping with what has been reported elsewhere, in addition to reporting several new, important findings.

We used FE1 < 200 µg/g to classify the presence of PEI. The limitations of the FE1 assay have been described previously[23]. In brief, the FE1 assay shows high sensitivity and specificity for diagnosing severe PEI, but is less sensitive and specific than direct pancreatic function tests and the coefficient of faecal fat absorption in the diagnosis of mild and moderate PEI. FE1 is estimated to yield erroneous results in approximately 10% of patients[46]. Although it was not possible to judge if falsely low FE1 results accounted for any of the PEI not explained by our model, the high rate of clinical response to PERT suggests that most results were valid. Despite its limitations, FE1 is the only test for PEI available at most centres, therefore our study reflects the challenges in diagnosing PEI in clinical practice.

CONCLUSION

More than half of the PEI in our cohort could be explained by one of four established risk factors: Chronic pancreatitis, pancreatic cancer, upper GI surgery and type 2 diabetes. There should be a low threshold for testing for PEI in these patients. The novel finding that PPI therapy may also be associated with PEI requires further study, and, in the interim, we recommend repeating FE1 after a washout period. Approximately one in five cases of PEI could not be explained by our multivariable model or pancreatic imaging. Provided the possibilities of false positive FE1 results and rarer aetiologies of PEI have been explored, we propose that the term 'idiopathic PEI' may be a useful addition to the lexicon to describe this group.

ARTICLE HIGHLIGHTS

Research background

Pancreatic exocrine insufficiency (PEI) is a consequence of impaired production, drainage or function of pancreatic enzymes. The classical presenting symptom is steatorrhoea, however testing for PEI is often recommended in patients with non-specific symptoms, such as abdominal pain or diarrhoea. PEI is a known sequela of chronic pancreatitis, pancreatic cancer, and pancreatic resection. It is also thought to be associated with numerous other conditions, including: Previous acute pancreatitis, coeliac disease, diabetes, upper gastrointestinal (GI) surgery, liver cirrhosis, smoking, alcohol excess, human immunodeficiency virus infection, cardiac failure, chronic kidney disease, hyperparathyroidism, haemochromatosis and older age. However, the evidence base supporting the above associations is very heterogeneous.

Research motivation

The evidence base supporting many associations with PEI is weak. Strengthening the evidence base will prevent unnecessary investigation in low risk patients, and the

identification of potential new associations may impact clinical practice and guide the direction of future research.

Research objectives

This study aimed to explore all previously reported associations with PEI simultaneously, in a large cohort of general gastroenterology outpatients. In addition, we studied three associations not previously explored: Proton pump inhibitor (PPI) therapy, cholecystectomy, and bile acid malabsorption, all of which are physiologically plausible causes of PEI.

Research methods

A retrospective cohort study was performed. General gastroenterology outpatients tested for PEI with faecal elastase-1 (FE1) were identified and information retrieved from the electronic patient record. PEI was defined as FE1 < 200 μg/g. Multiple imputation, an advanced statistical technique that reduces bias, was used to handle missing data. Univariable logistic regression was used to study which presenting symptoms predicted PEI. Multivariable logistic regression was used to explore the relationship between all previously reported associations and PEI.

Research results

Steatorrhoea and weight loss were the only symptoms that predicted PEI. Chronic pancreatitis, pancreatic cancer, previous upper GI surgery and type 2 diabetes were confirmed to be associated with PEI; and between them explained over half of the cases. None of the other purported associations were found to be associated with PEI. This is the first study to investigate, and detect, an association between PPI therapy and PEI.

Research conclusions

The threshold for testing for PEI should be low in patients with one or more significant risk factor. Symptoms, apart steatorrhoea and weight loss, are not predictive of PEI, and the diagnostic yield will be low in the absence of a risk factor. Patients on PPI therapy who have a low (positive) FE1 result should, where possible, discontinue PPI therapy and have the test repeated after a washout period.

