Reducing disease progression after acute pancreatitis

PhD Thesis

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II. List of abbreviations

AP	acute pancreatitis
APA	American Pancreatic Association
ARP	acute recurrent pancreatitis
AUC	area under the curve
CECT	contrast-enhanced computed tomography
CFTR	cystic fibrosis transmembrane conductance regulator
COVID-19	coronavirus disease 2019
CP	chronic pancreatitis
CPA1	carboxypeptidase A1
CTRC	chymotrypsin C
HPSG	Hungarian Pancreatic Study Group
IAP	International Association of Pancreatology
IBD	inflammatory bowel disease
JPN guideline	Japanese guidelines for the management of acute pancreatitis
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
OR	odds ratio
PC	pancreatic cancer
PCR	polymerase chain reaction
PIN	personal identification number
PRSS1	cationic trypsinogen
RCT	randomized controlled trial
SLE	systemic lupus erythematosus
SPINK1	serin protease inhibitor Kazal type 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TG	triglyceride
US	ultrasonography

III. Scientific metrics, list of publications

Number of publications **related to the subject** of the thesis:	3 (3 first author)
Cumulative impact factor of publications related to the thesis:	14.777
D1: -, Q1: 3, Q2: -, Q3: -, Q4: -	
Number of **total accepted/published** articles:	17 (5 first author)
Cumulative impact factor of the published articles:	66.707
D1: 3, Q1: 13, Q2: 1, Q3: -, Q4: -	
Number of total citations according to **MTM2:**	68 independent
https://m2.mtmt.hu/gui2/?type=authors&mode=browse&sel=10070 611&view=dataSheet	
Hirsch Index: 4	
Number of total citations according to Google Scholar	139
https://scholar.google.com/citations?view_op=list_works&hl=en&h l=en&user=fxRkqtMAAAAJ	
Hirsch Index: 6	

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Juhász MF, Farkas N, Szentesi A, Wedrychowicz A, Nita AF, Lásztity N, Tészás A, Tokodi I, Vincze Á, Eross B, Izbéki F, Czakó L, Papp M, Hegyi P, Párniczky A. Pancreatic family history does not predict disease progression but connotes alcohol consumption in adolescents and young adults with acute pancreatitis: Analysis of an international cohort of 2,335 patients. **Front Med** (Lausanne). 2022 Sep 12;9:801592. doi: 10.3389/fmed.2022.801592. PMID: 36172540; PMCID: PMC9511134.
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Q1, IF: 2.279

IV. Thesis introduction

Acute pancreatitis (AP) is an inflammatory disorder of the pancreas, most frequently elicited by gallstones and alcohol (1, 2). It is one of the most common, potentially dangerous reasons behind abdominal pain in the adult emergency department (3). While most cases are mild, without complications, 10-30% of patients will develop moderate or severe disease resulting in longer hospitalization, local or systemic complications and an up to 40% mortality (4-6).

IV.1. Epidemiology of acute pancreatitis

Reports on the incidence of AP currently vary between 2.7-135/100,000/year globally, with a slightly higher value observed in North America (7.1-135/100,000/year) (7, 8). The incidence shows an increasing tendency: changes observed over time in Europe by Roberts et al. (7) are visualized in Figure 1. A recent, comprehensive meta-analysis noted an average annual increase of 3% in the global incidence of AP since 1961 (8). Most authors attribute this change to increased pancreatic enzyme testing in the emergency setting, and the evolution of several risk factors of AP over time, such as metabolic syndrome and biliary disease, advancing age and alcohol consumption (9-12). At the same time, mortality shows a decreasing tendency, likely due to earlier diagnosis and improved therapy (13). A study by Lankisch et al. discussing gender differences assessed 50 years' cohort studies that included at least a 100 patients and found a slight male predominance – 55% of patients are male (14).
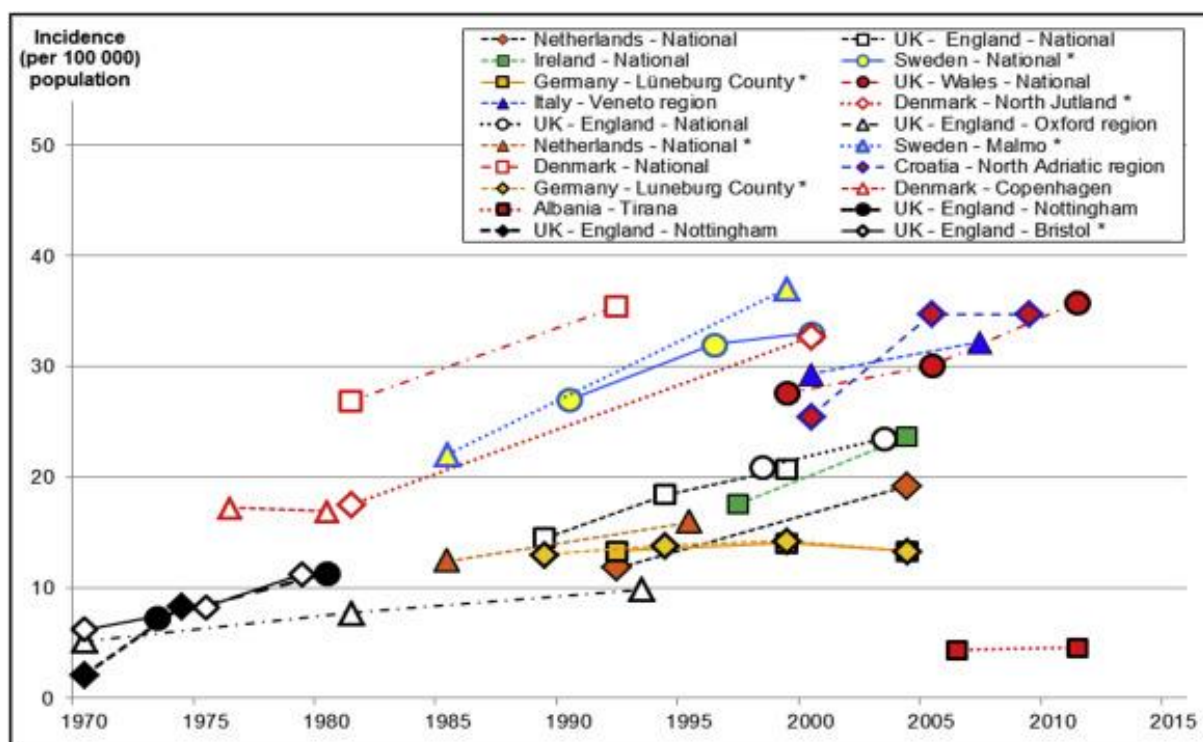

Figure 1. Changes over time in the incidence of acute pancreatitis in Europe. Reprinted from *Pancreatology, Vol 17, Issue 2, Roberts S.E. et al., The incidence and aetiology of acute pancreatitis across Europe, Pages 155-165, Copyright (2017)*, with permission from Elsevier (7).

IV.2. Diagnosis and etiological workup in acute pancreatitis
IV.2.1. Diagnostic criteria and workup
The diagnosis of AP is based on the fulfilment of at least 2 out of the following 3 criteria: 1: abdominal pain that is consistent with the disease; 2: serum lipase (or amylase) values that exceed at least three times the upper limit of their normal threshold; 3: imaging findings characteristic of AP observed with contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI) or abdominal ultrasonography (US) (5). All currently used AP management guidelines strongly agree with the application of this diagnostic system (15-19).

The abdominal pain in AP is typically epigastric, may radiate to the back and it is usually severe, but intensity can vary (16).

While studies state that lipase is the superior diagnostic test (compared to amylase), most papers observe similar specificity and diagnostic accuracy (20, 21). Still, most authors suggest that serum lipase should be preferred over amylase in the diagnosis of AP (18, 21). There are two strong arguments behind this recommendation: one is that lipase does seem to have an advantage over amylase in sensitivity; the other is that while amylase values usually normalize within 3-5 days from the onset of the disease, lipase offers a wider diagnostic window, as it remains elevated for longer (an estimated additional 2 days) (21-23). Some authors also argue, that amylase can frequently be elevated in non-pancreatic conditions, such as decreased glomerular filtration, salivary gland diseases and extrapancreatic abdominal inflammation (appendicitis, cholecystitis, intestinal obstruction, etc.) but the same could be said for lipase, which can also be elevated in renal disease, various abdominal pathologies and in diabetes – although three-fold elevation is rare for both enzymes (16, 24-26). In light of these observations, there is an ongoing debate, whether only lipase should be measured as part of a more cost-efficient approach. The Japanese (JPN) guideline recommends using amylase only "when the measurement of lipase is difficult" (18), it seems that performing both measurements only results in a slight improvement of diagnostic performance, that probably makes simultaneous measurement unnecessary (21, 27, 28). Over the last decades, several other pancreatic enzymes were investigated as potential diagnostic tests, neither of them seems to reach the diagnostic capabilities of lipase or amylase (29). One of the more promising is the rapid urinary trypsinogen-2 test, with a sensitivity and specificity of 80-85% and 90-93% respectively (still considerably less than the 97-99% specificity of amylase and lipase) and the advantage of being non-invasive, but limited by availability (15, 30, 31).

CECT is the gold-standard imaging methodology in the diagnosis of AP on its local complications (5). However, in most cases, it's unnecessary – suspicious symptomatology will be confirmed by the pancreatic enzyme measurement. Instead, performing an abdominal US is recommended in all patients on admission, since it is an accessible and sensitive approach for the establishment of biliary etiology, and it does not expose the patient to ionizing radiation (15, 16, 19, 32). Alterations confirming the diagnosis of AP can commonly be detected with abdominal US, but it has several limitations: the limited visibility of the pancreas and peripancreatic region (due to bowel gas and obesity), the operator dependent performance and the less accurate visualization of the inflammation in the peripancreatic region (33). The currently used guidelines recommend reserving CECT for cases where symptoms and enzyme elevation (and initial US) are unequivocal, when no clinical improvement is seen next to

conservative treatment within 48-96 hours or if the patient's condition deteriorates (15, 16). After 96 hours from symptom onset, CECT has a close to 100% sensitivity for pancreatic necrosis (34). In contrast, early performance of CECT does not result in altered patient management, probably because pancreatic or peripancreatic necrosis does not become evident in the first 48-72 hours (35, 36). Imaging alterations characteristic of AP are: focal or diffuse pancreatic enlargement, decreased echogenicity on abdominal US; focal or diffuse enlargement, edematous density changes, indistinct pancreatic margins, stranding in the surrounding pancreatic fat, fluid or necrotic collection on CECT (5).

IV.2.2. Etiology and pathomechanism of acute pancreatitis

Biliary obstruction and excessive alcohol consumption amount for 50-80% of all AP cases (2), with an estimated 60-75/100,000 annual incidence of biliary AP among adults with gallstones and a 2.5-3% AP risk in heavy drinkers (37, 38). In the United States, biliary and alcoholic AP show a balanced distribution, while in Europe and Asia biliary cases occur twice as frequently (2). Other etiological factors include hypertriglyceridemia, certain drugs (most commonly: 5-acetylsalicylic acid, azathioprine, L-asparaginase, valproic acid), infections (e.g. mumps, Coxsackie B, and hepatitis viruses, *Mycoplasma pneumoniae*, *Ascaris lumbricoides*), autoimmune pancreatitis, systemic diseases (e.g. inflammatory bowel disease (IBD) and lupus erythematosus (SLE)), hypercalcemia and AP can be secondary to endoscopic retrograde cholangiopancreatography and abdominal trauma (15, 39-42). Smoking and diabetes are also observed to increase the risk of developing AP (43, 44). In 15-30% of cases, no risk factor is identified (although it should be noted that there can be great differences in the thoroughness of etiological workup between centers), these cases are deemed idiopathic (2).

Genetic risk factors have also been identified. Mutations in the cationic trypsinogen (*PRSS1*) gene can elicit AP, while mutations in the serin protease inhibitor Kazal type 1 (*SPINK1*), carboxypeptidase A1 (*CPA1*), chymotrypsin C (*CTRC*) and cystic fibrosis transmembrane conductance regulator (*CFTR*) genes can increase the risk of AP (42).
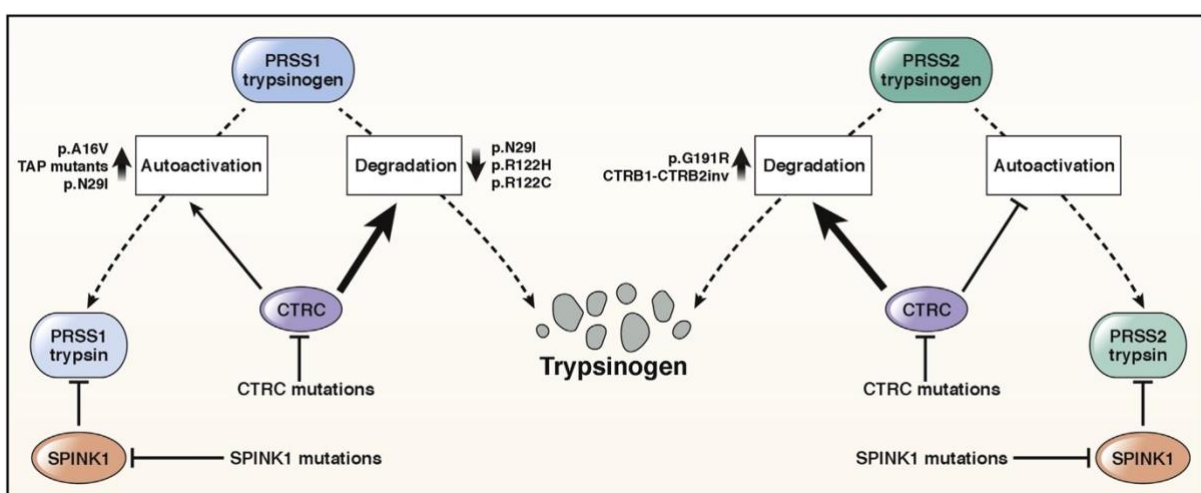
Figure 2. Genetic risk factors associated with the trypsin-dependent pathologic pathway. Reprinted from *Gastroenterology, Vol 156, Issue 7, Mayerle J. et al., Genetics, Cell Biology, and Pathophysiology of Pancreatitis, Pages 1951-1968, Copyright (2019)*, with permission from Elsevier (45). CTRC: chymotrypsin C; PRSS1: cationic trypsinogen; PRSS2: anionic trypsinogen; SPINK1: serine protease inhibitor Kazal type 1; TAP: trypsinogen activation peptide.

The key step in the pathogenesis of AP is acinar cell injury, elicited either directly by acinar cell toxins such as alcohol, nicotine, or bile acids; or indirectly by intraductal events such as an increase in pressure, exposure to bile, acidification in the duct lumen (42). These noxae lead to acinar cell death via several intracellular signaling pathways including premature trypsinogen activation, altered calcium signaling, endoplasmic reticulum stress and the impairment of mitochondrial function, autophagy and unfolded protein response (46, 47). Mutations in the *PRSS1*, *SPINK1* and *CTRC* genes directly target trypsinogen activation and regulation (Figure 2), while risk increasing *CFTR* mutations promote premature enzyme activation via intraductal fluid stasis and *CPA1* and some *PRSS1* mutations can result in proteins with abnormal folding structure, activating unfolded protein response (48). The in-depth review of cellular pathways and mechanisms is beyond the scope of this thesis; however, numerous excellent reviews are available on this topic (42, 48).

IV.2.3. Etiological workup
Determining the etiology of AP has an important role in the management – while the general therapeutic approach is the same, etiology-specific interventions might be necessary during hospitalization and eliminating the risk factor is essential for avoiding recurrent episodes. Guidelines offer various levels of detail on the recommended etiological workup. Generally, all patients should undergo: detailed medical history collection, laboratory examination, abdominal imaging, and some additional tests in case they are indicated, as shown on Figure 3 and discussed below (15, 16, 19).
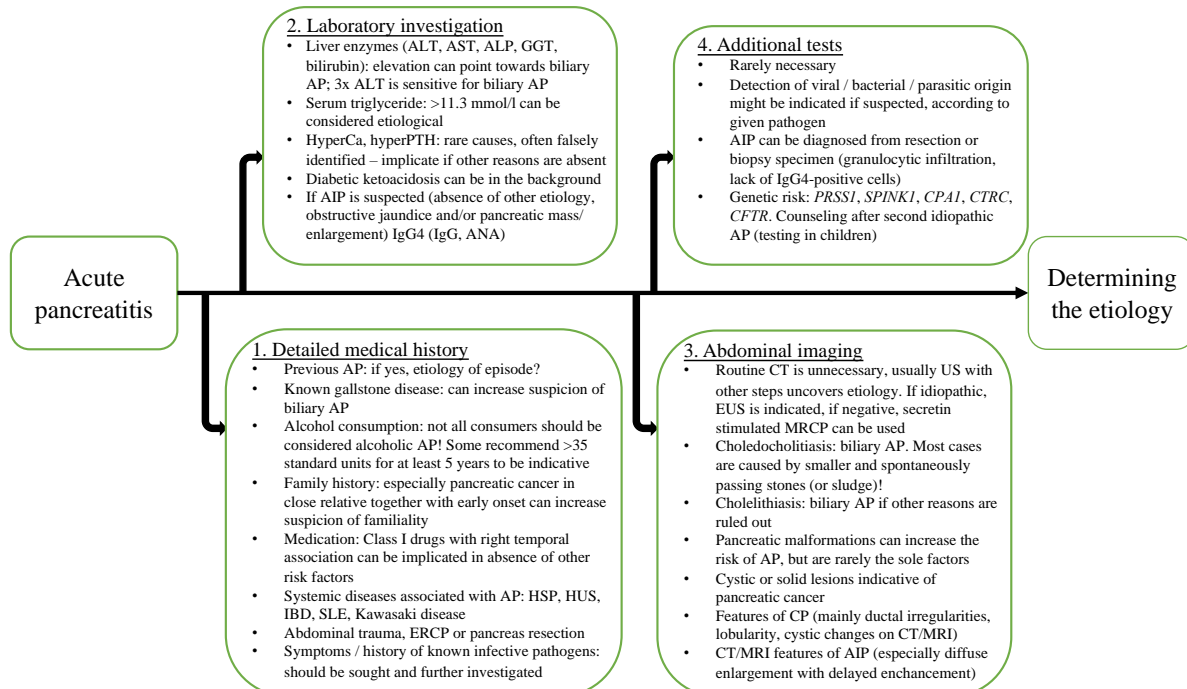
Figure 3. Etiological workup of acute pancreatitis. The figure is the authors' own work, mostly based on the articles cited in the "IV.2.3. Etiological workup" subsection of this thesis. AIP: autoimmune pancreatitis; ALP: alkaline phosphatase; ALT: alanine transaminase; AP: acute pancreatitis; AST: aspartate transaminase; Ca: calcium; CFTR: cystic fibrosis transmembrane conductance regulator; CTRC: chymotrypsin C; CP: chronic pancreatitis; CPA1: carboxypeptidase A1; CT: computed tomography; ERCP:

endoscopic retrograde cholangiopancreatography; EUS: endoscopic ultrasonography; GGT: gamma-glutamyl transferase; HSP: Henoch–Schönlein purpura; HUS: hemolytic uremic syndrome; MRCP: magnetic resonance cholangiopancreatography; MRI: magnetic resonance imaging; *PRSS1*: cationic trypsinogen; PTH: parathyroid hormone; SLE: systemic lupus erythematosus; *SPINK1*: serine protease inhibitor Kazal-type 1; US: ultrasonography.

In the personal medical history, known gallstone disease or past biliary colics can suggest biliary etiology. Biliary AP is most dependably established in case a stone can be seen in the common bile duct (most frequently on abdominal US) (42). This however, is infrequent: most cases of biliary AP are caused by sludge, or small stones, the approximate rate of spontaneous stone passage being 80% (49, 50). Serum alanine transaminase is the most sensitive laboratory marker, with >150 U/L (which is around three times the upper limit) having a 95% positive predictive value for biliary AP (51). However, around 10% of patients have normal liver function tests on admission (52). Stones in the gallbladder, as they can be chronically present, should only be used to determine a biliary origin in case other plausible etiologies are ruled out. It should also be noted that the sensitivity of abdominal US for detecting gallstones considerably decreases in AP (67-87%), probably due to frequent bowel distention, with an even lower reliability in obese patients (53).

As discussed above, alcohol consumption is often cited to be the second most common etiological factor in AP (2). Care must be taken that not all AP episodes where the patient consumes alcohol should be regarded as alcohol-induced, as this can hinder uncovering other factors in the background. There is no consensus on what amount should be accepted as causative, most studies use a 50 g/day threshold, but expert recommendations vary between 50 and 80 g/day, with some authors also suggesting taking the length of consumption into account (i.e. at least several years of consumption required, for example minimum 5 years in the review of Lee et al.) (38, 42, 54). A meta-analysis by Irvin et al. from 2009 found an approximately exponential dose-response relationship between alcohol consumption and AP, suggesting a 4 drinks per day (around 40 g/day) threshold as risk-increasing for AP or chronic pancreatitis (CP) (55). A more recent meta-analysis reassured the exponential relationship and the 40 g/day threshold in women, but found a linear relationship in men (Figure 4) (56). The available literature indicates that most patients who develop CP, have a long history of heavy alcohol consumption (57).