Research perspectives

We recommend that our finding that PPI therapy may be associated with PEI or a falsely positive FE1 result is now investigated with a prospective interventional study.

REFERENCES

1 **Löhr JM**, Dominguez-Munoz E, Rosendahl J, Besselink M, Mayerle J, Lerch MM, Haas S, Akisik F, Kartalis N, Iglesias-Garcia J, Keller J, Boermeester M, Werner J, Dumonceau JM, Fockens P, Drewes A, Ceyhan G, Lindkvist B, Drenth J, Ewald N, Hardt P, de Madaria E, Witt H, Schneider A, Manfredi R, Brøndum FJ, Rudolf S, Bollen T, Bruno M; HaPanEU/UEG Working Group. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). *United European Gastroenterol J* 2017; **5**: 153-199 [PMID: 28344786 DOI: 10.1177/2050640616684695]

2 **Pezzilli R**, Morselli Labate AM, Ceciliato R, Frulloni L, Cavestro GM, Comparato G, Ferri B, Corinaldesi R, Gullo L. Quality of life in patients with chronic pancreatitis. *Dig Liver Dis* 2005; **37**: 181-189 [PMID: 15888283 DOI: 10.1016/j.dld.2004.10.007]

3 **Sikkens EC**, Cahen DL, van Eijck C, Kuipers EJ, Bruno MJ. Patients with exocrine insufficiency due to chronic pancreatitis are undertreated: a Dutch national survey. *Pancreatology* 2012; **12**: 71-73 [PMID: 22487479 DOI: 10.1016/j.pan.2011.12.010]

4 **Domínguez-Muñoz JE**. Pancreatic exocrine insufficiency: diagnosis and treatment. *J Gastroenterol Hepatol* 2011; **26** Suppl 2: 12-16 [PMID: 21323992 DOI: 10.1111/j.1440-1746.2010.06600.x]

5 **Hollemans RA**, Hallensleben NDL, Mager DJ, Kelder JC, Besselink MG, Bruno MJ, Verdonk RC, van Santvoort HC; Dutch Pancreatitis Study Group. Pancreatic exocrine insufficiency following acute pancreatitis: Systematic review and study level meta-analysis. *Pancreatology* 2018; **18**: 253-262 [PMID: 29482892 DOI: 10.1016/j.pan.2018.02.009]

6 **Huang W**, de la Iglesia-García D, Baston-Rey I, Calviño-Suarez C, Lariño-Noia J, Iglesias-Garcia J, Shi N, Zhang X, Cai W, Deng L, Moore D, Singh VK, Xia Q, Windsor JA, Domínguez-Muñoz JE, Sutton R. Exocrine Pancreatic Insufficiency Following Acute Pancreatitis: Systematic Review and Meta-Analysis. *Dig Dis Sci* 2019; **64**: 1985-2005 [PMID: 31161524 DOI: 10.1007/s10620-019-05568-9]

7 **Leeds JS**, Hopper AD, Hurlstone DP, Edwards SJ, McAlindon ME, Lobo AJ, Donnelly MT, Morley

S, Sanders DS. Is exocrine pancreatic insufficiency in adult coeliac disease a cause of persisting symptoms? *Aliment Pharmacol Ther* 2007; **25**: 265-271 [PMID: 17269988 DOI: 10.1111/j.1365-2036.2006.03206.x]

8   **Piciucchi M**, Capurso G, Archibugi L, Delle Fave MM, Capasso M, Delle Fave G. Exocrine pancreatic insufficiency in diabetic patients: prevalence, mechanisms, and treatment. *Int J Endocrinol* 2015; **2015**: 595649 [PMID: 25892991 DOI: 10.1155/2015/595649]

9   **Chaudhary A**, Domínguez-Muñoz JE, Layer P, Lerch MM. Pancreatic Exocrine Insufficiency as a Complication of Gastrointestinal Surgery and the Impact of Pancreatic Enzyme Replacement Therapy. *Dig Dis* 2020; **38**: 53-68 [PMID: 31422398 DOI: 10.1159/000501675]