Figure 4. Pooled dose-response relationship between alcohol intake amount and acute pancreatitis risk. Reprinted from Samokhvalov AV et al. Alcohol Consumption as a Risk Factor for Acute and Chronic Pancreatitis: A Systematic Review and a Series of Meta-analyses. *EBioMedicine,* 2015 under Creative Commons licence CC BY-NC-ND 4.0. AP: acute pancreatitis.
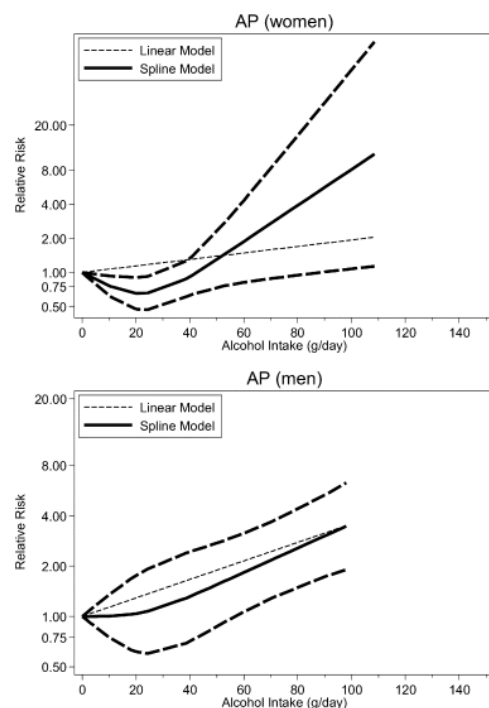
As with alcohol consumption, in most other etiologies of AP, clinicians should be aware, that the presence of the risk factor does not necessarily mean that it is what caused the AP episode, or if it is, other factors can be present. IBD and SLE are listed as systematic causes, with a 210/100,000/year annual incidence and a 0.67-0.8% prevalence of AP among these patients respectively (58-60). While the currently available literature suggests, that IBD and SLE themselves can cause AP (through autoimmune processes in both, vascular processes in SLE and granulomatous inflammation in IBD), not all patients develop AP. General causes, such as gallstones and alcohol consumption can also be present in this population, and some of the used therapeutic agents are also associated with AP (61, 62). More than 200 drugs are discussed in association with AP, often only based on single case reports without positive rechallenges. A systematic review found that only 45 substances had at least one case report with a positive rechallenge and the exclusion of other AP etiologies, of these, they found 19 to have a probable or definite cause-effect relationship with AP (40). Positive rechallenge is often not attempted due to ethical concerns, but appropriate temporal association with class Ia drugs in absence of other etiologies can suggest drug induced AP (63). There are various other risk factors for which no tests exist that could prove with certainty, their causative role. Assessing the temporal association – as with drugs – can strongly suggest the etiological role in acute onset systemic diseases, abdominal trauma and invasive procedures, but this should not preclude further etiological investigation.

Besides these mentioned items (known gallstone disease, alcohol consumption, presence and chronology of known risk factors) a detailed medical history should also include personal and family history of pancreatic diseases, which can help with the workup, as well as circumstances and symptoms suggestive of infectious causes, that can be further confirmed according to the pathogen in question (usually serology).

Aside from liver enzymes, metabolic factors should be sought in the laboratory examination. According to current consensus recommendations, hypertriglyceridemia can be regarded as causative in case serum triglyceride is >11.3 mmol/L and biliary AP is not diagnosed and no heavy alcohol consumption is present (16). The risk of AP is around 5% in these patients, whereas in patients with >22.6 mmol/L it is 10-20% (64). Hypertriglyceridemia likely also plays an important role in the development of AP in diabetic ketoacidosis. Diagnosis can be complicated in these patients, since both abdominal pain and aspecific amylase elevation can be present – imaging can be decisive (65, 66). Hypercalcemia (usually as a result of hyperparathyroidism) is a rare cause of AP, in case no other etiology is found, laboratory calcium values can be considered indicative, but the underlying reason (commonly parathyroid adenoma) should also be managed (42, 67, 68).

Autoimmune pancreatitis, acute exacerbation of CP and AP caused by pancreatic neoplasms are not discussed in detail in this thesis. The diagnosis of these conditions is based on characteristic imaging alterations (the use of abdominal US is insufficient, CT or MRI should be performed); exocrine and endocrine dysfunction and AP history in CP; IgG4 and other organ involvement in autoimmune pancreatitis (69-71).

After etiological workup of varying thoroughness, 10-35% of all AP cases are deemed idiopathic (2). Multiple studies focus on the work-up of presumed idiopathic cases, subjecting these patients to additional imaging and laboratory tests. The guidelines state that "in patients

considered to have idiopathic AP, after negative routine work-up for biliary etiology" endoscopic ultrasonography (EUS) or magnetic resonance cholangiopancreatography (MRCP) is indicated (15). These imaging modalities have a higher accuracy for detecting common bile duct stones than laboratory examination and abdominal US (72). However as outlined above, the confirmation of the causative role of several risk factors is dependent on the absence of others – accordingly, some authors suggest performing EUS in all patients where no heavy drinking or frank biliary stones are present (73). Using EUS, MRCP and CECT, etiological factors can be found in 1 out of 3 idiopathic AP patients, most often (around 50% of cases) biliary stones or occult microlithiasis (74). Other encountered factors include: sphincter of Oddi dysfunction, anatomical anomalies, autoimmune pancreatitis, CP and pancreatic cancer (73). A recent meta-analysis recommends that EUS and MRCP should both be used, as complementary methods, since the former is more adequate in detecting biliary obstruction and CP, while the latter has a better diagnostic performance for anatomical variations in the pancreatobiliary duct system (75).

IV.2.4. Genetic risk factors, family history

As mentioned above, mutations in the *PRSS1* gene can elicit AP, while certain mutations in the *SPINK1*, *CPA1*, *CTRC* and *CFTR* genes are known to increase the risk of pancreatitis (42). Such predisposing mutations are more likely in patients with idiopathic AP, although they can be present next to other etiologies as well. Their role is increasingly recognized, however, their exact prevalence and impact (especially in the long-term) is still unknown.

Recommendations on when to perform genetic testing are available in two of the currently used guidelines (15, 16). The American College of Gastroenterology suggests that genetic testing can have an important role in individuals with idiopathic AP and a family history of pancreatic diseases (especially in case of more than one affected family members). The International Association of Pancreatology and the American Pancreatic Association (IAP/APA) recommend that if after thorough investigation the etiology of AP remains unspecified and especially after more than one episode, the patient should undergo genetic counseling (not necessarily genetic testing). To summarize, the available recommendations are vague, focus mostly on people with idiopathic AP and recurrent episodes or a family history of pancreatic diseases. They also do not in fact recommend the performance of genetic testing in any adult patient with AP. Pediatric guidelines on the other hand highlight that genetic testing for known risk-increasing mutations in the above mentioned genes should be performed in case of two or more episodes of AP, or even after a single episode in case of a family history of pancreatic diseases (76). There is an increasing body of scientific evidence that these recommendations are underpowered, and genetic testing should be a tool used more frequently (77).

Family history is indeed an important indicator, but there can be several other reasons behind familial aggregation aside from genetic predisposition, such as: patterns of alcohol consumption and smoking, dietary habits associated with gallstone formation, diabetes, hypercholesterolemia, etc. The connection of a family history of pancreatic diseases and non-genetic risk factors of AP is yet unexplored and it was one of our main aims to shed light on this aspect of etiological work-up. The restriction of testing to idiopathic cases can also be overly limiting, since most of these mutations cannot elicit AP solely by themselves and will likely be present along with other non-genetic etiological factors.

Either way; information on the presence of a family history of pancreatic disease and the presence of predisposing genetic alterations can be crucial in the management of AP patients. It is, since these individuals possess an unamendable risk factor, increasing the risk of acute recurrent pancreatitis (ARP), CP and pancreatic cancer (PC) – active efforts should be made to avoid or delay disease progression towards additional episodes, chronic inflammation and tumorigenesis. Not to mention the future possibilities provided by the evolving field of gene therapy.

IV.4. Long-term therapy of acute pancreatitis

Over the past decades, multiple well-designed clinical trials and meta-analyses have led to vast improvements in the in-hospital management of AP. The use of enteral nutrition and on demand oral refeeding, with parenteral nutrition only in select cases has taken over the former routine use of nil per os and parenteral nutrition, that is now known to be associated not only with increased complications, but higher mortality as well (78-80). The empiric use of antibiotics was still commonly recommended the early 2000's, based on underpowered studies with variable quality and results (81). The execution of high quality randomized controlled trials (RCTs) has shed light on the lack of benefit – now antibiotic use is restricted to the treatment of infected complications and concomitant extrapancreatic infections (15, 82, 83). Thanks to these and other advances in therapeutics and the optimization of fluid therapy the overall mortality of AP is now below 1% (84).

There is however, a grey area in the management of these patients, where existing interventions could be improved and there is a dire need for new ones: the long-term prevention of disease progression.

IV.4.1. Identification of patients at risk for progressive disease

10-30% of all patients with AP will develop ARP. A meta-analysis of 14 observational studies found a 10% prevalence of CP in patients with a single episode of AP, and 36% in patients with at least 1 recurrence (77). And the transition to CP is quite rapid – in a Danish prospective study following 352 AP patients for 30 years, the mean time between the index AP and CP diagnosis was 3.5 years (85). Progressive disease is one of the major concerns in AP – each episode poses the risk of severe disease course and mortality and CP is a debilitating disease, with endocrine and exocrine insufficiency, intermittent or constant pain and a higher risk for PC (86).
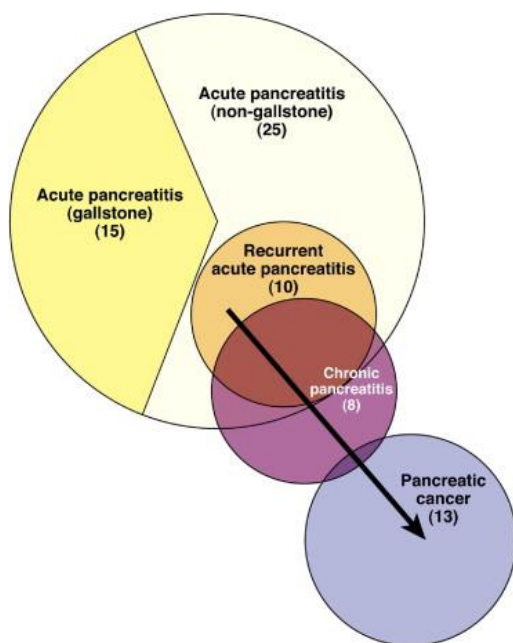
Figure 5. Incidence rates for pancreatitis and pancreatic cancer in the United States. Numbers in parentheses indicate approximate yearly incidence rates per 100,000 persons. The arrow indicates the relationship between benign and malignant disease. Recurrent AP develops predominantly in patients with non–gallstone-related pancreatitis, although it can develop in patients with gallstone-related pancreatitis when cholecystectomy has been delayed or refused. Reprinted from *Gastroenterology, Vol 144 Issue 6, Yadav D., Lowenfels A.B., The Epidemiology of Pancreatitis and Pancreatic Cancer, Pages 1252-1261, Copyright (2013)*, with permission from Elsevier (87).

An important consideration is: how can we identify the risk factors for disease progression or the patients at risk for a progressive disease? While gallstones account for 39-44% of AP cases, alcohol for 17-25% and 15-22% are idiopathic, alcohol becomes the predominant etiological factor in ARP and CP (present in 25-50% and 40-70% respectively) (2, 86, 88). At the same time the prevalence of biliary etiology reduces to 10-30% in ARP, and it is very rarely (0-2%) present in CP, around 2-6% of patients with a first episode of biliary AP are reported to develop CP (88, 89). This is in direct relationship with the timing of cholecystectomy: the more it is delayed, the higher the likelihood of a recurrent episode (90, 91). The presence of this factor in CP can be explained by either the sufficiency of the pancreatic insult during the first AP episode (and the recurrent episode in case it occurred) for the development of chronic inflammation, the underreporting of alcohol consumption by participants of these studies, or non-identification of the presence of other risk factors (86, 89). Since genetic alterations are an unamendable risk factor, their frequency also increases in a progressive disease, the prevalence of different risk-increasing mutations being between 3-30% in CP (86).

Aside from alcohol consumption, smoking is another key risk factor for the development of CP. The 2015 meta-analysis by Sankaran et al. found smoking to be present in 47-73% of CP cases (77). In their cross-sectional analysis, Ahmed and colleagues found smoking to be independently associated with CP with an odds ratio (OR) of 2.90 (95% confidence interval (CI): 1.42-5.93) (89). Other independent risk factors in their analysis were: alcoholic AP (OR: 4.22, 95% CI: 1.83-9.73), idiopathic AP (OR: 3.98, 95% CI: 1.64-9.65), necrotizing AP (OR: 6.65, 95% CI: 3.40-13.01) and recurrent episodes (OR: 2.90, 95% CI: 2.07-4.05, per episode). Similarly, most studies describe alcoholic and idiopathic etiology, necrosis, smoking, and ARP to show an association with CP development (77). Male sex also seems to show an association with CP development, and some studies also suggest the role of initial AP severity, although this is contested (77).

In the past few years, with the emergence of machine learning methods in medical science, there have been attempts at developing systems capable of predicting AP recurrence. Chen and colleagues developed a CECT-based radiomics model that predicted the occurrence of RAP

during a mean follow-up of 5 years in their validation cohort with an area under the curve (AUC) of 0.929 (92). Hu et al. recently tested a nomogram derived from blood biochemical values, with a fair performance (AUC=0.721) in the validation cohort followed up for an average of 3.5 years (93).

So far, such methods have not made their way into clinical practice – there is no widely accessible, validated tool to predict with an acceptable accuracy, which AP patients will progress towards ARP and CP. On the other hand, alcohol and smoking are eliminable risk factors, idiopathic AP can be further explored and there have been further attempts at interventions to reduce the risk of progressive disease.

IV.4.2. Therapeutic measures for preventing progression

The cornerstone of the management of these patients is the elimination of present risk factors. In biliary AP, all guidelines recommend the performance of cholecystectomy (15-19). As discussed above, this leads to the significant reduction of biliary etiology in ARP (mostly still present due to delayed operation or previously unidentified biliary background), and close to no occurrence in CP. The PONCHO trial, the largest RCT to date comparing same-admission versus delayed laparoscopic cholecystectomy in mild biliary AP patients, found no difference in operation-related complications, but a marked reduction in biliary complications favoring the same-admission group (91). While the risk of biliary events and ARP is significantly higher with delayed cholecystectomy, the risk of postoperative (mainly infective) complications is outstandingly high in moderate or severe AP patients undergoing early operation, up to 40-50% in a retrospective analysis (94). Accordingly, guidelines recommend delaying cholecystectomy in moderate / severe cases until the inflammation has resolved, and local complications have either resolved or stabilized (15, 16, 19).

Excessive alcohol consumption and smoking are highly prevalent risk factors in CP, and independent predictors of disease progression (86, 89). Their elimination is a key aspect in the post-episode care of AP patients (17). As adherence to abstinence programs can be low, supervision is important and scientific efforts should be made to develop a program with the best possible compliance and results (95, 96). A RCT of 120 AP patients by Nordback et al. assessed the effects on a single versus a biannually repeated, nurse-delivered intervention against alcohol consumption (97). The repeated intervention significantly reduced the development of ARP (8% vs. 21%), especially 6 months or later after the initial episode (2% vs. 13%). The Hungarian Pancreatic Study Group (HPSG) recently published the protocol of the 'Recurrent acute pancreatitis prevention by the elimination of alcohol and cigarette smoking' (REAPPEAR) RCT aiming to examine the effect of a 3-monthly versus annual nurse-delivered, combined alcohol and smoking cessation program on pancreatitis recurrence and mortality (98).

In non-biliary and non-alcoholic AP, there is a lack of interventions against disease progression, which is in particular an issue in idiopathic AP, associated with ARP and CP development. A meta-analysis of mostly observational studies found that cholecystectomy after an episode of presumed idiopathic AP is associated with a lower recurrence rate (99). Räty et al. randomized idiopathic AP patients to laparoscopic cholecystectomy versus control visits and saw that 5 patients needed to be treated to prevent 1 idiopathic AP (100). These findings further reinforce that many idiopathic AP cases are in fact biliary. Thus the first step

in preventing recurrences in this patient population should be thorough etiological workup, as highlighted above. Nonetheless, additional options are currently lacking and are in high demand.

It seems that aside from lifestyle modification against alcohol and smoking, cholecystectomy in biliary AP, and the extensive etiological workup of idiopathic cases, there is not much else we can do to prevent the progression towards ARP and CP. That is why in the studies making up this thesis, aside from investigating the diagnostic and etiological approach, we decided to focus on further ARP preventive interventions in non-alcoholic, non-biliary AP. One such option, that requires further investigation, is a low-fat dietary intervention, which is frequently recommended in practice, but without convincing evidence.

V. Objectives

Our ultimate goal was to contribute to the field of gastroenterology, specifically in **reducing progression towards ARP and CP after AP**. For this purpose, we used three distinct methods of clinical research:

1. We conducted a **multicentric, international cohort analysis**, comparing both pediatric and adult AP patients with versus without a **family history of pancreatic disease**, to (1) assess whether family history shows an **association with ARP and CP** and to (2) examine the **possible reasons behind familial aggregation**. Knowledge of the answer to these questions can greatly contribute to the prevention of progression towards ARP and CP.

2. We conducted a **systematic review** of all clinical data available on individuals with AP and confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The available case reports were low in quality and they all conducted incomplete etiological workup. This way, we **highlighted the importance of etiological workup**, which is essential for the proper management of AP patients and for avoiding disease progression.

3. We designed and initiated a **RCT comparing the effect of two diets with different fat contents on progression towards ARP and CP after AP**. Dietary fat reduction has long been regarded to help avoid recurrent episodes, but evidence is conflicting, no RCTs are available. If our RCT proves dietary fat reduction to be effective, it would be the first available post-AP intervention in idiopathic cases.

VI. Diagnosis and etiological workup

In the first part of our work included in this thesis, we wished to explore the role of a family history of pancreatic disease and etiological work-up of AP. Both of these are crucial for the long-term management of patients, mainly in determining the risk of progression towards ARP and CP, and identifying factors that can be eliminated in order to reduce this progression. Firstly, it was not clear whether a family history of pancreatic diseases is indeed a prognostic factor of disease progression, also, other factors can lie in the background of familial aggregation aside from genetic – we explored associations with alcohol consumption, smoking, diabetes and hyperlipidemia. The main importance of this question is that these risk factors can be influenced, thus such knowledge can be used for the benefit of patients.

Secondly, the SARS-CoV-2 pandemic provided an excellent opportunity to shed light on shortcomings in the etiological work-up of AP patients. We conducted a systematic review of all the available clinical reports and in the majority of case reports, SARS-CoV-2 was implicated as the cause of AP, without conducting a thorough etiological workup, as recommended by the available guidelines. This of course, is also crucial, as correctly identifying and removing risk factors is the primary method of reducing disease progression.

VI.1. Pancreatic family history doesn't predict disease progression, but connotes alcohol consumption in adolescents and young adults with acute pancreatitis: Analysis of an international cohort of 2,335 patients.

VI.1.1. Introduction

AP is the sudden onset inflammation of the pancreas, elicited by gallstones or alcohol consumption in 70-80% of adult cases (101). In pediatric AP, the picture is much more diverse: biliary obstruction and drugs account for half of the cases, other etiologies are below 5-10% and the rate of idiopathic cases is higher, around 20-30% as opposed to the 10-20% found in adults (102-105). In idiopathic cases, there is a higher possibility of inherited genetic alterations in the background, posing a constant and unamendable risk factor, thus increasing the likelihood of and speeding up progression towards ARP, CP and PC (106). Guidelines recommend that after a second idiopathic AP episode, children should go through genetic testing (76), and adults should receive genetic counseling (not necessarily testing) (15). So genetic background is often established late and often missed altogether – especially in adults or when other etiologies are present. There is however an easily assessable factor that could point towards genetic predisposition, and be useful in such cases: positive pancreatic family history.

The importance of gathering pancreatic (AP, ARP, CP, PC, etc.) family history is well-established in pediatric pancreatitis, with a family history of AP and CP being strongly associated with earlier ARP and CP onset (107), and the guidelines recommend genetic testing after a single idiopathic episode in case family history is present (76). Adult CP guidelines also strongly recommend assessment (100% agreement) (108), however, there is scarce evidence supporting this recommendation – we failed to identify any clinical studies examining the connection between ARP, CP and pancreatic family history. Recent years' literature on ARP

and CP highlights the importance of both the identification of risk factors for disease progression and uncovering underlying mechanisms (109, 110). Thus, even though assessing family history is uncomplicated, examining it poses two major points of importance: observing whether it is a risk factor for disease progression in adults; and mapping associations with possible explanatory factors, to reach a greater understanding of AP, ARP and CP.

Our aim was to examine associations between pancreatic family history, ARP and CP rate, idiopathic etiology, and risk factors of AP in different pediatric and adult age groups. Our findings suggest that: (1) family history should not be used as a prognostic factor for ARP or CP in adults, (2) familial aggregation is mostly due to genetic factors in early childhood and (3) due to increased alcohol consumption and smoking in adolescence and early adulthood.

VI.1.2. Methods

VI.1.2.1. Study design, data collection

This study is a secondary analysis of the international, multicenter, prospective AP registry maintained by the HPSG. Between 2012 and 2019, 2,559 episodes of AP were enrolled in the registry. The diagnosis was established according to the IAP/APA guidelines (15). A list of study sites can be found below (Figure 6 and Table 1). A rigorous, four-tier quality control system was applied to ensure the accuracy of these data. For more details on this system, see the previous publication from this registry by Párniczky et al. (111).

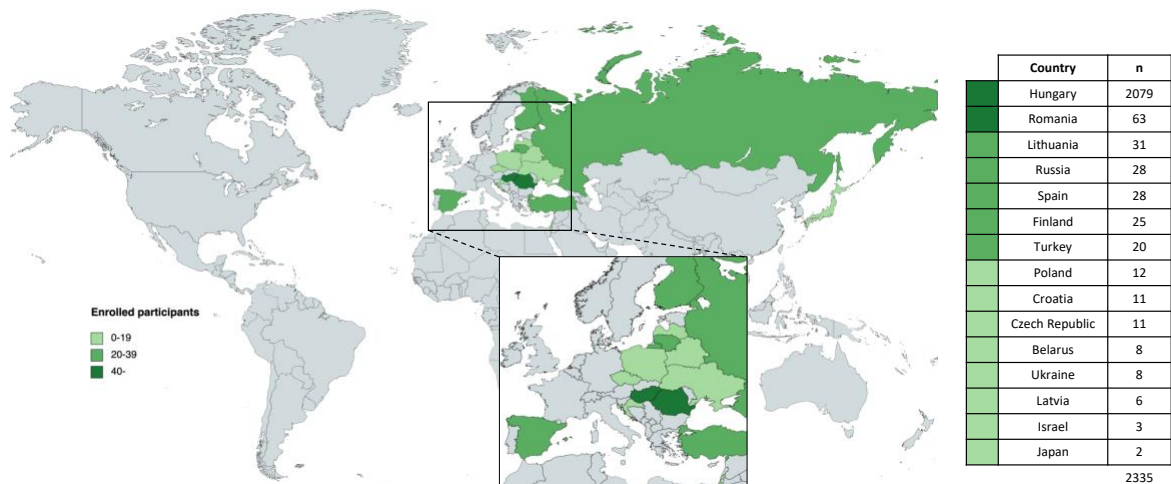| Country	n
Hungary	2079
Romania	63
Lithuania	31
Russia	28
Spain	28
Finland	25
Turkey	20
Poland	12
Croatia	11
Czech Republic	11
Belarus	8
Ukraine	8
Latvia	6
Israel	3
Japan	2
	2335

Figure 6. Distribution of participant enrolment in countries involved. n: number of enrolled participants.

Country	City	Institution	n
Belarus	Gomel	Gomel Regional Clinical Hospital	8
Croatia	Rijeka	Clinical Hospital Center Rijeka	11
Czech Republic	Ostrava	Vítkovice Hospital	11
Finland	Helsinki	Helsinki University Central Hospital	25
Hungary	Békéscsaba	Dr. Réthy Pál Hospital	67
	Budapest	Bethesda Children's Hospital	3
		Bajcsy-Zsilinszky Hospital	113
		Buda Hospital of the Hospitaller Order of Saint John of God	6
		First Department of Pediatrics, Semmelweis University	9
		Pál Heim National Pediatric Institute	10
		Second Department of Internal Medicine, Semmelweis University	2
		Second Department of Pediatrics, Semmelweis University	3
	Debrecen	Department of Internal Medicine, University of Debrecen	165
		Department of Surgery, University of Debrecen	5
	Gyula	Pándy Kálmán Hospital of County Békés	31
	Kecskemét	Bács-Kiskun County University Teaching Hospital	10
	Kiskunhalas	Kiskunhalas Semmelweis Hospital	1
	Makó	Healthcare Center of County Csongrád	10
	Miskolc	Borsod-Abaúj-Zemplén County Hospital and University Teaching Hospital	19
	Pécs	Depatrment of Pediatrics, University of Pécs	9
		First Department of Medicine, University of Pécs	794
	Szeged	Albert Szent-Györgyi Clinical Center of Pediatrics and Child Health Centre	8
		First Department of Medicine, University of Szeged	299
		Second Department of Medicine, University of Szeged	81
		Department of Anaesthesiology and Intensive Therapy, University of Szeged	12
	Székesfehérvár	Szent György University Teaching Hospital of County Fejér	380
	Szentes	Dr. Bugyi István Hospital	21
	Szombathely	Markusovszky University Teaching Hospital	19
	Zalaegerszeg	St. Rafael Hospital of Zala County	2
Israel	Jerusalem	Hadassah Hospital	3
Japan	Tokyo	Keio University	2
Latvia	Riga	Pauls Stradiņš Clinical University Hospital	6
Lithuania	Vilnius	Vilnius University Hospital Santariskiu Klinikos	31
Poland	Kraków	Jagiellonian University Medical College	12
Romania	Bucharest	Central Military Emergency Hospital "Dr Carol Davila"	1
		Grigore Alexandrescu Children`s Hospital, Carol Davila University	8
	Targu Mures	Mures County Emergency Hospital	54
Russia	St. Petersburg	Saint Luke Clinical Hospital	28
Spain	Sant Pere de Ribes	General Surgery, Consorci Sanitari del Garrof	28
Turkey	Istanbul	Hospital of Bezmialem Vakif University, School of Medicine, Istanbul	20
Ukraine	Kiev	Bogomolets National Medical University	8
		Total number of participants	**2335**

Table 1. Distribution of centres and enrolled participants. n: number of participants

VI.1.2.2. Participants

In the present analysis, both adult and pediatric AP patients with available data on the presence/absence of pancreatic family history – including AP, CP, ARP, autoimmune pancreatitis (AIP), PC – were included (2,335 patients, with 2,470 prospectively collected episodes of AP). In our analyses we compared patients with a negative pancreatic family history to patients with a positive pancreatic family history for: AP, CP, ARP, AIP or PC. To observe age-specific changes in our observed variables, we divided the cohort into age-based subgroups: 0-5, 6-11, 12-17, 18-29, 30-41, 42-53, 54-65, 66- years. To avoid arbitrary threshold selection, we adhered to the following rhetoric: we planned to divide children to as many equal age-interval groups as possible; since two groups are not yet informative and four resulted in very low participant numbers, we decided to use three equal age intervals. In case of adult participants we doubled this interval (from 6 to 12 years), since changes are not as swift as in childhood. We intended to maintain the 6 year interval in early adulthood, however, the 18-23 group would have had zero patients with positive pancreatic family history.

VI.1.2.3. Variables

All analyzed variables – including demographical data, data on comorbidities, smoking, alcohol consumption, complications, severity, etiology and number of episodes – are provided in the data quality table (Table 2). We adhered to the revised Atlanta criteria in determining the complications and severity of AP: cases were considered mild if no local complications or organ failure occurred, moderate of local complications and/or organ failure lasting less than 48 hours occurred, severe if organ failure persisted beyond 48 hours. (5). While the prospective data collection period only covers eight years, a detailed personal medical history was taken, especially regarding pancreatic disease, and we accounted for this data in determining the presence of ARP and the number of episodes. Patients were assessed to have 'hyperlipidemia' if their AP was caused by hypertriglyceridemia or if they were diagnosed with a non-transient dyslipidemia.

We compared our examined cohort to the entirety of the AP cases enrolled in our registry, to see whether our analyzed population is representative of the average AP experiencing population. Since almost all patients (96.6%) had data on the presence of pancreatic diseases in the family, our cohort was representative in terms of age, gender, AP severity, mortality, length of hospitalization, and etiology.

EPIDEMIOLOGY, ETIOLOGY	OVERALL	UPLOADED DATA	%
Age	2470	2470	100
Gender	2470	2470	100
Etiology	2470	2470	100
Average uploaded data	*7410*	*7410*	*100*

PERSONAL AND FAMILY MEDICAL HISTORY	OVERALL	UPLOADED DATA	%
Acute pancreatitis in the personal history	2470	2470	100
Number of previous episodes among recurrent cases	517	483	93
Chronic pancreatitis in the personal history	2470	2470	100
History of diabetes mellitus	2470	2466	100
History of non-transient dyslipidemia	2470	2118	86
Family history of pancreatic diseases	2470	2470	100
Average uploaded data	*12867*	*12477*	*97*

RISK FACTORS	OVERALL	UPLOADED DATA	%
Alcohol consumption	2470	2464	100
Smoking	2470	2464	100
Average uploaded data	4940	4928	*100*

OUTCOMES	OVERALL	UPLOADED DATA	%
Severity (mild/moderately severe/severe)	2470	2470	100
Mortality	2470	2470	100
Average uploaded data	4940	*4940*	*100*

| *TOTAL* | *30157* | *29755* | *99* |

Table 2. Data quality. The columns represent the overall number of enrolled participants examined for said variable; the number of participants with available data; the proportion of participants with available data, given as percentage.

VI.1.2.4. Statistical analysis

In case of categorical variables, we calculated event number and percentage of total, and mean and standard deviation (SD) for continuous data. To test for statistically significant differences between groups, the Chi-squared or Fisher exact tests were applied for categorical, the Student t-test for normally distributed continuous and Mann-Whitney U-test for non-normally distributed continuous variables, with an alpha value of 5%. Statistically significant P-values (p) appear in bold.

VI.1.2.5. Ethical approval

The Scientific and Research Ethics Committee of the Medical Research Council granted the ethical approval for this registry in 2012 (22254–1/2012/EKU). The institution's human

research committee approved the protocol for the registry before initiating participant enrolment. We are in compliance with the Declaration of Helsinki, reaffirmed in 2013. All patients provided their written, informed consent in case of participation.

VI.1.2.6. Study reporting
This study was reported according to the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) statement (112).

VI.1.3. Results

VI.1.3.1. Participants
Table 3 shows the characteristics of enrolled participants. A total of 2,335 patients were analyzed, of which 196 (8.4%) had a positive pancreatic family history. These patients were younger at the time of their first enrolment in our registry, and idiopathic AP etiology was more common. Mild disease course occurred significantly more often in case of the first registered AP episode, and any prospectively collected episode belonging to positive pancreatic family history group as well. The total number of episodes / person (accounting not only for registry enrolments but also episodes in medical history) was significantly higher in the positive pancreatic family history group.

	Positive pancreatic family history	Negative pancreatic family history	p
Number of patients	196	2139	
Female sex; n (%)	87 (44.4)	951 (44.5)	*0.984*
Age at first enrolment; years mean±SD	49.2±20.4	55.6±18.2	***<0.001***
AP etiology, first enrolment; n (%)			
biliary	66 (33.7)	868 (40.6)	*0.059*
alcoholic	31 (15.8)	393 (18.4)	*0.374*
hypertriglyceridemia	8 (4.1)	70 (3.3)	*0.546*
any combination of these three	15 (7.7)	92 (4.3)	***0.032***
idiopathic	51 (26.0)	418 (19.5)	***0.030***
other	25 (12.8)	298 (13.9)	*0.648*
AP severity, first enrolment; n (%)			
mild	154 (78.6)	1522 (71.2)	***0.027***
moderate	33 (16.8)	510 (23.8)	***0.026***
severe	9 (4.6)	107 (5.0)	*0.800*
AP severity, any registered episode; n (%)			
mild	168/216 (77.8)	1610/2254 (71.4)	***0.047***
moderate	39/216 (18.1)	533/2254 (23.6)	*0.063*
severe	9/216 (4.2)	111/2254 (4.9)	*0.621*
AP episodes / person; mean±SD	1.74±1.86	1.48±1.29	***0.010***

Table 3. Characteristics of participants. AP: acute pancreatitis; n: number; SD: standard deviation; %: percentage; p: P-value.

Regarding the age-distribution of positive family history: among adults, the observed rate was steadily around 8% (6.4-9.4%), but it was considerably higher in case of children, peaking 6-11 years (40.0%).

VI.1.3.2. Pancreatic family history and ARP, CP

Figure 7a shows the rate of ARP and CP (developed later or already diagnosed) with or without pancreatic family history categorized by the age of the index involvement in the AP registry. Higher rate of ARP was noted in childhood, even more so in the positive than the negative family history groups, but without statistical significance. Overall, a significantly higher rate of ARP and/or CP was found in the positive family history group (33.7% vs 25.9%, p=0.018).
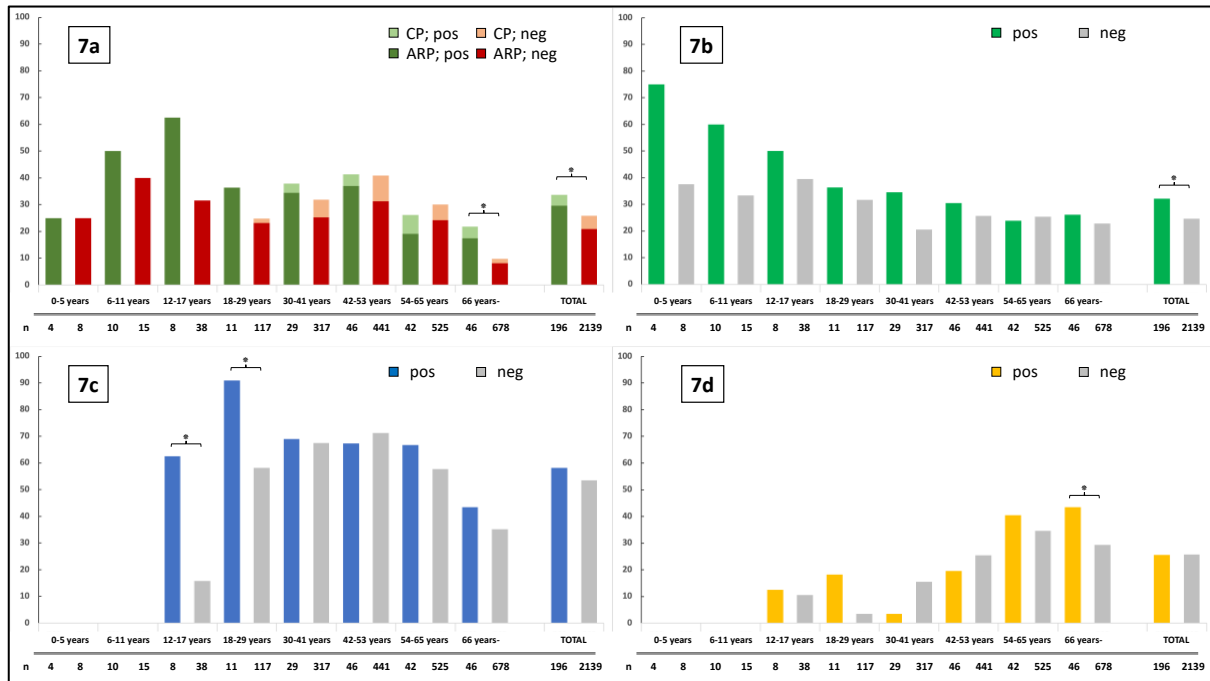

Figure 7. (7a): Rate of acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) in different age groups of acute pancreatitis (AP) patients with positive and negative pancreatic family history; (7b): rate of idiopathic etiology at time of the index AP registry enrolment; (7c): rate of current alcohol consumption and/or smoking at the time of the index AP registry enrolment; (7d): rate of diabetes and/or hyperlipidemia at the time of the index AP registry enrolment. Star sign indicates statistically significant difference between positive and negative pancreatic family history groups (<0.05). n: total number of participants with data on the examined variable; CP: chronic pancreatitis; ARP: acute recurrent pancreatitis; pos: positive pancreatic family history group; neg: negative pancreatic family history group.

VI.1.3.3. Association with idiopathic etiology, alcohol, smoking and metabolic risk factors

Among patients with a negative pancreatic family history, the rate of idiopathic episodes was higher in children (30-40%) than in adults (20-30%). We found an excess of idiopathic etiology in children with a positive family history (75% 0-5 years, 60% 6-11 years) which decreased over time to meet the negative group. Statistically significant difference was found overall (32.1% vs 24.6% in the positive vs negative groups, respectively, p=0.020) (Figure 7b).

We found a significantly higher rate of current alcohol consumption and/or smoking at the index case in the positive family history group in ages: 12-17 years (62.5% vs 15.8%, p=0.013), 18-29 years (90.9% vs 58.1%, p=0.049) but not overall (58.2% vs 53.4%, p=0.204). In the remaining age groups, balanced distribution was found (Figure 7c).

Significant difference between positive and negative family history groups regarding the presence of DM and/or hyperlipidemia at the time of the index case was observed only in

patients 66 years old or above (43.5% vs 29.4% respectively, p=0.044) but not overall (25.5% vs 25.7%, p=0.950), nor in any other age subgroup (Figure 7d).
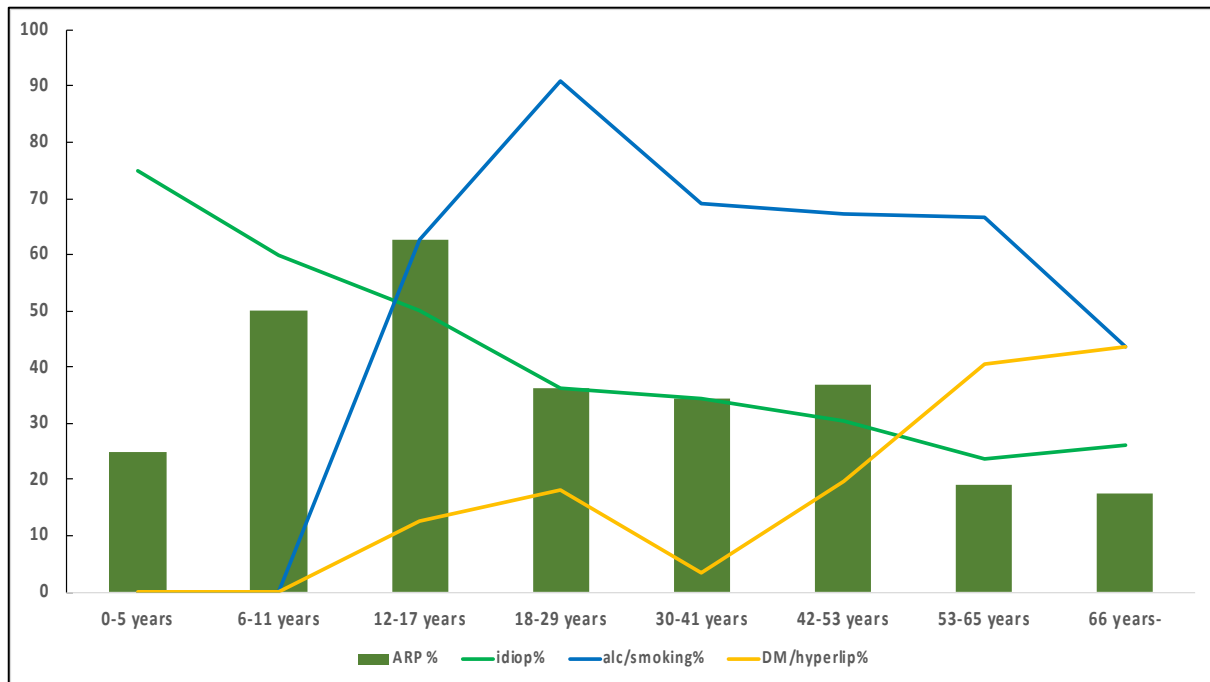

Figure 8. Pancreatitis recurrence rate (ARP%, dark green columns), idiopathic etiology rate (idiop%, light green line), alcohol and/or smoking prevalence (alc/smoking%, blue line) and diabetes and/or hyperlipidemia prevalence (DM/hyperlip%, yellow line) at the time of the index enrolment in the AP registry in the positive pancreatic family history group.

Figure 8 shows the recurrence rate and prevalence of discussed explanatory factors of familial aggregation in the positive pancreatic family history group, to facilitate the interpretation of the above presented results.

VI.1.4. Discussion

In our analysis, we evaluated ARP and CP rates and accompanying factors in different pediatric and adult age groups of AP, according to the presence of pancreatic family history.

Overall, we found a significantly higher rate of ARP or CP in the positive family history group. In the age-based subgroups we observed a consistently higher rate of ARP or CP in the positive groups, but without statistical significance: the reason behind this was a relatively low number of participants in the pediatric subgroups, and only subtle differences in the adult subgroups. It is likely that with higher patient numbers, the marked difference in the pediatric subgroups would be retained and statistical significance would be achieved, reflecting the available evidence. On the other hand, further increasing adult subgroups – while it could lead to significant results – would likely still be a clinically irrelevant difference. In our opinion, family history should not be used as a prognostic factor for recurrence and CP among adults.

The incidence of ARP peaked in those who had their index episode between 6-17 years, the highest percentage difference between positive and negative pancreatic family history groups was noted between 12-17 years.

While the negative family history group had a rate of idiopathic etiology consistently in the 20-40% range, the positive group had an excess of idiopathic AP in the pediatric age groups: peaking at 75% at 0-5 years then steadily decreasing to meet the negative group in adulthood. This is likely due to genetic risk factors being responsible for familial aggregation among pediatric patients, especially in early childhood. No differences in adults are in line with the findings of Jalaly et al., who performed genetic testing in 134 adults with idiopathic AP and found that family history does not predict pathogenic variants (113).

However, next to the decline of differences in idiopathic etiology, another factor emerged at 12-17 years: we found a significantly higher rate of alcohol consumption and/or smoking in patients with a positive pancreatic family history, who had their index episode in this, or the following age group (18-29 years). The most likely explanation is the well-documented association between parental and offspring alcohol consumption: a systematic review found that in 12 out of 12 included studies parents' drinking was predictive of adolescents' alcohol use (114), a cross-sectional study of 982 adolescents found hazardous paternal drinking to be strongly associated (OR=2.90) with use (115). Contrary to the seemingly similar rationale, empirical evidence does not support the association between parental and adolescent smoking (116, 117).