10   **Raphael KL**, Chawla S, Kim S, Keith CG, Propp DR, Chen ZN, Woods KE, Keilin SA, Cai Q, Willingham FF. Pancreatic Insufficiency Secondary to Tobacco Exposure: A Controlled Cross-Sectional Evaluation. *Pancreas* 2017; **46**: 237-243 [PMID: 27846134 DOI: 10.1097/MPA.0000000000000721]

11   **Layer P**, Yamamoto H, Kalthoff L, Clain JE, Bakken LJ, DiMagno EP. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. *Gastroenterology* 1994; **107**: 1481-1487 [PMID: 7926511 DOI: 10.1016/0016-5085(94)90553-3]

12   **Campbell JA**, Sanders DS, Francis KA, Kurien M, Lee S, Taha H, Ramadas A, Joy D, Hopper AD. Should we Investigate Gastroenterology Patients for Pancreatic Exocrine Insufficiency? *J Gastrointestin Liver Dis* 2016; **25**: 303-309 [PMID: 27689193 DOI: 10.15403/jgld.2014.1121.253.uks]

13   **Yilmaz A**, Hagberg L. Exocrine pancreatic insufficiency is common in people living with HIV on effective antiretroviral therapy. *Infect Dis (Lond)* 2018; **50**: 193-199 [PMID: 28838283 DOI: 10.1080/23744235.2017.1370126]

14   **Griesche-Philippi J**, Otto J, Schwörer H, Maisonneuve P, Lankisch PG. Exocrine pancreatic function in patients with end-stage renal disease. *Clin Nephrol* 2010; **74**: 457-464 [PMID: 21084049 DOI: 10.5414/cnp74457]

15   **Bauer S**, Ammann R. [Chronic pancreatitis and primary hyperparathyroidism]. *Schweiz Med Wochenschr* 1994; **124**: 1344-1348 [PMID: 8073234]

16   **Martínez MN**, García N, Beneitez C, Mayol MJ, Rivera L, Domínguez JR, Martínez A, Coronas M. [Pancreatic insufficiency: an infrequent manifestation of primary hyperparathyroidism]. *Gastroenterol Hepatol* 1997; **20**: 357-359 [PMID: 9377234]

17   **Jansen PL**, Thien T, Lamers CB, Yap SH, Reekers P, Strijk S. Exocrine pancreatic insufficiency and idiopathic haemochromatosis. *Postgrad Med J* 1984; **60**: 675-678 [PMID: 6494088 DOI: 10.1136/pgmj.60.708.675]

18   **Vujasinovic M**, Tretjak M, Tepes B, Marolt A, Slemenik Pusnik C, Kotnik Kerbev M, Rudolf S. Is pancreatic exocrine insufficiency a result of decreased splanchnic circulation in patients with chronic heart failure? *JOP.J Pancreas* 2016; **17**: 201-203. [DOI: 10.1016/j.pan.2014.05.735]

19   **Xia T**, Chai X, Shen J. Pancreatic exocrine insufficiency in patients with chronic heart failure and its possible association with appetite loss. *PLoS One* 2017; **12**: e0187804 [PMID: 29155861 DOI: 10.1371/journal.pone.0187804]

20   **Grassi M**, Lazzari S, Palmisano P, Nocchi S, Fontana M, Raffa S, Antonelli M. [Evaluation of exocrine pancreatic insufficiency in cirrhotic patients,using the fecal chymotrypsin test]. *Clin Ter* 1994; **144**: 501-509 [PMID: 8001334]

21   **Rothenbacher D**, Löw M, Hardt PD, Klör HU, Ziegler H, Brenner H. Prevalence and determinants of exocrine pancreatic insufficiency among older adults: results of a population-based study. *Scand J Gastroenterol* 2005; **40**: 697-704 [PMID: 16036530 DOI: 10.1080/00365520510023116]