Regarding DM and hyperlipidemia, metabolic risk factors for AP (118, 119), we found low prevalence in pediatric patients, in conformity with low childhood prevalence reported in the literature, 1.93/1,000 for type 1 DM, 0.46/1,000 for type 2 (120) and 2-4/1,000 for familial hypercholesterolemia (121-123). With the onset of childhood obesity, most prominently from early adolescence, the prevalence of type 2 DM and hyperlipidemic states start to rise, transitioning into the higher rate seen among adults: for DM, around 40-130/1,000 in the general adult population, 170-250/1,000 above 65 years (124-127). We expected to see significant differences or at least a tendency favoring the positive pancreatic family history group, since metabolic syndrome and DM both have genetic and learned behavioral components that could lead to their accumulation in the family (128). We only noted such difference above 66 years, with a tendency starting to show in the 54-65 years subgroup.

The prevalence of alcohol consumption, smoking, DM and hyperlipidemia are overrepresented in our cohort as compared to the general population. Quite understandably, these are all likely to accumulate in a cohort of AP patients, as risk factors of the disorder.

VI.1.4.1. Strengths and limitations

To our knowledge, this was the first cohort study to examine the ARP and CP prognostic role of family history in adults, and the first cohort representing both pediatric and adult patients seeking associations between pancreatic family history and clinical factors that could be in the background of this familial aggregation. One of the main strengths of this study is that the participants come from multiple centers, countries and continents, signifying wide representativeness. We applied a uniform data collection, following the same structure in all ages, thus enhancing comparability of adult and pediatric populations. Our patient enrolment encompassed a period of 8 years and the index case in the registry is not necessarily the first AP of the participant – thus we believe that our conclusions regarding ARP rate are valid.

Conclusions regarding CP rate however, should be handled with caution since they are probably underrepresented, especially in the pediatric age groups. Another limitation of this

study is that, even though in proportion to the enrolled adults, the number of pediatric patients is appropriate, it is still relatively low: while we observed the tendencies in ARP, idiopathic etiology and exogenous risk factors that we expected, these associations were not backed up by statistical significance due to low event numbers. It should also be stated that the first AP episode enrolled in our registry is not necessarily the first episode of the individual – although it was in most cases. We performed our analyses this way since our data of interest could not be gathered for non-enrolled episodes without a high possibility bias. Also, though our intent was to examine family history in a purely clinical context, and idiopathic etiology tendency matched our expectations, it is only a surrogate marker – genetic analysis of all patients would have clarified genetic background; this was currently beyond our scope.

VI.1.4.2. Implications
Positive family history most likely signifies genetic background in early childhood. During adolescence and early adulthood, alcohol consumption and smoking emerges – clinicians should be aware of the significant association with pancreatic family history (probably due to harmful consumption in the family) and consider targeted intervention in such cases. Our analysis revealed that contrary to current viewpoints positive pancreatic family history is not a prognostic factor for ARP and CP in adults, so it should not be used as such.

VI.2. Insufficient etiological workup of COVID-19 associated acute pancreatitis: A systematic mini-review

VI.2.1. Introduction

In 2019, a novel coronavirus emerged in Wuhan, China, causing multiple cases of severe pneumonia and launching the SARS-CoV-2 pandemic. The clinical syndrome seen in SARS-CoV-2 infection is called coronavirus disease 2019 (COVID-19). The main clinical symptoms of COVID-19 are fever, cough, myalgia and fatigue (129). Pulmonary involvement is the most frequent (130), but systemic dissociation is seen in severe cases. Furthermore, a significant proportion of patients exhibit gastrointestinal symptoms such as diarrhea, vomiting and abdominal pain. SARS-CoV-2 was also detected in stool specimens (131) and in the cytoplasm of gastric, duodenal and rectal glandular epithelial cells (132).

Viral infections such as mumps, Coxsackie, hepatitis and herpes viruses are known causes of pancreatitis (41). There is a strong possibility that, like other, less common causes of AP, infectious etiology is underdiagnosed on account of insufficient workup of idiopathic cases and cases where an apparent cause (e.g. alcohol consumption) is already established (74, 133, 134). On the other hand, during a pandemic of such proportions, polymerase chain reaction (PCR) testing is made widely available. This will of course lead to a proportion of patients with a variety of diseases, including AP, being diagnosed with SARS-CoV-2 infection. Given the right temporal association, even a more experienced practitioner could be led to ponder a cause-effect relationship between COVID-19 and AP. Even more so, taking into account the often-neglected etiological workup of idiopathic cases and the opportunity to aid the scientific and medical communities by providing information on presumed complications of the infection.

This systematic review aims to assess all publications containing COVID-19 AP cases and to determine the plausibility of an association between the two.

VI.2.2. Methods

VI.2.2.1. Protocol and registration

This systematic review was registered with PROSPERO as "Pancreas involvement in COVID-19: A systematic review" under registration number CRD42020186426. After completing the systematic search, we decided to deviate from the protocol for the eligibility of studies: we narrowed our focus to AP from the original plan of any pancreatic involvement. We did so because slight pancreatic enzyme elevation in COVID-19 patients, reported by two studies (135, 136), has already been discussed by de-Madaria et al. (137) and information on pancreatic cancer patients, reported by three studies (138-140) is at this point far too scarce to even discuss its relation with COVID-19 and effect on outcomes. There were no other deviations from the protocol.

VI.2.2.2. Eligibility criteria

Any study, regardless of design, was considered eligible if it contained the original data on at least 1 SARS-CoV-2-infected individual diagnosed with AP. Only human studies were eligible; studies containing solely animal or in vitro data were excluded.

VI.2.2.3. Systematic search and selection; data extraction

Using the same search key as detailed in the supplementary material, the systematic search was conducted in five databases: Embase, MEDLINE (via PubMed), CENTRAL, Web of Science and Scopus. The last systematic search was carried out on 14 May 2020. The search was restricted to 2020, and no other filters were applied. Citations were exported to a reference management program (EndNote X9, Clarivate Analytics). Two independent review authors conducted the selection by title, abstract and full text based on the previously disclosed, predetermined set of rules. After each selection step, Cohen's kappa coefficient (κ) (141) was calculated. An independent third party settled any disagreements. Citing articles and references in the studies assessed for eligibility in the full text phase were reviewed to identify any additional eligible records. Data was extracted from all eligible studies into a standardized Excel sheet designed on the basis of recommendations from the Cochrane Collaboration (142).

VI.2.2.4. Risk of bias assessment and determination of quality of evidence

The Joanna Briggs Institute Critical Appraisal Checklist for Case Reports (143) was used to assess risk of bias in case reports, and the Newcastle–Ottawa Scale (144) was used for cohorts. Due to the design and quality of the included studies, the 'Grading of Recommendations, Assessment, Development and Evaluations' (GRADE) approach was not used and a very low grade of evidence was automatically established.

VI.2.2.5. Statistical analysis

Only qualitative synthesis was performed; no statistical analysis was carried out.

VI.2.3. Results

VI.2.3.1. Systematic search and selection

The details of the systematic search and selection are presented on Figure 9.
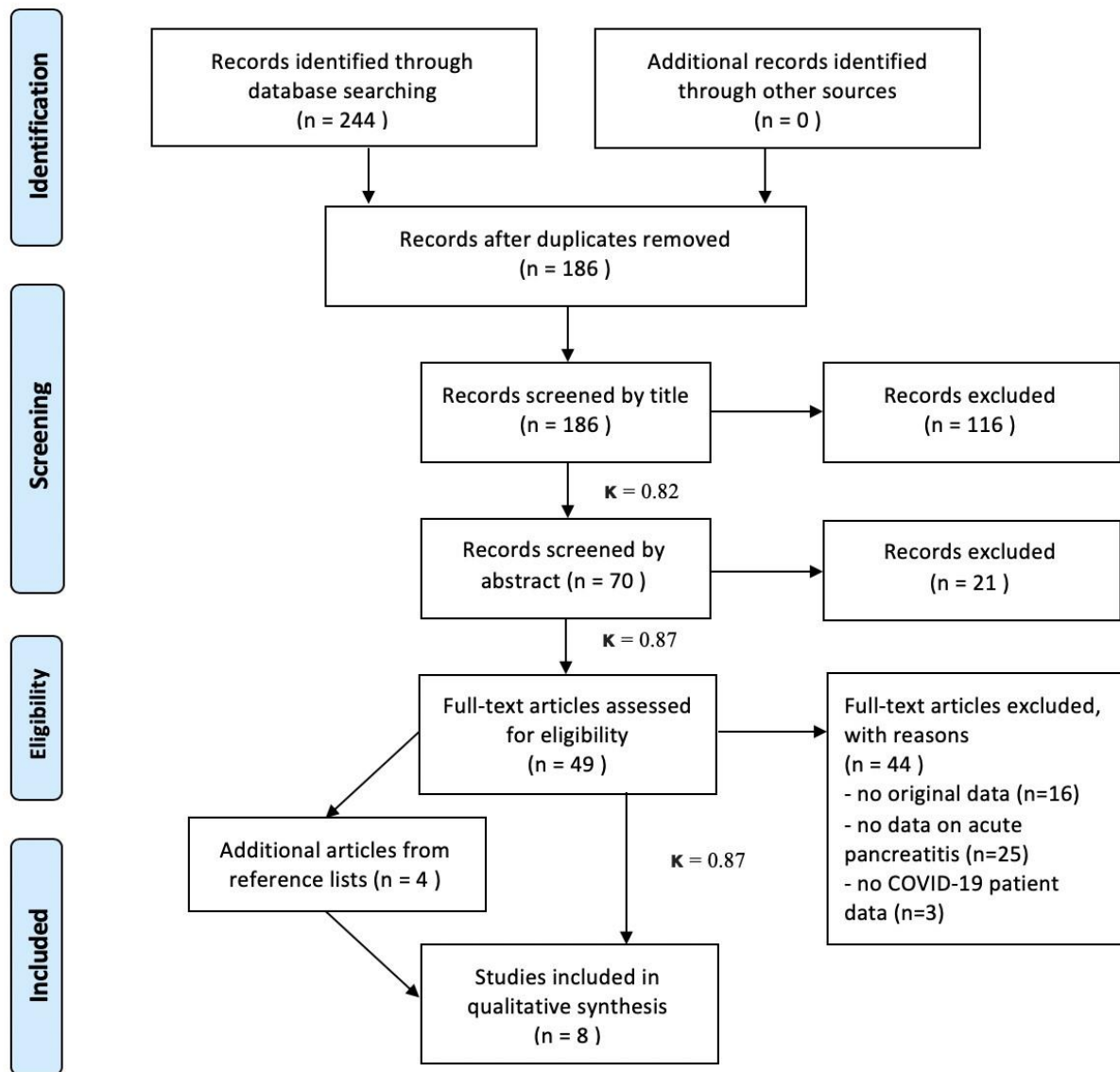
PRISMA 2009 Flow Diagram

Figure 9. PRISMA flow diagram demonstrating selection of studies to be included in the review. K represents Cohen's Kappa values indicating the rate of agreement between selection coordinators.

VI.2.3.2. Characteristics of included studies

In total, six case reports and two retrospective cohort studies were included in this systematic review (see Table 4).

Author (Country)	Study design	Study population	AP n (%)	Description
Aloysius et al. (145) (USA)	Case report	One AP patient with COVID-19	1 (100)	36-year-old obese female presenting with AP. No sign of biliary pathology, denies alcoholism, TG unremarkable.
Anand et al. (146)(UK)	Case report	One AP patient with COVID-19	1 (100)	A 59-year-old cholecystectomized woman with minimal alcohol consumption, readmitted with abdominal symptoms five days after discharge with doxycycline for coinfection. CT showed signs of AP on a formerly atrophic pancreas.
Gou et al. (147) (China)	Case report	Four "pancreatic disease" patients with COVID-19 pneumonia	1 (25)	One female AP (51), biliary etiology confirmed, showed initial COVID-19 symptoms 18 days after admission.
Hadi et al. (148) (Denmark)	Case report	Three family members with COVID-19	2 (67)	Idiopathic AP in mother (68) and daughter (47), both requiring intensive care and ventilation.
Hossain et al. (149) (USA)	Retrospective cohort	119 COVID-19 patients presenting at ER with non-respiratory symptoms	3/32 (9.4)	Out of the 101 instances where abdominal/pelvic CT was obtained, 32 had acute/significant findings, including three cases of pancreatitis. No more information available on these patients.
Li et al. (150) (China)	Retrospective cohort	25 death cases with COVID-19	1 (4)	A 56-year-old male patient had AP as an "underlying disease" – it is not clear whether this is from his medical history or was present concomitantly.
Meireles et al. (151) (Portugal)	Case report	One AP patient with COVID-19	1 (100)	36-year-old female, AP symptoms started on day 11 of disease, US and CT showed no signs of biliary pathology/ischemia. No information on alcohol consumption. Negatively screened for multiple viruses.
Morrison et al. (152) (USA)	Case report	Two cases of acute hypertriglyceridemia in COVID-19 patients	1 (50)	Acute hypertriglyceridemia-induced AP after treatment with tocilizumab, ritonavir, lopinavir, ribavirin, hydroxychloroquine and propofol

Table 4. Characteristics of included studies. AP n (%) is the number (percentage) of patients with acute pancreatitis.

Information on the diagnostic criteria and etiological factors of AP was collected from the appropriate case reports in Table 5. Of the six cases, five fulfilled the diagnostic criteria for acute pancreatitis (15), and in one case (152) enzyme elevation reached the threshold. However, abdominal pain could not be reported on account of the patient being ventilated and sedated, and no imaging findings were disclosed. A case report by Gou et al. was not included in this table, as biliary etiology was determined and COVID-19 symptoms first emerged on day 18 of the patient's hospital stay; thus, the infection was not assumed as an etiological factor (147).

In a retrospective cohort of COVID-19 mortality cases by Li et al., AP is listed as an underlying disease in a single patient without further clarification as to whether it is a past event from the patient's medical history or it occurred during COVID-19-related hospitalization (150). Hossain et al. noted three cases of AP among 119 patients presenting to the ER with non-respiratory symptoms who turned out to have concomitant SARS-CoV-2 infection (149).

Author (country)	Diagnostic workup			COVID-19 (PCR)	Etiological workup									Quality of case reports	
	Abdominal pain	Enzyme elevation (3x)	Imaging		Biliary	Alcohol	HTG (>11.5 mmol/L)	Drug	Hypercalcemia	Ischemia	Auto-immunity	Viral (except nCoV)	Anatomy	JBI Overall rating (/8)	Written according to CARE
Aloysius et al. (USA)	+	+	-	+	?	-	-	-	?	?	?	?	-	3	no
Anand et al. (UK)	+	?	+	+	?	-	?	+	?	?	?	?		0	no
Hadi et al. (Denmark)	?	+	+	+	?	-	-	?	-	+	?	?	?	4	no
	+	+	?	+	?	?	?	+	-	+	?	?	?	2	
Meireles et al. (Portugal)	+	+	-	+	?	-	-	-	-	-	-	-	-	1	no
Morrison et al. (USA)	?	+	?	+	?	?	+	+	?	+	?	?	?	1	no

Table 5. Diagnostic and etiological workup and quality assessment of the studies. The Atlanta criteria were used for diagnosis. Biliary microlithiasis was included in the "biliary" etiology, so an EUS or MRCP was needed to rule out this factor. Ischemia was considered in the case of shock and vasopressor therapy and was ruled out by angio-CT. Anatomical malformations were ruled out by CT. The two columns on the right demonstrate the quality of included case reports based on risk of bias according to the overall Joanna Briggs Institute (JBI) Critical Appraisal score and adherence to Case Report (CARE) guidelines on reporting cases.

VI.2.4. Discussion

The multiple hit theory can be implemented in the pathogenesis of AP (153); therefore, information on possible contributing factors was collected for each case (Table 5). Multiple etiological factors are often responsible for AP (153), but the lack of proper workup often leads to cases being deemed idiopathic or an important factor not being discovered due to the presence of a more convenient diagnosis (133). In addition to the established etiological factors, various mechanisms have been postulated as the cause of pancreatic damage in COVID-19.

SARS-CoV-2 enters epithelia through the angiotensin-converting enzyme 2 (ACE-2) (154), which is abundantly expressed in the pancreas. SARS-CoV-2 RNA and protein were also shown by in situ hybridization and immunohistochemistry from autopsy samples of infected patients' pancreas (155). Aloysius proposed that virus replication may have a direct cytopathic effect or elicit pancreatic cell death as a consequence of the immune response (145). Furthermore, microvascular injury and thrombosis have been described as a consequence of COVID-19 (156, 157), which, complicated with shock and gastrointestinal hypoperfusion (158), could also cause pancreatic damage (159).

However, a cause-effect relationship has not been investigated directly so far. Also, before entertaining the possibility of a new virus as a causative agent in cases where no apparent

etiological factors are present, other, less frequent causes of AP must be considered. In such cases, the IAP/APA recommendations should be followed (15, 74, 133).

For instance, drugs used in treating COVID-19 may cause pancreatic damage directly or indirectly. A patient whose case was presented by Anand et al. as idiopathic AP was on a course of doxycycline, which is a drug with a documented probable association with pancreatitis (160). Several drugs currently used or being considered for COVID-19 might play a role in the pathogenesis of pancreatitis, such as enalapril, asparaginase, estrogens and steroids (160). Hypertriglyceridemia, another established etiological factor frequently neglected, can also occur as a consequence of therapy, as in the case described by Morrison et al. (152). Not only tocilizumab (161), but propofol and ritonavir could also have been responsible for the elevation of serum triglyceride levels in this case (162). Hypertriglyceridemia-associated drug-induced AP was observed (163, 164) in association with the following drugs being tested for COVID-19 according to our search on clinicaltrials.gov: lisinopril, asparaginase, estrogens, isotretionin, steroids, propofol and ruxolitinib.

In a case reported by Aloysius et al. (145), there are no apparent etiological factors present in the description. Even so, the report does not describe any further efforts to identify the seemingly idiopathic etiology, such as EUS. While Meireles et al. thoroughly ruled out AP-associated viruses and even screened for antinuclear antibodies (ANA), they also did not utilize EUS during the etiology search.

Other than the highlighted problems tied to the etiological workup, we would like to briefly address an issue with diagnosis. Two studies not included in this review (135, 136) labeled patients with serum amylase and/or lipase values higher than the upper limit of normal to possess "pancreatic injury". As de-Madaria et al. pointed out (137) in reflecting on Wang et al. (135), the elevation of pancreatic enzyme levels in the blood is not necessarily a consequence of an insult to the pancreas. Possible reasons are high prevalence of renal impairment and diabetes mellitus, gastroenteritis and metabolic changes, such as acidosis, or even salivary glandular entry by SARS CoV-2 [37-40] (165-168). More importantly, a slight elevation in serum amylase and/or lipase levels alone is not established as an indicator of pancreatic damage. The Atlanta diagnostic criteria should be applied when determining the presence of AP (15).

The case reports in our review carry considerable risk of bias and their deviation from the CARE guideline (169) on reporting methods. As demonstrated, the etiological workup of patients was incomplete, and often COVID-19 was named as the causative agent of AP, while other established factors were also present.

Considering limitations, incomplete reporting of the included studies encompasses a high risk of bias in our analysis.

To conclude, we strongly emphasize the need for guideline adherence when diagnosing and uncovering the underlying etiological factors of AP, even during a pandemic. As specific therapeutic options (15) are available depending on etiology, neglecting these steps can hinder direct therapy and lower the chances of recovery, while increasing the probability of complications and recurrent episodes.

VI.2.4.1. Implications…

…for practice: Appropriate diagnostic and etiological workup of AP is strongly recommended and bears therapeutic consequences.

…for research: Higher-quality clinical data supported by basic science findings are required to evaluate a possible causative association between SARS-CoV-2 and AP.

…for editors: The demand for the fast dissociation of knowledge should not lower the quality of research published in scientific journals.

VII. Interventions against disease progression

Knowing what risk factors lie behind familial aggregation and the correct establishment of AP etiology have one main point of importance: avoiding disease progression. If we identify a risk factor that can be eliminated, efforts can be made towards elimination. However, if we identify a risk factor that cannot be eliminated (i.e. genetic mutations) or we conduct a thorough investigation and fail to identify a risk factor, there is not much we can do, but stay on high alert and avoid all other possible risks (alcohol consumption, etc.). We aimed to find and additional way of avoiding / delaying disease progression, by initiating a RCT, in which we investigate the effect of dietary fat reduction on AP recurrence, an intervention frequently recommended, although yet without sufficient evidence.

VII.1. The EFFect Of dietary fat content on the Recurrence of pancreaTitis (EFFORT): protocol of a multicenter randomized controlled trial

VII.1.1. Introduction

Around 10-30% of patients with AP will develop ARP and 10% progress to chronic pancreatitis CP (77). While interventions exist to avoid recurrences in the case of the two major etiologies – abstinence in alcoholic AP and cholecystectomy in biliary AP – there are no preventive therapeutic options for patients with idiopathic ARP. One possibility would be to comply with a low-fat diet, which is widely recommended to AP patients, regardless of etiology.