22   **Herzig KH**, Purhonen AK, Räsänen KM, Idziak J, Juvonen P, Phillps R, Walkowiak J. Fecal pancreatic elastase-1 levels in older individuals without known gastrointestinal diseases or diabetes mellitus. *BMC Geriatr* 2011; **11**: 4 [PMID: 21266058 DOI: 10.1186/1471-2318-11-4]

23   **Shandro BM**, Nagarajah R, Poullis A. Challenges in the management of pancreatic exocrine insufficiency. *World J Gastrointest Pharmacol Ther* 2018; **9**: 39-46 [PMID: 30397535 DOI: 10.4292/wjgpt.v9.i5.39]

24   **Isherwood J**, Oakland K, Khanna A. A systematic review of the aetiology and management of post cholecystectomy syndrome. *Surgeon* 2019; **17**: 33-42 [PMID: 29730174 DOI: 10.1016/j.surge.2018.04.001]

25   **Lam KW**, Leeds J. How to manage: patient with a low faecal elastase. *Frontline Gastroenterol* 2021; **12**: 67-73 [PMID: 33489070 DOI: 10.1136/flgastro-2018-101171]

26   **Rolny P**, Jagenburg R. Exocrine pancreatic function, fecal fat, and blood glucose in patients with pancreatitis. *Scand J Gastroenterol* 1980; **15**: 727-732 [PMID: 7209383 DOI: 10.3109/00365528009181522]

27   **Wang J**, Barbuskaite D, Tozzi M, Giannuzzo A, Sørensen CE, Novak I. Proton Pump Inhibitors Inhibit Pancreatic Secretion: Role of Gastric and Non-Gastric H+/K+-ATPases. *PLoS One* 2015; **10**: e0126432 [DOI: 10.1371/journal.pone.0126432]

28   **Department of Health**.   UK chief medical officer's alcohol guidelines review. London: Department of Health; 2016

29   **Duggan SN**, Ní Chonchubhair HM, Lawal O, O'Connor DB, Conlon KC. Chronic pancreatitis: A diagnostic dilemma. *World J Gastroenterol* 2016; **22**: 2304-2313 [PMID: 26900292 DOI: 10.3748/wjg.v22.i7.2304]

30   **Peduzzi P**, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of

events per variable in logistic regression analysis. *J Clin Epidemiol* 1996; **49**: 1373-1379 [PMID: 8970487 DOI: 10.1016/s0895-4356(96)00236-3]

31   **Janssen KJ**, Donders AR, Harrell FE Jr, Vergouwe Y, Chen Q, Grobbee DE, Moons KG. Missing covariate data in medical research: to impute is better than to ignore. *J Clin Epidemiol* 2010; **63**: 721-727 [PMID: 20338724 DOI: 10.1016/j.jclinepi.2009.12.008]

32   **Machicado JD**, Chari ST, Timmons L, Tang G, Yadav D. A population-based evaluation of the natural history of chronic pancreatitis. *Pancreatology* 2018; **18**: 39-45 [PMID: 29221631 DOI: 10.1016/j.pan.2017.11.012]

33   **Bartel MJ**, Asbun H, Stauffer J, Raimondo M. Pancreatic exocrine insufficiency in pancreatic cancer: A review of the literature. *Dig Liver Dis* 2015; **47**: 1013-1020 [PMID: 26211872 DOI: 10.1016/j.dld.2015.06.015]

34   **Tseng DS**, Molenaar IQ, Besselink MG, van Eijck CH, Borel Rinkes IH, van Santvoort HC. Pancreatic Exocrine Insufficiency in Patients With Pancreatic or Periampullary Cancer: A Systematic Review. *Pancreas* 2016; **45**: 325-330 [PMID: 26495777 DOI: 10.1097/MPA.0000000000000473]

35   **Lee AHH**, Ward SM. Pancreatic exocrine insufficiency after total gastrectomy – a systematic review. *JOP.J Pancreas* 2019; **20**: 130-137 [DOI: 10.3998/panc.2018.19]

36   **Borbély Y**, Plebani A, Kröll D, Ghisla S, Nett PC. Exocrine Pancreatic Insufficiency after Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2016; **12**: 790-794 [PMID: 26965152 DOI: 10.1016/j.soard.2015.10.084]

37   **Vujasinovic M**, Kunst G, Breznikar B, Rozej B, Tepes B, Rudolf S, Kuster A. Is pancreatic exocrine insufficiency a cause of malabsorption in patients after bariatric surgery? *JOP.J Pancreas* 2016; **17**: 402-405 [DOI: 10.1016/j.pan.2013.04.146]

38   **Keszthelyi D**, Masclee AA. Effects of proton pump inhibitor therapy in the distal gut: putting the pieces together. *Dig Dis Sci* 2012; **57**: 2487-2489 [PMID: 22899240 DOI: 10.1007/s10620-012-2339-5]

39   **Yang AL**, Vadhavkar S, Singh G, Omary MB. Epidemiology of alcohol-related liver and pancreatic disease in the United States. *Arch Intern Med* 2008; **168**: 649-656 [PMID: 18362258 DOI: 10.1001/archinte.168.6.649]

40   **Pendharkar SA**, Mathew J, Zhao J, Windsor JA, Exeter DJ, Petrov MS. Ethnic and geographic variations in the incidence of pancreatitis and post-pancreatitis diabetes mellitus in New Zealand: a nationwide population-based study. *N Z Med J* 2017; **130**: 55-68 [PMID: 28207725]

41   **Aoufi Rabih S**, García Agudo R, Legaz Huidobro ML, Ynfante Ferrús M, González Carro P, Pérez Roldán F, Ruiz Carrillo F, Tenías Burillo JM. Exocrine pancreatic insufficiency and chronic pancreatitis in chronic alcoholic liver disease: coincidence or shared toxicity? *Pancreas* 2014; **43**: 730-734 [PMID: 24713840 DOI: 10.1097/MPA.0000000000000085]

42   **Yadav D**, Hawes RH, Brand RE, Anderson MA, Money ME, Banks PA, Bishop MD, Baillie J, Sherman S, DiSario J, Burton FR, Gardner TB, Amann ST, Gelrud A, Lawrence C, Elinoff B, Greer JB, O'Connell M, Barmada MM, Slivka A, Whitcomb DC; North American Pancreatic Study Group. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. *Arch Intern Med* 2009; **169**: 1035-1045 [PMID: 19506173 DOI: 10.1001/archinternmed.2009.125]

43   **Pelli H**, Lappalainen-Lehto R, Piironen A, Sand J, Nordback I. Risk factors for recurrent acute alcohol-associated pancreatitis: a prospective analysis. *Scand J Gastroenterol* 2008; **43**: 614-621 [PMID: 18415757 DOI: 10.1080/00365520701843027]

44   **DiMagno EP**, Go VL, Summerskill WH. Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. *N Engl J Med* 1973; **288**: 813-815 [PMID: 4693931 DOI: 10.1056/NEJM197304192881603]

45   **Arasaradnam RP**, Brown S, Forbes A, Fox MR, Hungin P, Kelman L, Major G, O'Connor M, Sanders DS, Sinha R, Smith SC, Thomas P, Walters JRF. Guidelines for the investigation of chronic diarrhoea in adults: British Society of Gastroenterology, 3rd edition. *Gut* 2018; **67**: 1380-1399 [PMID: 29653941 DOI: 10.1136/gutjnl-2017-315909]

46   **Vanga RR**, Tansel A, Sidiq S, El-Serag HB, Othman MO. Diagnostic Performance of Measurement of Fecal Elastase-1 in Detection of Exocrine Pancreatic Insufficiency: Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2018; **16**: 1220-1228.e4 [PMID: 29374614 DOI: 10.1016/j.cgh.2018.01.027]