Though it is indeed frequently recommended, maintaining a low-fat diet after AP is not included in any of the guidelines (15-17) and evidence is scarce. In a prospective cohort of more than 36,000 participants, Prizment et al. found increased total and saturated fat intake to be associated with AP (170). Setiawan et al. observed a positive association between saturated fat intake and gallstone-related AP, but not with non-gallstone-related AP, ARP or CP (171). Oskarsson et al. prospectively studied a cohort of non-gallstone-related AP patients with no clear associations between overall diet quality and pancreatitis recurrence or progression (172). Aside from the recognized connection between high fat intake and gallstone formation, thus biliary AP (173, 174), there are hypotheses as to why fat excess could be a risk factor for non-biliary pancreatitis as well. One possible reason can be the elevated serum triglyceride (TG) levels, a known etiological factor for AP, stimulating free fatty acid production which is believed to be pancreatotoxic (46, 170, 175, 176). Zhang et al. found that a chronic high-fat diet in rats increased levels of pancreatic free fatty acids and lipid peroxidation, associated with pancreatic injuries and collagen synthesis via activated pancreatic stellate cells (177). Animal experiments have also described a more severe AP course in animals on high-fat diets (178).

While the aforementioned cohort trials boast an impressive number of participants, the study design is not suitable to determine a cause-effect relationship between dietary fat content and pancreatitis recurrence.

Our aim was to conduct a RCT comparing two low-fat diets that contain the same amount of calories and protein but have different fat contents (15 and 30% respectively) in order to determine the effect of dietary fat content reduction on AP recurrence. We wanted to include patients with idiopathic ARP as this is the group without a preventive therapeutic option. Our

hypothesis is that while patients on both arms will benefit from receiving nutritional guidance, those with less fat in their diet will see an additional benefit due to the further reduction in serum lipids.

VII.1.2. Methods, design

VII.1.2.1. Trial design, study setting

This study will be a multicenter, prospective, parallel-group RCT with a superiority framework. Participants will be randomly assigned in a 1:1 ratio to one of 2 different dietary interventions which are: a 'reduced fat diet'-arm and a 'standard healthy diet'-arm (largely based on WHO recommendations) to be further detailed in the 'Interventions'-section of this protocol.

The chief study site will be an academic hospital (1st Department of Medicine, Medical School, University of Pécs in Pécs, Hungary), other academic hospitals and hospitals with internal medicine departments regularly treating AP both in and out of Hungary will be invited to join the study. List of study sites can be obtained at clinicaltrials.gov.

VII.1.2.2. Eligibility criteria

The inclusion and exclusion criteria for this trial are detailed in Table 6. A participant must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for enrolment.

Inclusion criteria

1. Individuals with at least two episodes of acute pancreatitis in the 2 years preceding the inclusion with

2. The last episode being idiopathic, who are

3. At least 14 years old.

Exclusion criteria

1. Individuals already receiving regular nutritional guidance (with medical indication),

2. Individuals in critical condition or in terminal stage of cancer (with an expected survival <2 years) ,

3. Individuals undergoing treatment for active malignancy,

4. Individuals with known cholecystolithiasis,

5. Individuals with uncontrolled diabetes mellitus (admitted lack of compliance with antidiabetic therapy / HbA1c ≥7% / indication of uncontrolled diabetes mellitus in last 24 months' anamnesis / newly discovered diabetes mellitus)

6. Individuals who are pregnant or nursing

7. Individuals with a BMI < 18.5

8. Individuals who are regularly receiving systemic corticosteroids

9. Individuals consuming more alcohol than: 5 units per day or 15 units per week for men; 4 units per day or 8 units per week for women.

Table 6. Inclusion and exclusion criteria. One unit of alcohol equals 10 ml or 8 g of pure alcohol. HbA1c: hemoglobin A1c; BMI: body mass index.

VII.1.2.3. Interventions

Participants will be randomly assigned in a 1:1 ratio to one of 2 different dietary interventions which are as follows: (1) a 'reduced fat diet' in which the daily calorie intake will be composed of 15% fat, 65% carbohydrates, 20% proteins; (2) a 'standard healthy diet' (which also qualifies

as a low-fat diet and is largely based on WHO recommendations) in which the daily calorie intake will be composed of 30% fat, 50% carbohydrates and 20% proteins.

Diets will be individualized to each participant. We will provide, for both arms, recommendations and meal-plans prepared every 200 kcals between 1800 and 3000 kcal. Before performing the dietary intervention, study dieticians will be required to use one of these sample diets and tailor it to the exact calorie needs of the participant (and if necessary, make alterations based on the country of the enrolling center).

Consultations will take place in an outpatient setting. When assigned to an intervention, first, patients will complete a food frequency questionnaire (FFQ – the National Health and Nutrition Examination Survey FFQ) to assess their eating habits. Then, based on their assigned intervention group they will receive recommendations according to the given diet. These consultations will be conducted by study dieticians centrally trained and evaluated by a qualified dietician coordinator. Relatives of the participants will also be allowed to attend these consultations, since the cooperation and involvement of family members can augment adherence and it is possible that the participant is not personally involved with the alimentation of the household.

The FFQ applied in this study is not only capable of assessing fat, carbohydrate and protein consumption but will provide a more detailed breakdown of dietary intake. Such detail is needed to account for other dietary variables possibly skewing data (not very likely due to randomization) and to conduct subgroup analyses – for details, see 'Statistical analysis plan'.

VII.1.2.4. Discontinuation criteria

Participants will be advised to discontinue their allocated intervention (through personal communication or if impossible, other means – phone, e-mail, mail) if any of the following happens:

(1) The participant withdraws his/her consent, (2) fails to attend two consecutive visits (3) develops one of the conditions mentioned in the exclusion criteria, or (4) completes the study. In these cases, participants will be advised to keep a balanced diet (according to WHO recommendations) with appropriate amount of calories to their age, gender, body weight and physical activity (179).

Based on any positive results of our study, dietary recommendation for this patient population might change and testing the long-term effect of these diets on pancreatitis recurrence, progression to CP and mortality might become necessary in form of a separate controlled trial.

VII.1.2.5. Adherence

Compliance with dietary interventions is often problematic, this was taken into account when estimating the required sample size. We will, however, attempt to augment adherence via a repeated dietary intervention at the second visit, by completing FFQs with participants with the explicit purpose of estimating adherence and by reminding participants that through the evaluation of their BMI, laboratory results and FFQs we will have a good overview on whether or not they complied with the recommendations. These data will also be used to give motivational feed-back to the participants at the second visit.

Additionally, before participants consent to take part in the study they will be provided with detailed information on the composition and fiscal aspects of both diets so as to reduce drop-

outs after-randomization. Our center will also maintain a "hotline" – a telephone number that can be reached during working hours to answer questions that emerged regarding the diet.

VII.1.2.6. Concomitant care
Concomitant interventions that do not categorically alter the diet of participants will not be limited.

VII.1.2.7. Outcomes
VII.1.2.7.1. Primary outcome measures
The primary outcome measure for this trial will be (1) a composite endpoint: the recurrence of AP (given as a rate of event) AND/OR all-cause mortality.

VII.1.2.7.2. Secondary outcome measures
Secondary outcome measures will be the following: (1) Pancreas-specific mortality; (2) Cardiovascular cause mortality, (3) newly diagnosed CP, (4) changes in BMI compared to baseline (both total and percentage), serum lipid parameters (values and change from baseline), including: (5) total cholesterol, (6) TG, (7) HDL-cholesterol and (8) LDL-cholesterol; (9) serum albumin value and change from baseline, levels of (10-13) vitamins A, D, E and K (value and change from baseline); (14) blood pressure (systolic and diastolic) values and change compared to baseline. We will also assess (15) current smoking at the time of each visit, (16) adherence to dietary recommendations (as determined by the results of a food frequency questionnaire); (17) adverse events (given as rate of events). We will also assess (18) quality of life with the EQ-5D-5L questionnaire (see in supplementary material) and (19) muscle strength using a handgrip dynamometer (value and change from baseline for both).

VII.1.2.8. Additional data collected at baseline
The index visit will entail an additional patient questionnaire and retrospective chart review collecting data on: comorbidities (diabetes, hypertension, chronic heart disease, chronic kidney disease, chronic liver disease, stroke, etc.), socioeconomic status (education, occupation, income, subjective social status) and past pancreatic history: how many episodes of AP, etiology of former episodes, is CP present. In case the patient has a new episode of AP during the study period, its etiology will also be recorded.
Data collection forms are available in our supplementary material.

VII.1.2.9. Biologic sample collection
At enrollment and every visit, basic laboratory tests from blood will be carried out and participants will provide blood for storage in the biobank.
Laboratory parameters measured are shown on the data collection forms in our supplementary material. In case of alarming laboratory results, a physician will be notified, who will decide whether further medical attention is necessary. All patients will receive the results of their laboratory tests in written form.
The samples in the biobank will be stored at $-80°C$ and identified by the personal identification number (PIN) given at study entry. All samples will be collected and sent together to the laboratory when the patient number reached the pre-set goal for analysis.

From the collected biological samples, we will – for not diagnostic, but research purposes – conduct genetic analyses. In case the result of these analyses contains information that impacts the health of either the participant or their relatives, we will inform them via one of the provided methods of availability.

VII.1.2.10. Participant timeline

All participants will appear at the study site according to the study schedule (Table 7).

To determine eligibility, physical examination, BMI measurement, laboratory testing and a review of the individuals' medical history and documentation in order to rule out AP with an established etiology will be performed. At the time of allocation and before receival of the intervention baseline values for outcomes (4-15, 18, 19) will be collected and participants will be physically examined as well as a FFQ will be completed with the help of a study administrator, all in an outpatient setting. All outcomes will be assessed at 3, 6, 12, 18 and 24 month visits. Participants will receive a repeated dietary intervention at months 3, 6, 12 and 18.

STUDY PERIOD	Screening -4 – 0 weeks	Allocation 0 week	Visit 2 3 months	Visit 3 6 months	Visit 4 12 months	Visit 5 18 months	Close-out 24 months
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS (dietary consultation)							
Reduced-fat group		X	X	X	X	X	
WHO-diet group		X	X	X	X	X	
ASSESSMENTS:							
Physical examination	X	X	X	X	X	X	X
BP, HR measurement		X	X	X	X	X	X
BMI measurement	X	X	X	X	X	X	X
Laboratory testing	X	X	X	X	X	X	X
Handgrip test		X	X	X	X	X	X
Food Frequency Questionnaire		X	X	X	X	X	X
Quality of life		X	X	X	X	X	X
Comorbidities, socioeconomic status, pancreatic history		X					

Table 7. SPIRIT schedule outlining timing of interventions and assessments. WHO: World Health Organization; BP: blood pressure; HR: heart rate; BMI: body mass index. This table is the author's own work.

VII.1.2.11. Sample size

As there are no similar studies to date, we will employ a two-stage trial design – we estimated a likely accurate participant number of 384 accounting for drop-outs, equally allocated (192-

192) to both intervention groups which we will refine according to the results of an interim analysis performed at the time of reaching 50% (n=192) of the planned participant number. We based this preliminary estimate on (1) recurrence rates among patients with at least 2 episodes of AP within 2 years from the HPSG AP registry and (2) an RCT conducted by Nordback et al. (97) examining the effect of two types of alcohol-intervention on pancreatitis recurrence.

VII.1.2.12. Recruitment
Recruitment will be performed in 2 distinct ways: (1) patients can be asked to participate during their pancreatitis-associated hospital stay, or (2) eligible patients identified through medical database search can be contacted with a proposal of participation. The planned start of recruitment is 2021.07.01. with a proposed end of 2026.07.01.

VII.1.2.13. Sequence generation, allocation concealment mechanism
Central randomization will be used with randomly permuted block size and allocation ratio of 1:1 using a computer-generated random sequence. Participants will be stratified based on (1) the presence of CP and (2) the presence of DM. Inclusion criteria and exclusion criteria will be checked prior to computer-aided randomization via an online platform to ensure that only eligible patients are included in the trial. The platform generates a PIN. The computer-aided randomization ensures allocation concealment. The randomization procedure will be performed by the same person who screened and consented the patient.

VII.1.2.14. Blinding
Due to their role in delivering the individualized dietary intervention, study dieticians cannot be blinded to the group of the participants. Since they complete the FFQs with the participants, the assessment of dietary habits will not be blinded. Doctors caring for the participants and assessors of all other outcomes (laboratory parameters, BMI, blood pressure, adverse events) as well as statisticians handling the data will be blinded to the participants' allocated group. Participants will also be blinded – they will be informed of the trial structure and that they will be randomized to one of two diets with different dietary fat contents but they will be warned in advance that dieticians will not reveal to them whether they are in the 'reduced fat diet' arm or the 'standard healthy diet' arm. Naturally, they will be informed and allowed to ask in detail regarding the composition of these two diets, but it is our firm belief, that based only on this information and the meal-plan that the dietician will give to the participants, the vast majority will not know which arm they are on.

VII.1.2.15. Data management, analysis and monitoring
VII.1.2.15.1. Data management and monitoring
Investigators will be responsible for the accuracy, reliability and quality of the collected data. Detailed data flow will be described in a Data Management Plan. Data from completed electronic case report forms (eCRFs) will be validated under the direction of the Data Manager on the DMC according to a Data Cleaning Plan. Any missing, implausible, or inconsistent recordings in the eCRFs will be referred back to the Investigator using a data query form and will be documented for each subject before clean file status is declared. All changes to eCRFs will be recorded.

The DMC will perform an independent assessment of trial-related documents and activities to ensure respect for subjects' rights, safety and well-being and to guarantee the plausibility of clinical data. The similarity of groups at baseline will also be checked.

After written consent of the subjects, data will be recorded by the investigators. Clinical research data will be processed separately from participants' personal data. Data may only be accessed by persons acting under the authority of the controller and in accordance with the authorization system established within the controller's organizational structure, only to the extent and in the manner necessary for the performance of tasks. Personal data will not be made accessible to third parties.

VII.1.2.15.2. Statistical analysis plan

In the final analysis, the intention-to-treat analysis will be favored over per-protocol (or "as-treated") analysis. We expect there will be no missing data for the primary outcome. In case there is, we will use available case analysis. The "last observation carried forward" strategy will be followed to impute missing data for other outcomes measured during the study, including data from the National Health Insurance Fund (or similar organizations in case of foreign centers).

In descriptive statistics, the count and percentage will be provided for each treatment arm for binary outcomes. For continuous outcomes, n, mean, median, interquartile (Q3–Q1), standard deviation, minimum, and maximum values will be provided for each treatment arm. In a univariate comparative analysis, we will calculate relative risk with 95% confidence interval (CI) when comparing the primary endpoint between two groups (alpha=5%) with a reference arm using non-repeated intervention complemented with chi-square or Fisher's exact test (the same strategy will be followed for binary secondary outcomes). For continuous variables, we will use t-test assuming unequal variances or the Mann-Whitney test. We will perform univariate (Kaplan-Meier and Cox-regression) and multivariate (Cox-regression) survival analysis for binary outcomes. An adjustment will be carried out at least for age, sex, BMI, smoking and education.

Results derived from the FFQs of the patients will give ground for subgroup analyses based on dietary factors. Pre-planned subgroup analyses will be based on: dietary adherence, alcohol consumption, daily calorie intake, true fat consumption, unsaturated and saturated fat consumption, trans-fat consumption and processed food consumption. We are also planning to conduct subgroup analyses based on the presence of known genetic variants in AP.

All analyses will be carried out with SPSS version 26 and Stata version 15.

VII.1.2.15.3. Trial organization, committees and boards

The corresponding center of the EFFORT study is the Centre for Translational Medicine at the University of Pécs Medical School (www.tm-centre.org), whereas the coordinator and designer research team is the HPSG (https://tm-centre.org/en/study-groups/hungarian-pancreatic-study-group/). The HPSG has been running high-quality international, multicentre clinical trials since 2014 (180-183) and has published relevant guidelines for pancreatic diseases to improve patient care in pancreatology (76, 184).

The Steering Committee (SC) will be led by PH (principal investigator, gastroenterologist, specialist in internal medicine and clinical pharmacology). SC members will be MFJ (study

coordinator), NF (biostatistician); ZsV (dietician coordinator); FI, LCza, MP, AP (center representatives). There will be independent members as well, and the SC will include a patient representative. The SC will supervise the trial primarily and will make decisions regarding all critical questions (e.g., premature termination of the study, dropouts, etc.).

All data gathered for research purposes will be handled confidentially and anonymously, which will be ensured by the Data Monitoring Committee (DMC). For each participant, a PIN will be generated that will be present on all forms and documents of each individual.

The International Advisory Board (ITAB) will include MW, SJP, FJ and GC.

The study was designed by the SC and was supported by the University of Pécs, Medical School. The sponsor had no role in the design of the trial and will have no access to the randomization codes or the data.

Five eligible patients were invited to review the protocol and to discuss any concerns or doubts that emerged. Remarks made during this meeting were incorporated into the final version of the protocol. The participant prospects positively responded to the concept of the study and highlighted its importance, agreed that the primary outcome was crucial. They deemed the forms and questionnaires understandable and appropriate. We originally planned only 2 follow-ups at months 12 and 24, but upon discussing it with the participant prospects they highlighted the importance of frequent controls in supporting dietary adherence, thus we modified the study schedule to include more visits. We also added the option of calling for dietary advice and for relatives to attend the dietary consultation to augment adherence, as described in the 'Adherence' and 'Description of interventions' sections of the protocol. The participant prospects described no negative feelings or ethical concerns regarding blood sample tests and the two interventions used in the study.

The independent Safety Monitor will be LCzo. The monitor will ensure the safety of the patients.

VII.1.2.15.4. Interim analyses

(1) Upon reaching 10% of the target sample size an interim safety analysis will be performed wherein the Safety Monitoring Board will review data of the patients and determine whether the occurrence of any negative effects can be linked to any of the interventions and if needed the given intervention or the trial will be terminated for the safety of the patients.

At the point of the safety analysis, patient data will only be made available to the Safety Monitoring Board and they will make the final decision whether or not to terminate the trial.

(2) Upon reaching 50% of the target sample size an interim analysis will be performed in order the refine the number of participants necessary to complete the trial (see 'Sample size').

VII.1.2.15.5. Safety

As our primary interest was the safety of participants, we did not overstep the WHO recommended maximum 30% fat intake (which already qualifies as a low-fat diet) just to better observe differences in AP recurrence. Maintaining such a balanced diet or a diet with an added reduction in fat content similar to what we aim to assess poses no health risks whatsoever. Adverse events in these cases might be due to a formerly excessive eater attempting controlled intake, such as irritation, fatigue, maybe headache. Other minor and moderate events may occur, but we expect no serious side effects with either of the interventions. In case a potentially

serious health problem is detected by the investigators related to the intervention, the Safety Monitoring Board will be notified. To avoid detection bias in assessing adverse events doctors conducting patient examination will be advised to ask all patients about the presence of nausea, abdominal pain and changes in stool.

The frequent dietary monitoring will also allow for the prompt recognition and treatment of malnourished participants.

Upon reaching 10% of the target sample size an interim safety analysis will be performed wherein the Safety Monitoring Board will review data of the patients and determine whether the occurrence of any negative effects can be linked to any of the interventions and if needed the given intervention or the trial will be terminated for the safety of the patients.

VII.1.2.16. Ethics, dissemination

This trial is registered on clinicaltrials.gov (NCT04761523).

This study was approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (40304-11/2020/EÜIG), on 2020.08.17.

Planned start of patient recruitment: 2021.07.01.

Anticipated study duration: 5-6 years.

Study results will be published in an international scientific journal. Study sponsors have no role in writing the publication, deciding to publish and choosing the target journal.

VII.1.2.17. Protocol amendments

In case of any changes and deviations from the original protocol, investigators and past participants will be contacted via email, letter, or phone; future participants will be notified in person during inclusion; deviations from the original protocol will be indicated on clinicaltrials.gov and in any and all publications originating from the acquired data.

V.1.2.18. Consent

Informed consent for participation in the study and providing biological samples will be collected by medical doctors. For a model adult consent form see our supplementary material, that can be obtained via viewing the online publication (open access). Consent forms are tailored to the age of the participant, each having received ethical approval.

VII.1.3. Discussion

It has been a long-standing conviction that dietary fat content, even in the absence of immoderate calorie intake and putting biliary factors aside, can influence pancreatic pathogenesis. This study is the first to test this hypothesis in a randomized, controlled setting. The results of our study will determine the effect of modifying the dietary fat content on AP recurrence, mortality, serum lipids and weight loss in idiopathic ARP cases ie. the patient group in which there is a dire need for interventions to positively influence the course and progression of the disease.

VII.1.3.1. Strengths and limitations

The main strength of this study is that it is the first RCT to test the effect of dietary fat content on pancreatitis recurrence, thus providing high quality evidence for one of the central questions of pancreatology.

Limitations: As we tried to counteract the expected low event rate and finer differences between interventions with a select population of frequent relapsers and a larger estimated sample size it is likely that enrolment will be slow. This could be ameliorated by multiple centers joining and supplying eligible participants already in their care. While it will provide insight on the effect of dietary fat content on recurrence, this comparison in itself is unsuitable to determine the effect of a low-fat diet compared to not dieting / excessive eating. We did not include such an arm as we found it unethical to not provide an individual with dietary recommendations after AP. However, we plan to estimate this effect, by comparing the groups with the best and worst dietary adherence based on the result of FFQs.

VII.1.3.2. Implication for research: ketogenic diet

Originally, we planned to include a 3rd arm in our trial: a ketogenic diet arm. Several meta-analyses of RCTs compare such a diet to a low-fat diet in healthy individuals, or patients with malignancies, observing a favorable effect on diastolic blood pressure (DBP), serum TG and HDL-cholesterol levels (185-188). However, issues regarding feasibility emerged. A ketogenic diet arm would have significantly raised the required patient number while introducing additional exclusion criteria to an already select patient population. Interview of participant prospects (see 'Roles and responsibilities) also revealed a low willingness to adhere with this diet. However, we encourage fellow researchers to pursue the possibility of the beneficial effect of ketosis on disorders of the pancreas.

VIII. Discussion

VIII.1. The role of genetics and family history

While guidelines and the available evidence are explicit regarding the importance of routine laboratory tests and imaging modalities in determining the etiology and further examining presumed idiopathic cases, the certainty of current recommendations is less clear when it comes to genetic analysis. As stated above, the IAP/APA guidelines recommend that if after thorough investigation the etiology of AP remains unspecified and especially after more than one episode, the patient should undergo genetic counseling (not necessarily genetic testing) (15). Pediatric guidelines recommend genetic testing in case of two or more episodes of AP, or even after a single episode in case of a family history of pancreatic diseases (76).

Growing evidence suggests, that the progression from AP towards ARP and CP can have strong genetic components, mostly in idiopathic cases, but next to other etiological factors (e.g. alcohol consumption) as well (189). The value of genetic testing currently mainly lies in determining whether this risk increasing factor exists or not, and in case it does, knowledge of the exact mutation can allow for risk assessment and genetic counseling regarding inheritance patterns. Some authors suggest that genetic testing should be performed in young (in some papers <25 years) individuals with idiopathic AP, and in patients with ARP or CP and a family history of pancreatic diseases (190, 191). With the continuing improvement of genetic analysis methods, recommendations on performing genetic testing will likely spread to include all ARP and CP patients. However, the ultimate goals in this area – personalized medicine and targeted gene therapy – are still further down the line.

It should also be stated that, as we demonstrated in our cohort analysis included in this thesis, a family history of pancreatic disease does not necessarily convey pancreatitis risk-increasing genetic mutations. Our data suggests that alcohol consumption (possibly via genetic and behavioral components) is an important consideration in adolescents and young adults who have pancreatic diseases in their family history. It should be explored and interventions should be sought if the factor is present.

VIII.2. Diagnostic and etiological workup

In the initial phase of the SARS-CoV-2 pandemic, multiple case reports implicated the infection as the etiological factor of AP. We conducted a systematic review to overview and evaluate these papers. In some of the identified case reports, diagnostic uncertainty was present and all of the papers failed to conduct a thorough etiological investigation. Upon closer examination, we managed to find possible risk factors in all of the presented cases. We also observed high risk of bias and poor methodological quality.

This highlighted a central issue in the management of AP patients (even irrespective of the SARS-CoV-2 pandemic): the often neglected diagnostic and etiological workup. Maybe the most problematic part of the diagnostic criteria in practice is the pancreatic enzyme elevations. Performance of serum amylase and/or lipase tests can be missed altogether in patients in abdominal pain (although this is more of an issue among pediatric patients), which can lead to a missed diagnosis (192). Or, elevations in pancreatic enzymes not reaching three-times the

upper limit can be perceived as a fulfilled criteria for AP or regarded as pancreatic injury, as did one the papers in our review (135). Clinicians and researchers should keep in mind that, as discussed above, both amylase and lipase can commonly be elevated due to extrapancreatic reasons (16, 24-26).

Still, the relatively uncomplicated sequence of diagnostic steps is performed in most cases – the same cannot be said for etiological workup. While abdominal imaging (most commonly US) is frequently performed, and liver function results are sought, most other tests towards uncovering etiological factors are neglected. In a cohort analysis of around 2,400 AP cases by Zádori et al. serum TG measurement was performed in only 28% of the presumed idiopathic cases (133). As discussed in the introduction of this thesis, additional imaging tests have an important role in the workup of these patients. The IAP/APA guidelines recommend that all patients negative for biliary obstruction undergo EUS or MRCP examination to determine biliary microlithiasis, neoplasms and CP (15). On the contrary, the same paper by Zádori et al. demonstrated that only 5 and 4% of patient undergo EUS and MRCP respectively at the time of their first "idiopathic" AP, and only 14 and 12% at the time of the second "idiopathic" AP (133). Another common issue, is that there is no clear cut-off to determine a casual association between alcohol consumption and AP, leading to common mislabeling of cases as alcoholic (56). The presence of gallbladder stones and no other imaging alterations also frequently leads to assuming a biliary etiology – which is not necessarily the case.

VIII.3. Prevention of disease progression: dietary fat reduction?

The main reason why prompt etiology establishment, seeking genetic risk factors and familial aggregation is important, is so that we can identify patients at a higher risk of disease progression and that we can try to stop or delay this disease progression. In case these patients possess a risk factor that can be removed, we should remove it as soon as possible – every recurrent episode holds the possibility of complications or death; CP poses serious morbidity, mortality, at times with constant pain; PC is still one of the most lethal malignancies. If, for example, biliary obstruction elicited the AP, cholecystectomy should be performed (15). The American Gastroenterological Association recommends brief alcohol intervention for alcoholic AP patients (17), although all patients might benefit from alcohol cessation. Smoking is also associated with an increased risk of AP and CP, some authors suggest that smoking cessation interventions should also routinely be performed after the index AP (193, 194). Hypertriglyceridemia-induced AP patients can be worked up for secondary causes of hypertriglyceridemia and they benefit from non-pharmacological interventions (diet, exercise, etc.) and statin or fibrate therapy in the long run (195).

On the other hand, there are no readily available interventions to prevent or delay disease progression in patients without identified risk factors. That is why we designed and initiated a RCT, the EFFORT study. With this study, we wish to explore, whether dietary fat reduction can lead to a reduced risk of AP recurrence and CP development. We chose this intervention, as maintaining a low-fat diet is often recommended after an episode of AP in order to avoid recurrences. However, this recommendation is not included in the available guidelines and evidence from animal models and human cohort analyses are controversial. Our study will be the first to test this frequently recommended intervention in a randomized setting, following up

patients for 2 years, collecting clinical and laboratory data. In case dietary fat reduction proves successful in delaying disease progression, it will be the first and only preventive therapeutic option we can recommend in idiopathic AP and it could also benefit patients with another, identified risk factor. In case no clinically relevant difference is noted, that can also be used to patients' benefit, as they can avoid unnecessary dietary restriction in the future.

VIII.4. Summary of main clinical implications of the thesis work

The thesis and the included work ultimately focuses on avoiding or delaying the progression of AP towards ARP and CP, by examining and highlighting the role of family history and appropriate etiological work-up, and initiating a RCT to see whether reducing dietary fat content can reduce AP recurrence. We used three different clinical scientific methodologies, which were, in the presented order: cohort analysis, systematic review and RCT. The main clinical implications of these works are: the novel observation of the association between family history and alcohol consumption or smoking in young adults with AP; underlining the importance of etiological workup and guideline adherence; and based on the results of the EFFORT study, establishing whether dietary fat reduction should be recommended after AP to avoid recurrences.

IX. Summary of novel findings and perspectives

Pancreatic family history doesn't predict disease progression, but connotes alcohol consumption in adolescents and young adults with acute pancreatitis: Analysis of an international cohort of 2,335 patients

- We conducted the first cohort analysis comparing AP patients with versus without a family history of pancreatic disease. We also explored the possible explanatory factors of familial aggregation.
- We found that contrary to current viewpoints positive pancreatic family history is not a prognostic factor for ARP and CP in adults, so it should not be regarded that way.
- Regarding the reasons of familial aggregation:
  o Positive family history most likely signifies genetic background in early childhood.
  o Among adolescents and young adults with a family history of pancreatic disease, alcohol consumption and smoking are prevalent – clinicians should be aware and turn to intervention in such cases.
  o We found no apparent association between family history and diabetes or hyperlipidemia.

Insufficient etiological workup of COVID-19 associated acute pancreatitis: A systematic mini-review

- We conducted the first systematic review of clinical reports of patients with a confirmed SARS-CoV-2 infection and AP.
- All of the included case reports failed to conduct a thorough etiological investigation. We were able to identify other possible causes in most. We also noted a high risk of bias in these papers.
- With our review we highlighted a central issue in the management of AP: the lack of guideline adherence in terms of diagnostic and especially etiological workup.

The EFFect Of dietary fat content on the Recurrence of pancreaTitis (EFFORT): protocol of a multicenter randomized controlled trial

- We designed and launched the first RCT examining the role of dietary fat reduction after AP – this is often recommended for patients in order to avoid recurrences, although without sufficient evidence.
- The study will follow-up idiopathic patients for 2 years, collecting clinical and laboratory data.
- In case dietary fat reduction is effective, this will be the first known intervention, if not, unnecessary dietary restriction can be avoided in the future.

X. Author's contributions

In all three included articles, the author played a main role in the conceptualization of the work, planning and performing of analyses, making of the tables and figures and writing of the manuscripts.

Pancreatic family history doesn't predict disease progression, but connotes alcohol consumption in adolescents and young adults with acute pancreatitis: Analysis of an international cohort of 2,335 patients

The author took part in the patient enrolment and clinical data collection from AP patients into the HPSG AP registry as well as the quality control of entered data, conceptualization of the work, curation of data tables, data analysis, making figures and tables, writing of the manuscript.

Insufficient etiological workup of COVID-19 associated acute pancreatitis: A systematic mini-review

The author took part in the conceptualization and registering of the review, designing the search key, performing the systematic search and selection, data collection from the included papers, risk of bias analysis, preparation of figures and tables, writing of the manuscript.

The EFFect Of dietary fat content on the Recurrence of pancreaTitis (EFFORT): protocol of a multicenter randomized controlled trial

The author took part in the conceptualization of the study and protocol, registration of the study, communication with participant prospect and international board members to improve design, preparation of tables and figures, preparation of questionnaires, submission for ethical approval, communicating with future centers, writing of the protocol. The study launched in the summer of 2022, 10 participants are enrolled so far (as of October 2022).

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Pancreatic family history does not predict disease progression but connotes alcohol consumption in adolescents and young adults with acute pancreatitis: Analysis of an international cohort of 2,335 patients

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Background: In pediatric acute pancreatitis (AP), a family history of pancreatic diseases is prognostic for earlier onset of recurrent AP (ARP) and chronic pancreatitis (CP). No evidence supports the same association in adult-onset pancreatitis. Age-specific reasons for familial aggregation are also unclear. We aimed to examine the prognostic role of pancreatic family history for ARP/CP and observe possible underlying mechanisms.

Methods: We conducted a secondary analysis of the Hungarian Pancreatic Study Group's (HPSG) multicenter, international, prospective registry of patients with AP, both children and adults. We compared the positive family history and the negative family history of pancreatic diseases, in different age groups, and analyzed trends of accompanying factors. Chi-square and Fisher exact tests were used.

Results: We found a higher rate of ARP/CP in the positive pancreatic family history group (33.7 vs. 25.9%, *p* = 0.018), peaking at 6−17 years. Idiopathic AP peaked in childhood in the positive family history group (75% 0−5 years) and was consistently 20−35% in the negative group. A higher rate of alcohol consumption/smoking was found in the positive groups at 12−17 years (62.5 vs. 15.8%, *p* = 0.013) and 18−29 years (90.9 vs. 58.1%, *p* = 0.049). The prevalence of diabetes and hyperlipidemia steadily rose with age in both groups.

Conclusion: Positive family history most likely signifies genetic background in early childhood. During adolescence and early adulthood, alcohol consumption and smoking emerge—clinicians should be aware and turn to intervention in such cases. Contrary to current viewpoints, positive pancreatic family history is not a prognostic factor for ARP and CP in adults, so it should not be regarded that way.

Introduction

Acute pancreatitis (AP) is the sudden onset inflammation of the pancreas, elicited by gallstones or alcohol consumption in 70–80% of adult cases (1). In pediatric AP, the picture is much more diverse: biliary obstruction and drugs account for half of the cases, other etiologies are below 5–10% and the rate of idiopathic cases is higher, around 20–30% as opposed to the 10% found in adults (2–5). In idiopathic cases, there is a higher possibility of inherited genetic alterations in the background, posing a constant and unamendable risk factor, thus increasing the likelihood of and speeding up progression toward acute recurrent pancreatitis (ARP), chronic pancreatitis (CP), and pancreatic cancer (PC) (6). Guidelines recommend that after a second idiopathic AP episode, children should go through genetic testing (7), and adults should receive genetic counseling (not necessarily testing) (8). Therefore, genetic background is often established late and often missed altogether—especially in adults or when other etiologies are present. There is however an easily assessable factor that could point towards genetic predisposition, and be useful in such cases: positive pancreatic family history.

The importance of gathering pancreatic (AP, ARP, CP, PC, etc.) family history is well-established in pediatric pancreatitis, with a family history of AP and CP being strongly associated with earlier ARP and CP onset (9), and the guidelines recommend genetic testing after a single idiopathic episode in case family history is present (7). Adult CP guidelines also strongly recommend assessment (100% agreement) (10); however, there is scarce evidence supporting this recommendation—we failed to identify any clinical studies examining the connection between ARP, CP, and pancreatic family history. Recent years' literature on ARP and CP highlights the importance of both the identification of risk factors for disease progression and uncovering underlying mechanisms (11, 12). Thus, even though assessing family history is uncomplicated, examining it poses two major points of importance: observing whether it is a risk factor for disease progression in adults; and mapping associations with possible explanatory factors, to reach a greater understanding of AP, ARP, and CP.

Our aim was to examine associations between pancreatic family history, ARP and CP rates, idiopathic etiology, and risk factors of AP in different pediatric and adult age groups. Our findings suggest that (1) family history should not be used as a prognostic factor for ARP or CP in adults, (2) familial aggregation is mostly due to genetic factors in early childhood, and (3) due to increased alcohol consumption and smoking in adolescence and early adulthood.

Materials and methods

Study design and data collection

This study is a secondary analysis of the international, multicenter, prospective AP registry maintained by the Hungarian Pancreatic Study Group (HPSG). Between 2012 and 2019, 2,559 episodes of AP were enrolled in the registry. The diagnosis was established according to the International

Association of Pancreatology/American Pancreatic Association (IAP/APA) guidelines (8). A list of study sites can be found in our Supplementary material (**Supplementary Figure 1** and **Supplementary Table 1**). A rigorous, four-tier quality control system was applied to ensure the accuracy of these data. For more details on this system, see the previous publication from this registry by Párniczky et al. (13).

Participants

In the present analysis, both adult and pediatric AP patients with available data on the presence/absence of pancreatic family history—such as AP, CP, ARP, autoimmune pancreatitis (AIP), and PC—were included (2,335 patients, with 2,470 prospectively collected episodes of AP). In our analyses, we compared patients with a negative pancreatic family history to patients with a positive pancreatic family history for AP, CP, ARP, AIP, or PC. To observe age-specific changes in our observed variables, we divided the cohort into age-based subgroups: 0–5, 6–11, 12–17, 18–29, 30–41, 42–53, 54–65, and 66 years. To avoid arbitrary threshold selection, we adhered to the following rhetoric: we planned to divide children into as many equal age-interval groups as possible; since two groups are not yet informative and four resulted in very low participant numbers, we decided to use three equal age intervals. In the case of adult participants, we doubled this interval (from 6 to 12 years) since changes are not as swift as in childhood. We intended to maintain the 6-year interval in early adulthood; however, the 18–23 group would have had zero patients with positive pancreatic family history.

Variables

All analyzed variables—such as demographical data, data on comorbidities, smoking, alcohol consumption, complications, severity, etiology, and number of episodes—are provided in the data quality table in our Supplementary material (**Supplementary Table 2**). We adhered to the revised Atlanta criteria in determining the complications and severity of AP: cases were considered mild if no local complications or organ failure occurred, moderate if local complications and/or organ failure lasting less than 48 h occurred, and severe if organ failure persisted beyond 48 h (14). While the prospective data collection period only covers 8 years, a detailed personal medical history was taken, especially regarding the pancreatic disease, and we accounted for these data in determining the presence of ARP and the number of episodes. Patients were assessed to have "hyperlipidemia" if their AP was caused by hypertriglyceridemia or if they were diagnosed with a non-transient dyslipidemia.

We compared our examined cohort to the entirety of the AP cases enrolled in our registry to see whether our analyzed population is representative of the average AP experiencing population. Since almost all patients (96.6%) had

data on the presence of pancreatic diseases in the family, our cohort was representative in terms of age, gender, AP severity, mortality, length of hospitalization, and etiology (**Supplementary Figure 2**).

Statistical analysis

In the case of categorical variables, we calculated event number and percentage of the total and mean and standard deviation (SD) for continuous data. To test for statistically significant differences between groups, the chi-squared or Fisher's exact tests were applied for categorical, Student's t-test for normally distributed continuous, and the Mann-Whitney U test for non-normally distributed continuous variables, with an alpha value of 5%. Statistically significant p-values (p) appear in bold.

Ethical approval

The Scientific and Research Ethics Committee of the Medical Research Council granted the ethical approval for this registry in 2012 (22254–1/2012/EKU). The institution's human research committee approved the protocol for the registry before initiating participant enrolment. We are in compliance with the Declaration of Helsinki, reaffirmed in 2013. All patients provided their written, informed consent in case of participation.

Study reporting

This study was reported according to the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) statement (15).

Results

Participants

Table 1 shows the characteristics of enrolled participants. A total of 2,335 patients were analyzed, of which 196 (8.4%) had a positive pancreatic family history. These patients were younger at the time of their first enrolment in our registry, and idiopathic AP etiology was more common. Mild disease course occurred significantly more often in the case of the first registered AP episode and any prospectively collected episode that belonged to a positive pancreatic family history group as well. The total number of episodes/persons (accounting not only for registry enrolments but also for episodes in medical history) was significantly higher in the positive pancreatic family history group.

TABLE 1 Characteristics of participants.

	Positive pancreatic family history	Negative pancreatic family history	p
Number of patients	196	2,139	
Female sex; n (%)	87 (44.4)	951 (44.5)	0.984
Age at first enrolment; years mean ±SD	49.2 ± 20.4	55.6 ± 18.2	<0.001
AP etiology, first enrolment; n (%)			
Biliary	66 (33.7)	868 (40.6)	0.059
Alcoholic	31 (15.8)	393 (18.4)	0.374
Hypertriglyceridemia	8 (4.1)	70 (3.3)	0.546
Any combination of these three	15 (7.7)	92 (4.3)	0.032
Idiopathic	51 (26.0)	418 (19.5)	0.030
Other	25 (12.8)	298 (13.9)	0.648
AP severity, first enrolment; n (%)			
Mild	154 (78.6)	1522 (71.2)	0.027
Moderate	33 (16.8)	510 (23.8)	0.026
Severe	9 (4.6)	107 (5.0)	0.800
AP severity, any registered episode; n (%)			
Mild	168/216 (77.8)	1610/2254 (71.4)	0.047
Moderate	39/216 (18.1)	533/2254 (23.6)	0.063
Severe	9/216 (4.2)	111/2254 (4.9)	0.621
AP episodes / person; mean ±SD	1.74 ± 1.86	1.48 ± 1.29	0.010

AP, acute pancreatitis; n, number; SD, standard deviation; %, percentage; p, p-value.

Regarding the age distribution of positive family history, among adults, the observed rate was steadily around 8% (6.4–9.4%), but it was considerably higher in the case of children, peaking at 6–11 years (40.0%; Supplementary Figure 3).

Pancreatic family history, acute recurrent pancreatitis, and chronic pancreatitis

Figure 1A shows the rate of ARP and CP (developed later or already diagnosed) with or without pancreatic family history categorized by the age of the index involvement in the AP registry. The higher rate of ARP was noted in childhood, even more so in the positive than the negative family history groups, but without statistical significance. Overall, a significantly higher rate of ARP and/or CP was found in the positive family history group (33.7 vs. 25.9%, p = 0.018). A figure not separating ARP and CP is available in our Supplementary material (Supplementary Figure 4).

Association with idiopathic etiology, alcohol, smoking, and metabolic risk factors

Among patients with a negative pancreatic family history, the rate of idiopathic episodes was higher in children (30–40%) than in adults (20–30%). We found an excess of idiopathic etiology in children with a positive family history (75% 0–5 years, 60% 6–11 years), which decreased over time to meet the negative group. Statistically significant difference was found overall (32.1 vs. 24.6% in the positive vs. negative groups, respectively, p = 0.020; Figure 1B).

We found a significantly higher rate of current alcohol consumption and/or smoking at the index case in the positive family history group in ages 12–17 years (62.5 vs. 15.8%, p = 0.013) and 18–29 years (90.9 vs. 58.1%, p = 0.049) but not overall (58.2 vs. 53.4%, p = 0.204). In the remaining age groups, balanced distribution was found (Figure 1C).
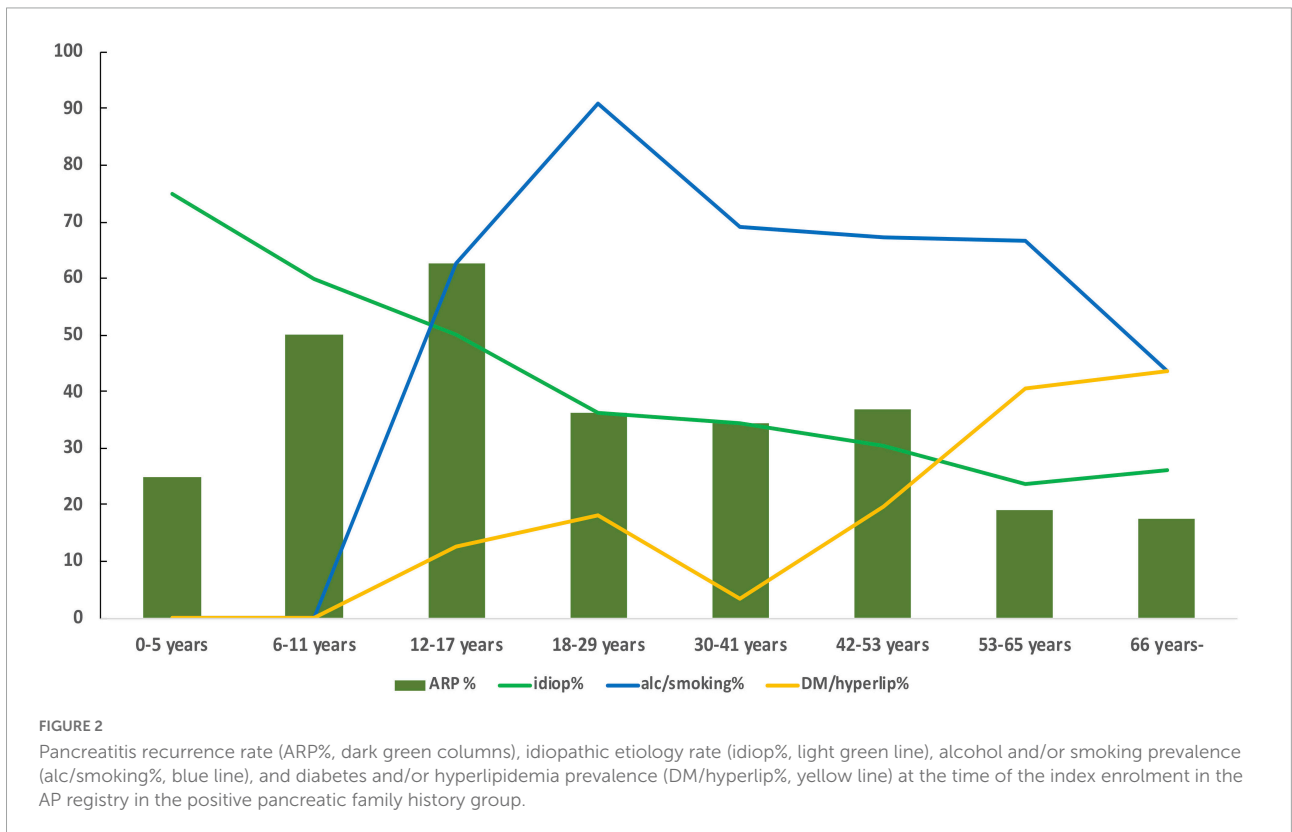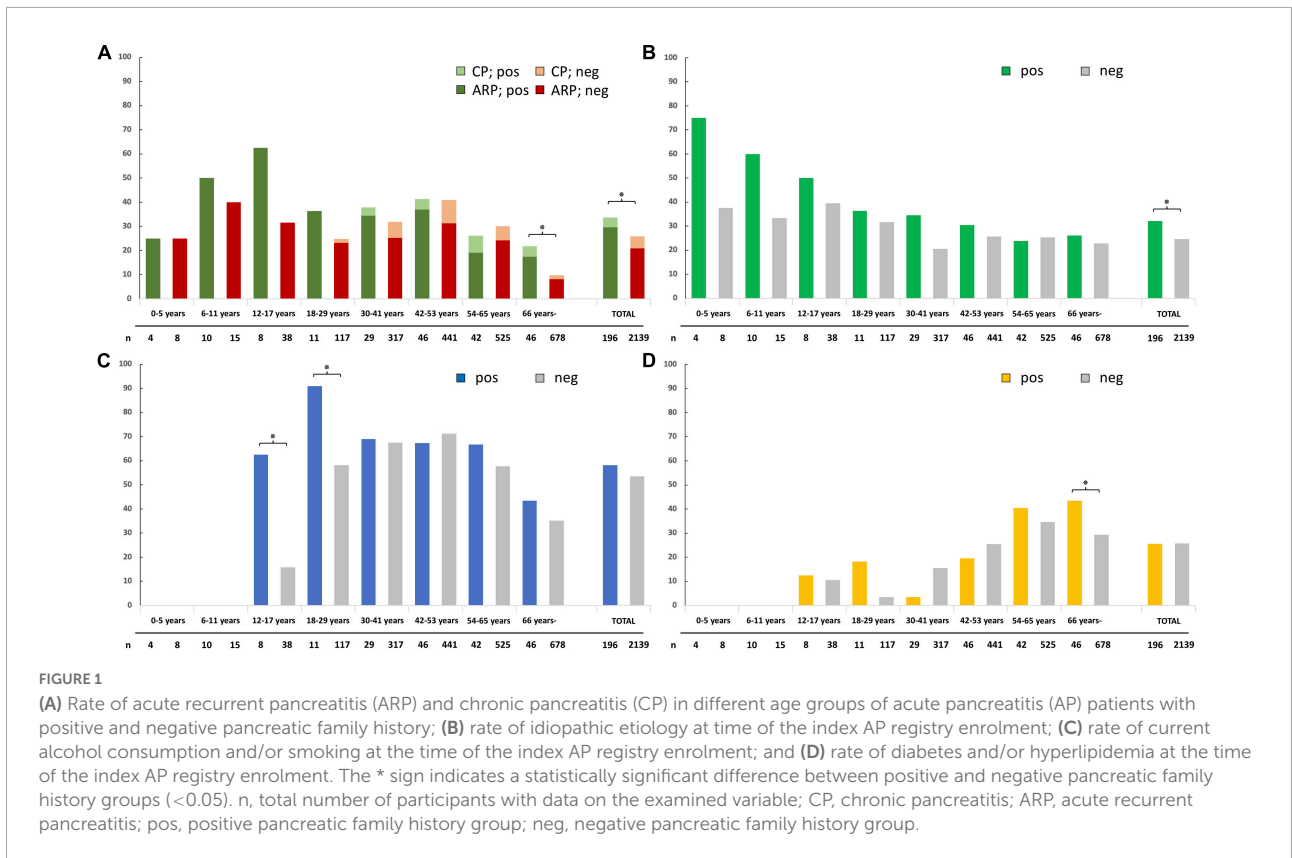
A significant difference between positive and negative family history groups regarding the presence of diabetes mellitus (DM) and/or hyperlipidemia at the time of the index case was observed only in patients 66 years old or above (43.5 vs. 29.4%, respectively, p = 0.044) but not overall (25.5 vs. 25.7%, p = 0.950) or in any other age subgroup (Figure 1D).

Figure 2 shows the recurrence rate and prevalence of discussed explanatory factors of familial aggregation in the positive pancreatic family history group to facilitate the interpretation of the above-presented results.

Discussion

In our analysis, we evaluated ARP and CP rates and accompanying factors in different pediatric and adult age groups of AP, according to the presence of pancreatic family history.

Overall, we found a significantly higher rate of ARP or CP in the positive family history group. In the age-based subgroups, we observed a consistently higher rate of ARP or CP in the positive groups, but without statistical significance. The reason

FIGURE 1
(A) Rate of acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) in different age groups of acute pancreatitis (AP) patients with positive and negative pancreatic family history; **(B)** rate of idiopathic etiology at time of the index AP registry enrolment; **(C)** rate of current alcohol consumption and/or smoking at the time of the index AP registry enrolment; and **(D)** rate of diabetes and/or hyperlipidemia at the time of the index AP registry enrolment. The * sign indicates a statistically significant difference between positive and negative pancreatic family history groups (<0.05). n, total number of participants with data on the examined variable; CP, chronic pancreatitis; ARP, acute recurrent pancreatitis; pos, positive pancreatic family history group; neg, negative pancreatic family history group.

FIGURE 2
Pancreatitis recurrence rate (ARP%, dark green columns), idiopathic etiology rate (idiop%, light green line), alcohol and/or smoking prevalence (alc/smoking%, blue line), and diabetes and/or hyperlipidemia prevalence (DM/hyperlip%, yellow line) at the time of the index enrolment in the AP registry in the positive pancreatic family history group.

behind this was a relatively low number of participants in the pediatric subgroups and only subtle differences in the adult subgroups. It is likely that with higher patient numbers, the marked difference in the pediatric subgroups would be retained and statistical significance would be achieved, reflecting the available evidence. On the other hand, further increasing adult subgroups—while it could lead to significant results—would likely still be a clinically irrelevant difference. In our opinion, family history should not be used as a prognostic factor for recurrence and CP among adults.

The incidence rate of ARP peaked in those who had their index episode between 6 and 17 years, the highest percentage difference between positive and negative pancreatic family history groups was noted between 12 and 17 years.

While the negative family history group had a rate of idiopathic etiology consistently in the 20–40% range, the positive group had an excess of idiopathic AP in the pediatric age groups: peaking at 75% at 0–5 years then steadily decreasing to meet the negative group in adulthood. This is likely due to genetic risk factors being responsible for familial aggregation among pediatric patients, especially in early childhood. No differences in adults are in line with the findings of Jalaly et al. who performed genetic testing in 134 adults with idiopathic AP and found that family history does not predict pathogenic variants ([16]).

However, next to the decline of differences in idiopathic etiology, another factor emerged at 12–17 years; we found a significantly higher rate of alcohol consumption and/or smoking in patients with a positive pancreatic family history, who had their index episode in this, or the following age group (18–29 years). The most likely explanation is the well-documented association between parental and offspring alcohol consumption: a systematic review found that in 12 out of 12 included studies, parents' drinking was predictive of adolescents' alcohol use ([17]), and a cross-sectional study of 982 adolescents found hazardous paternal drinking to be strongly associated (OR = 2.90) with use ([18]). Contrary to the seemingly similar rationale, empirical evidence does not support the association between parental and adolescent smoking ([19], [20]).

Regarding DM and hyperlipidemia, metabolic risk factors for AP ([21], [22]), we found low prevalence in pediatric patients, in conformity with low childhood prevalence reported in the literature, 1.93/1,000 for type 1 DM, 0.46/1,000 for type 2 ([23]), and 2–4/1,000 for familial hypercholesterolemia ([24]–[26]). With the onset of childhood obesity, most prominently from early adolescence, the prevalence of type 2 DM and hyperlipidemic states start to rise, transitioning to the higher rate seen among adults: for DM, around 40–130/1,000 in the general adult population and 170–250/1,000 above 65 years ([27]–[30]). We expected to see significant differences or at least a tendency favoring the positive pancreatic family history group since metabolic syndrome and DM both have genetic and learned behavioral components that could lead to their accumulation in

the family ([31]). We only noted such difference above 66 years, with a tendency starting to show in the 54–65 years' subgroup.

The prevalence rates of alcohol consumption, smoking, DM, and hyperlipidemia are over-represented in our cohort as compared to the general population. Quite understandably, these are all likely to accumulate in a cohort of patients with AP, as risk factors for the disorder.

Strengths and limitations

To our knowledge, this was the first cohort study to examine the ARP and CP prognostic role of family history in adults and the first cohort representing both pediatric and adult patients seeking associations between pancreatic family history and clinical factors that could be in the background of this familial aggregation. One of the main strengths of this study is that the participants come from multiple centers, countries, and continents, signifying wide representativeness. We applied a uniform data collection, following the same structure in all ages, thus enhancing the comparability of adult and pediatric populations. Our patient enrolment encompassed a period of 8 years and the index case in the registry is not necessarily the first AP of the participant—thus, we believe that our conclusions regarding the ARP rate are valid.

Conclusions regarding CP rate, however, should be handled with caution since they are probably under-represented, especially in the pediatric age groups. Another limitation of this study is that, even though in proportion to the enrolled adults, the number of pediatric patients is appropriate, it is still relatively low, while we observed the tendencies in ARP, idiopathic etiology, and exogenous risk factors that we expected, these associations were not backed up by statistical significance due to low event numbers. It should also be stated that the first AP episode enrolled in our registry is not necessarily the first episode of the individual—although it was in most cases. We performed our analyses this way since our data of interest could not be gathered for non-enrolled episodes without a high possibility of bias. In addition, though our intent was to examine family history in a purely clinical context, and idiopathic etiology tendency matched our expectations, it is only a surrogate marker—genetic analysis of all patients would have clarified genetic background; this was currently beyond our scope.

Implications

Positive family history most likely signifies genetic background in early childhood. During adolescence and early adulthood, alcohol consumption and smoking emerge—clinicians should be aware of the significant association with pancreatic family history (probably due to harmful

consumption in the family) and consider targeted intervention in such cases. Our analysis revealed that contrary to current viewpoints, positive pancreatic family history is not a prognostic factor for ARP and CP in adults, so it should not be used as such.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Scientific and Research Ethics Committee of the Medical Research Council (Hungary). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

MJ, AP, and PH formulated the original concept. AS, AW, AN, NL, AT, IT, ÁV, BE, FI, LC, MP, and NF contributed to this concept. MJ, AP, PH, AS, AW, AN, NL, AT, IT, ÁV, BE, FI, LC, and MP took part in data acquisition. NF and MJ conducted the analyses. MJ and AP drafted the manuscript. PH, AS, AW, AN, NL, AT, IT, ÁV, BE, FI, LC, MP, and NF revised it critically for intellectual content. All authors have read and approved the final version of the manuscript.

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Conflict of interest

The reviewer KM declared a shared affiliation, with no collaboration, with several of the authors MJ, NF, AS, AV, BE, PH, and AP to the handling editor at the time of the review.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.801592/full#supplementary-material

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SYSTEMATIC REVIEWS

Insufficient etiological workup of COVID-19-associated acute pancreatitis: A systematic review

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Abstract

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, mostly causing respiratory symptoms, is also known to affect the gastrointestinal tract. Several case reports hypothesize that SARS-CoV-2 could be an etiological factor in acute pancreatitis (AP).

AIM

To assess all the available evidence in the literature relating to coronavirus disease 2019 (COVID-19) and AP.

METHODS

We performed a systematic review of the available literature on the topic. The systematic search was conducted on 15 May 2020 on MEDLINE, EMBASE, CENTRAL, Web of Science and Scopus with a search key using the terms "amylase," "lipase," "pancr*," "COVID-19" and synonyms. Due to the low quality and poor comparability of the studies, a meta-analysis was not performed.

RESULTS

Six case reports and two retrospective cohorts were included, containing data on eleven COVID-19 patients with AP. Five patients had AP according to the Atlanta classification. Other publications did not provide sufficient information on the diagnostic criteria. Most cases were considered SARS-CoV-2-induced, while

several established etiological factors were not investigated. We were able to identify other possible causes in most of them.

CONCLUSION
We strongly highlight the need for adherence to the guidelines during a diagnostic and etiological workup, which could alter therapy.

Key Words: Pancreas; COVID-19; Pancreatic involvement; Pancreatitis; Amylase; Lipase

Core Tip: As the severe acute respiratory syndrome coronavirus 2 pandemic spreads, numerous coronavirus disease 2019 patients will be diagnosed with acute pancreatitis (AP). Viral infections are known etiological factors of AP, but taking a look at the available literature several shortcomings of the diagnostic end etiological workups were uncovered, therefore the causative relationship between coronavirus disease 2019 and AP cannot be established. We highlight the fundamental role of guideline adherence in the diagnosis and etiological workup of AP since etiology-specific therapeutic options are available. Identifying underlying etiological factors is the foundation of high-quality patient care in AP.

INTRODUCTION

In 2019, a novel coronavirus emerged in Wuhan, China, causing multiple cases of severe pneumonia and launching the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. The clinical syndrome seen in SARS-CoV-2 infection is called coronavirus disease 2019 (COVID-19). The main clinical symptoms of COVID-19 are fever, cough, myalgia, and fatigue[1]. Pulmonary involvement is the most frequent[2], but systemic dissociation is seen in severe cases. Furthermore, a significant proportion of patients exhibit gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain. SARS-CoV-2 was also detected in stool specimens[3] and in the cytoplasm of gastric, duodenal, and rectal glandular epithelial cells[4].

Viral infections such as mumps, Coxsackie, hepatitis, and herpes viruses are known causes of pancreatitis[5]. There is a strong possibility that, like other, less common causes of acute pancreatitis (AP), infectious etiology is underdiagnosed on account of the insufficient workup of idiopathic cases and cases where an apparent cause (*e.g.*, alcohol consumption) is already established[6-8].

On the other hand, during a pandemic of such proportions, polymerase chain reaction testing is made widely available. This will of course lead to a proportion of patients with a variety of diseases, including AP, being diagnosed with SARS-CoV-2 infection. Given the right temporal association, even a more experienced practitioner could be led to ponder a cause-effect relationship between COVID-19 and AP. Even more so, taking into account the often-neglected etiological workup of idiopathic cases and the opportunity to aid the scientific and medical communities by providing information on presumed complications of the infection.

This systematic review aims to assess all publications containing COVID-19 AP cases and to determine the plausibility of an association between the two.

MATERIALS AND METHODS

Protocol and registration

This systematic review was registered with PROSPERO as "Pancreas involvement in COVID-19: A systematic review" under registration number CRD42020186426. After completing the systematic search, we decided to deviate from the protocol for the eligibility of studies: We narrowed our focus to AP from the original plan of any pancreatic involvement. We did so because slight pancreatic enzyme elevation in COVID-19 patients, reported by two studies[9,10], has already been discussed by de-Madaria *et al*[11] and information on pancreatic cancer patients, reported by three studies[12-14] is at this point far too scarce to even discuss its relation with COVID-19 and effect on outcomes. There were no other deviations from the protocol.

Eligibility criteria

Any study, regardless of design, was considered eligible if it contained the original data on at least 1 SARS-CoV-2-infected individual diagnosed with AP. Only human studies were eligible; studies containing solely animal or *in vitro* data were excluded.

Systematic search and selection; data extraction

Using the same search key as detailed in the supplementary material (Supplemental 1), the systematic search was conducted in five databases: EMBASE, MEDLINE (*via* PubMed), CENTRAL, Web of Science, and Scopus. The last systematic search was carried out on May 14, 2020. The search was restricted to 2020, and no other filters were applied. Citations were exported to a reference management program (EndNote X9, Clarivate Analytics). Two independent review authors (Ocskay K and Juhász MF) conducted the selection by title, abstract and full text based on the previously disclosed, predetermined set of rules. After each selection step, Cohen's kappa coefficient (κ)[15] was calculated. An independent third party (SK) settled any disagreements. Citing articles and references in the studies assessed for eligibility in the full-text phase were reviewed to identify any additional eligible records. Data were extracted from all eligible studies into a standardized Excel sheet designed on the basis of recommendations from the Cochrane Collaboration[16] (for details on data extraction, see Supplemental 2).

Risk of bias assessment and determination of the quality of evidence

The Joanna Briggs Institute Critical Appraisal Checklist for Case Reports[17] was used to assess the risk of bias in case reports, and the Newcastle–Ottawa Scale[18] was used for cohorts (results in Supplemental 3). Due to the design and quality of the included studies, the Grading of Recommendations, Assessment, Development, and Evaluations approach was not used and a very low grade of evidence was automatically established.

Statistical analysis

Only qualitative synthesis was performed; no statistical analysis was carried out.

RESULTS

Systematic search and selection

The details of the systematic search and selection are presented in Figure 1.

Characteristics of included studies

In total, six case reports and two retrospective cohort studies were included in this systematic review (Table 1). Information on the diagnostic criteria and etiological factors of AP was collected from the appropriate case reports in Table 2. Of the six cases, five fulfilled the diagnostic criteria for acute pancreatitis[19], and in one case[20] enzyme elevation reached the threshold. However, abdominal pain could not be reported on account of the patient being ventilated and sedated, and no imaging findings were disclosed. A case report by Gou *et al*[21] was not included in this table, as biliary etiology was determined and COVID-19 symptoms first emerged on day 18 of the patient's hospital stay; thus, the infection was not assumed as an etiological factor[21].

In a retrospective cohort of COVID-19 mortality cases by Li *et al*[22], AP is listed as an underlying disease in a single patient without further clarification as to whether it is a

Table 1 Characteristics of included studies

Ref.	Study design	Study population	AP, n (%)	Description
Aloysius *et al*[29], United States	Case report	One AP patient with COVID-19	1 (100)	36-year-old obese female presenting with AP. No sign of biliary pathology, denies alcoholism, TG unremarkable
Anand *et al*[44], United Kingdom	Case report	One AP patient with COVID-19	1 (100)	A 59-year-old cholecystectomized woman with minimal alcohol consumption, readmitted with abdominal symptoms five days after discharge with doxycycline for co-infection. CT showed signs of AP on a formerly atrophic pancreas
Gou *et al*[21], China	Case report	Four "pancreatic disease" patients with COVID-19 pneumonia	1 (25)	One female with AP (51), biliary etiology confirmed, showed initial COVID-19 symptoms 18 d after admission
Hadi *et al*[45], Denmark	Case report	Three family members with COVID-19	2 (67)	Idiopathic AP in mother (68) and daughter (47), both requiring intensive care and ventilation
Hossain *et al*[23], United States	Retrospective cohort	119 COVID-19 patients presenting at ER with non-respiratory symptoms	3/32 (9.4)	Out of the 101 instances where abdominal/pelvic CT was obtained, 32 had acute/significant findings, including three cases of pancreatitis. No more information available on these patients
Li *et al*[22], China	Retrospective cohort	25 death cases with COVID-19	1 (4)	A 56-year-old male patient had AP as an "underlying disease"–it is not clear whether this is from his medical history or was present concomitantly
Meireles *et al*[46], Portugal	Case report	One AP patient with COVID-19	1 (100)	36-year-old female, AP symptoms started on day 11 of disease, US and CT showed no signs of biliary pathology/ischemia. No information on alcohol consumption. Negatively screened for multiple viruses
Morrison *et al*[20], United States	Case report	Two cases of acute hypertriglyceridemia in COVID-19 patients	1 (50)	Acute hypertriglyceridemia-induced AP after treatment with tocilizumab, ritonavir, lopinavir, ribavirin, hydroxychloroquine, and propofol

AP *n* (%) is the number (percentage) of patients with acute pancreatitis. COVID-19: Coronavirus disease 2019; AP: Acute pancreatitis; US: Ultrasonography; CT: Computed tomography.

past event from the patient's medical history or it occurred during COVID-19-related hospitalization[22]. Hossain *et al*[23] noted three cases of AP among 119 patients presenting to the ER with non-respiratory symptoms who turned out to have concomitant SARS-CoV-2 infection[23].

DISCUSSION

The multiple-hit theory can be implemented in the pathogenesis of AP[24]; therefore, information on possible contributing factors was collected for each case (Table 2). Multiple etiological factors are often responsible for AP[24], but the lack of proper workup often leads to cases being deemed idiopathic or an important factor not being discovered due to the presence of a more convenient diagnosis[6]. In addition to the established etiological factors, various mechanisms have been postulated as the cause of pancreatic damage in COVID-19.

SARS-CoV-2 enters epithelia through the angiotensin-converting enzyme 2[25], which is abundantly expressed in the pancreas[26,27]. SARS-CoV-2 RNA and protein were also shown by *in situ* hybridization and immunohistochemistry from autopsy samples of infected patients' pancreas[28]. Aloysius proposed that virus replication may have a direct cytopathic effect or elicit pancreatic cell death as a consequence of the immune response[29]. Furthermore, microvascular injury and thrombosis have been described as a consequence of COVID-19[30,31], which, complicated with shock and gastrointestinal hypoperfusion[32], could also cause pancreatic damage[33].

However, a cause-effect relationship has not been investigated directly so far. Also, before entertaining the possibility of a new virus as a causative agent in cases where no apparent etiological factors are present, other, less frequent causes of AP must be considered. In such cases, the International Association of Pancreatology/American Pancreatic Association (IAP/APA) recommendations should be followed[6,7,19].

For instance, drugs used in treating COVID-19 may cause pancreatic damage directly or indirectly. A patient whose case was presented as idiopathic AP was on a course of doxycycline, which is a drug with a documented probable association with pancreatitis[34]. Several drugs currently used or being considered for COVID-19 might play a role in the pathogenesis of pancreatitis, such as enalapril, asparaginase,

Table 2 Diagnostic and etiological workup and quality assessment of the studies

Ref.	Diagnostic workup			COVID-19 (PCR)	Etiological workup									Quality of case reports	
	Abdominal pain	Enzyme elevation (3 x)	Imaging		Biliary	Alcohol	HTG (> 11.5 mmol/L)	Drug	Hyper-calcemia	Ischemia	Auto-immunity	Viral (except nCoV)	Anatomy	JBI Overall rating (/8)	Written according to CARE
Aloysius *et al*[29], United States	+	+	-	+	?	-	-	-	?	?	?	?	-	3	No
Anand *et al*[44], United Kingdom	+	?	+	+	?	-	?	+	?	?	?	?	-	0	No
Hadi *et al*[45], Denmark	?	+	+	+	?	-	-	?	-	+	?	?	?	4	No
	+	+	?	+	?	?	?	+	-	+	?	?	?	2	
Meireles *et al*[46], Portugal	+	+	-	+	?	-	-	-	-	-	-	-	-	1	No
Morrison *et al*[20], United States	?	+	?	+	?	?	+	+	?	+	?	?	?	1	No

The Atlanta criteria were used for diagnosis. Biliary microlithiasis was included in the "biliary" etiology, so endoscopic ultrasonography or magnetic resonance cholangiopancreatography was needed to rule out this factor. Ischemia was considered in the case of shock and vasopressor therapy and was ruled out by computed tomography angiogram. Anatomical malformations were ruled out by computed tomography. The two columns on the right demonstrate the quality of included case reports based on the risk of bias according to the overall Joanna Briggs Institute Critical Appraisal score and adherence to Case Report guidelines on reporting cases. CARE: Case Report Guidelines; JBI: Joanna Briggs Institute; PCR: Polymerase chain reaction.

estrogens, and steroids[34]. Hypertriglyceridemia, another established etiological factor frequently neglected, can also occur as a consequence of therapy, as in the case described by Morrison *et al*[20]. Not only tocilizumab[35] but propofol and ritonavir could also have been responsible for the elevation of serum triglyceride levels in this case[36]. Hypertriglyceridemia-associated drug-induced AP was observed[37,38] in association with the following drugs being tested for COVID-19 according to our search on clinicaltrials.gov: lisinopril, asparaginase, estrogens, isotretinoin, steroids, propofol, and ruxolitinib.

In a case reported by Aloysius *et al*[29], there are no apparent etiological factors present in the description. Even so, the report does not describe any further efforts to identify the seemingly idiopathic etiology, such as performing an endoscopic ultrasonogram. While thoroughly ruled out AP-associated viruses and even screened for antinuclear antibodies, they also did not utilize endoscopic ultrasonogram during the etiology search.
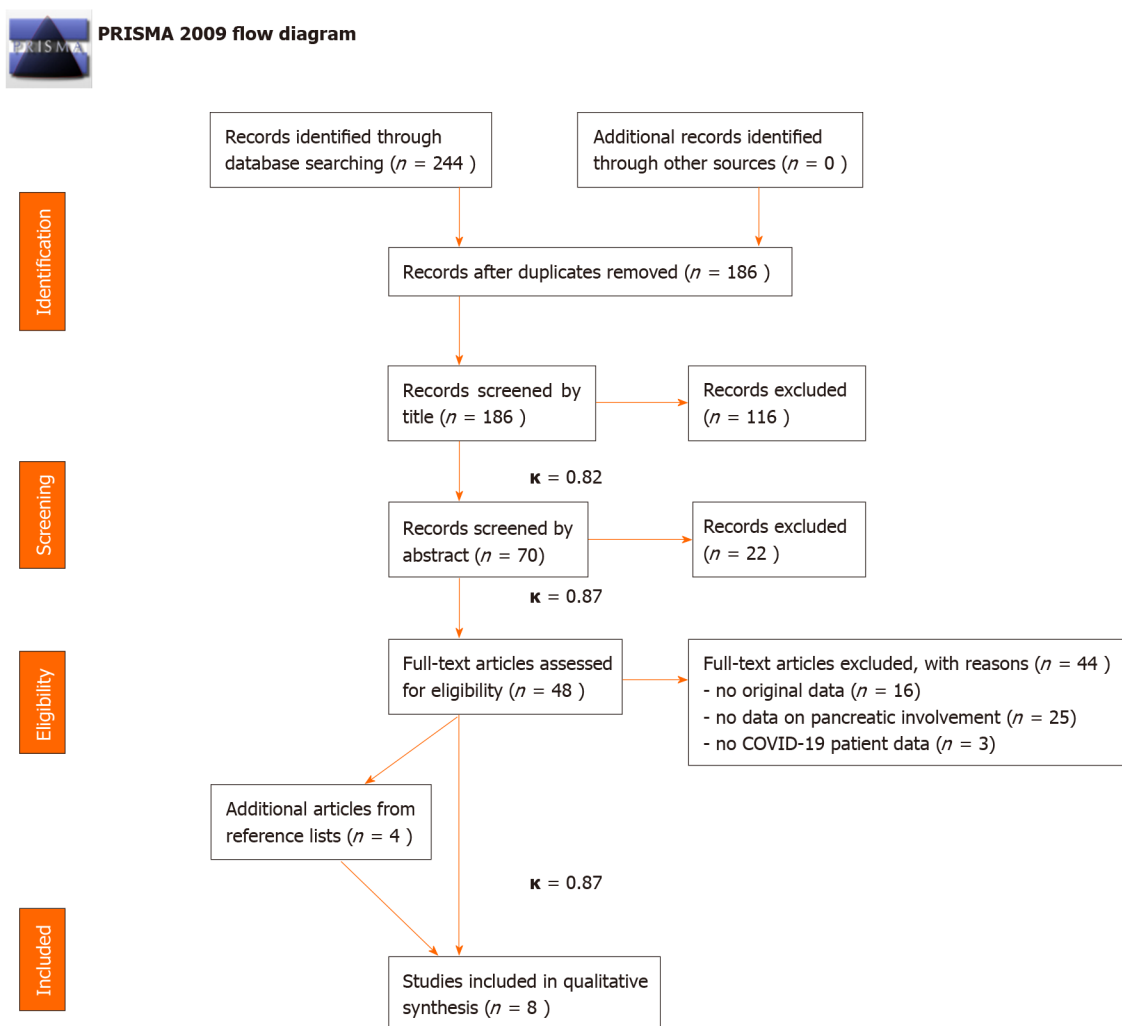
PRISMA 2009 flow diagram

Figure 1 PRISMA flow diagram demonstrating the selection of studies to be included in the review. κ represents Cohen's Kappa values indicating the rate of agreement between selection coordinators. COVID-19: Coronavirus disease 2019.

Other than the highlighted problems tied to the etiological workup, we would like to briefly address an issue with the diagnosis. Two studies not included in this review[9,10] labeled patients with serum amylase and/or lipase values higher than the upper limit of normal to possess "pancreatic injury". As de-Madaria *et al*[11] pointed out in reflecting on Wang *et al*[9], the elevation of pancreatic enzyme levels in the blood is not necessarily a consequence of an insult to the pancreas. Possible reasons are the high prevalence of renal impairment and diabetes mellitus, gastroenteritis, and metabolic changes, such as acidosis, or even salivary glandular entry by SARS CoV-2[39-42]. More importantly, a slight elevation in serum amylase and/or lipase levels alone is not established as an indicator of pancreatic damage. The Atlanta diagnostic criteria should be applied when determining the presence of AP[19].

The case reports in our review carry considerable risk of bias and their deviation from the Case Report guideline[43] on reporting methods. As demonstrated, the etiological workup of patients was incomplete, and often COVID-19 was named as the causative agent of AP, while other established factors were also present.

Considering limitations, incomplete reporting of the included studies encompasses a high risk of bias in our analysis[44-46].

CONCLUSION

To conclude, we strongly emphasize the need for guideline adherence when diagnosing and uncovering the underlying etiological factors of AP, even during a pandemic. As specific therapeutic options[19] are available depending on etiology, neglecting these steps can hinder direct therapy and lower the chances of recovery,

while increasing the probability of complications and recurrent episodes.

ARTICLE HIGHLIGHTS

Research background

Since the rapid progression of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, numerous publications postulated pancreatic involvement. Furthermore, angiotensin-converting enzyme 2 expression -the cellular entry point of the virus- was described in the pancreas.

Research motivation

Multiple etiological factors can be uncovered in a large proportion of acute pancreatitis cases. Therefore, the characterization of SARS-CoV-2 infection as a potential contributing factor was necessary.

Research objectives

Our aim was to review all available clinical evidence on acute pancreatitis cases in coronavirus disease 2019 (COVID-19) patients and to analyze the role of COVID-19 as an etiological factor.

Research methods

A systematic search was conducted in five databases on 14 May 2020 (registration number CRD42020186426). Record selection and data extraction were carried out by two independent review authors. Studies containing the original data of at least 1 SARS-CoV-2-infected individual diagnosed with acute pancreatitis were considered eligible. The Joanna Briggs Institute Critical Appraisal Checklist for Case Reports and the Newcastle–Ottawa Scale were used for risk of bias assessment.

Research results

Eight studies (six case reports and two retrospective cohort studies) were included in this systematic review. All acute pancreatitis cases lacked proper etiological workup, but SARS-CoV-2 infection was confirmed by polymerase chain reaction in all cases. High risk of bias and non-compliance with the Case Report guideline was noted in all case reports.

Research conclusions

Guideline adherence is a quality indicator of patient care. We advise all clinicians to conduct proper etiological workup before entertaining the possibility of SARS-CoV-2 as a causative agent of acute pancreatitis.

Research perspectives

The potential mechanisms of pancreatic damage in COVID-19 should be investigated utilizing basic research methods and animal models to evaluate a possible causative association between SARS-CoV-2 and AP.

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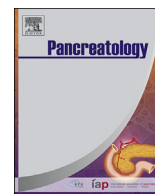
The EFFect of dietary fat content on the recurrence of pancreaTitis (EFFORT): Protocol of a multicenter randomized controlled trial

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ABSTRACT

Background: Around 20% of patients with acute pancreatitis (AP) will develop acute recurrent pancreatitis (ARP) and 10% will progress to chronic pancreatitis. While interventions to avoid recurrences exist for the two most common causes — abstinence for alcoholic and cholecystectomy for biliary pancreatitis — the are no known preventive measures in idiopathic ARP. Though it is not included in any of the guidelines, a low-fat diet is often recommended.

Our aim is to test dietary fat reduction's effect on AP recurrence in a randomized controlled setting, in order to provide high-quality evidence for the validity of such an intervention.

Methods, design: Participants with at least 2 episodes of AP in the preceding 2 years of which the last episode was idiopathic will be randomized to one of two diets with different fat contents: a 'reduced fat diet' (15% fat, 65% carbohydrate, 20% protein) and a 'standard healthy diet' (30% fat, 50% carbohydrate, 20% protein; based on WHO recommendations). Participants will be followed-up for 2 years (visits will be scheduled for months 3, 6, 12, 18 and 24) during which they will receive a repeated session of nutritional guidance, complete food frequency questionnaires and data on relapse, mortality, BMI, cardiovascular parameters and serum lipid values will be collected.

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Discussion: This study will determine the effect of modifying the dietary fat content on AP recurrence, mortality, serum lipids and weight loss in idiopathic cases.

Trial registration: The study is registered at clinicaltrials.gov under registration number NCT04761523

Ethical approval number: 40304-11/2020/EÜIG

1. Introduction

Acute pancreatitis (AP) is an inflammatory disorder of the pancreas, most frequently caused by excessive alcohol consumption and gallstones [1]. Around 20% of patients with AP will develop acute recurrent pancreatitis (ARP) and 10% progress to chronic pancreatitis (CP) [2]. While interventions exist to avoid recurrences in the case of the two major etiologies — abstinence in alcoholic AP and cholecystectomy in biliary AP — there are no preventive therapeutic options for patients with idiopathic ARP. One possibility would be to comply with a low-fat diet, which is widely recommended to AP patients, regardless of etiology.

Though it is indeed frequently recommended, maintaining a low-fat diet after AP is not included in any of the guidelines [3–5] and evidence is scarce. In a prospective cohort of more than 36,000 participants, Prizment et al. found increased total and saturated fat intake to be associated with AP [6]. Setiawan et al. observed a positive association between saturated fat intake and gallstone-related AP, but not with non-gallstone-related AP, ARP or CP [7]. Oskarsson et al. prospectively studied a cohort of non-gallstone-related AP patients with no clear associations between overall diet quality and pancreatitis recurrence or progression [8]. Aside from the recognized connection between high fat intake and gallstone formation, thus biliary AP [9,10], there are hypotheses as to why fat excess could be a risk factor for non-biliary pancreatitis as well. One possible reason can be the elevated serum triglyceride (TG) levels, a known etiological factor for AP, stimulating free fatty acid production which is believed to be pancreatotoxic [6,11–13]. Zhang et al. found that a chronic high-fat diet in rats increased levels of pancreatic free fatty acids and lipid peroxidation, associated with pancreatic injuries and collagen synthesis via activated pancreatic stellate cells [14]. Animal experiments have also described a more severe AP course in animals on high-fat diets [15].

While the aforementioned cohort trials boast an impressive number of participants the study design is not suitable to determine a cause-effect relationship between dietary fat content and pancreatitis recurrence.

Our aim was to conduct a randomized controlled trial (RCT) comparing two low-fat diets that contain the same amount of calories and protein but have different fat contents (15 and 30% respectively) in order to determine the effect of dietary fat content reduction on AP recurrence. We wanted to include patients with idiopathic ARP as this is the group without a preventive therapeutic option. Our hypothesis is that while patients on both arms will benefit from receiving nutritional guidance, those with less fat in their diet will see an additional benefit due to the further reduction in serum lipids.

2. Methods, design

2.1. Trial design, study setting

This study will be a multicenter, prospective, parallel-group RCT with a superiority framework. Participants will be randomly assigned in a 1:1 ratio to one of 2 different dietary interventions which are: a 'reduced fat diet'-arm and a 'standard healthy diet'-arm (largely based on WHO recommendations) to be further detailed in the 'Interventions'-section of this protocol.

The chief study site will be an academic hospital (1st Department of Medicine, Medical School, University of Pécs in Pécs, Hungary), other academic hospitals and hospitals with internal medicine departments regularly treating AP both in and out of Hungary will be invited to join the study. List of study sites can be obtained at clinicaltrials.gov.

2.2. Eligibility criteria

The inclusion and exclusion criteria for this trial are detailed in Table 1. A participant must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for enrolment.

2.3. Interventions

2.3.1. Description of interventions

Participants will be randomly assigned in a 1:1 ratio to one of 2 different dietary interventions which are as follows: (1) a 'reduced fat diet' in which the daily calorie intake will be composed of 15% fat, 65% carbohydrates, 20% proteins; (2) a 'standard healthy diet' (which also qualifies as a low-fat diet and is largely based on WHO recommendations) in which the daily calorie intake will be composed of 30% fat, 50% carbohydrates and 20% proteins.

Diets will be individualized to each participant. We will provide, for both arms, recommendations and meal-plans prepared every 200 kcals between 1800 and 3000 kcal. Before performing the dietary intervention, study dieticians will be required to use one of these sample diets and tailor it to the exact calorie needs of the participant (and if necessary, make alterations based on the country of the enrolling center).

Consultations will take place in an outpatient setting. When assigned to an intervention, first, patients will complete a food frequency questionnaire (FFQ — the National Health and Nutrition Examination Survey FFQ) to assess their eating habits. Then, based on their assigned intervention group they will receive recommendations according to the given diet. These consultations will be conducted by study dieticians centrally trained and evaluated by a qualified dietician coordinator. Relatives of the participants will also be allowed to attend these consultations, since the cooperation and involvement of family members can augment adherence and it is possible that the participant is not personally involved with the alimentation of the household.

The FFQ applied in this study is not only capable of assessing fat, carbohydrate and protein consumption but will provide a more detailed breakdown of dietary intake. Such detail is needed to account for other dietary variables possibly skewing data (not very likely due to randomization) and to conduct subgroup analyses — for details, see 'Statistical analysis plan'.

2.3.2. Discontinuation criteria

Participants will be advised to discontinue their allocated intervention (through personal communication or if impossible,

Table 1
Inclusion and exclusion criteria.

Inclusion criteria
1. Individuals with at least two episodes of acute pancreatitis in the 2 years preceding the inclusion with
2. The last episode being idiopathic, who are
3. At least 14 years old.

Exclusion criteria
1. Individuals already receiving regular nutritional guidance (with medical indication),
2. Individuals in critical condition or in terminal stage of cancer (with an expected survival <2 years),
3. Individuals undergoing treatment for active malignancy,
4. Individuals with known cholecystolithiasis,
5. Individuals with uncontrolled diabetes mellitus (admitted lack of compliance with antidiabetic therapy/HbA1c ≥7%/indication of uncontrolled diabetes mellitus in last 24 months' anamnesis/newly discovered diabetes mellitus)
6. Individuals who are pregnant or nursing
7. Individuals with a BMI < 18.5
8. Individuals who are regularly receiving systemic corticosteroids
9. Individuals consuming more alcohol than: 5 units per day or 15 units per week for men; 4 units per day or 8 units per week for women.

One unit of alcohol equals 10 ml or 8 g of pure alcohol. HbA1c: hemoglobin A1c; BMI: body mass index.

other means – phone, e-mail, mail) if any of the following happens:

(1) The participant withdraws his/her consent, (2) fails to attend two consecutive visits (3) develops one of the conditions mentioned in the exclusion criteria, or (4) completes the study. In these cases, participants will be advised to keep a balanced diet (according to WHO recommendations) with appropriate amount of calories to their age, gender, body weight and physical activity [16].

Based on any positive results of our study, dietary recommendation for this patient population might change and testing the long-term effect of these diets on pancreatitis recurrence, progression to CP and mortality might become necessary in form of a separate controlled trial.

2.3.3. Adherence
Compliance with dietary interventions is often problematic, this was taken into account when estimating the required sample size. We will, however, attempt to augment adherence via a repeated dietary intervention at the second visit, by completing FFQs with participants with the explicit purpose of estimating adherence and by reminding participants that through the evaluation of their BMI, laboratory results and FFQs we will have a good overview on whether or not they complied with the recommendations. These data will also be used to give motivational feed-back to the participants at the second visit.

Additionally, before participants consent to take part in the study they will be provided with detailed information on the composition and fiscal aspects of both diets so as to reduce dropouts after-randomization. Our center will also maintain a "hotline" – a telephone number that can be reached during working hours to answer questions that emerged regarding the diet.

2.3.4. Concomitant care
Concomitant interventions that do not categorically alter the diet of participants will not be limited.

2.4. Outcomes

2.4.1. Primary outcome measures
The primary outcome measure for this trial will be (1) a composite endpoint: the recurrence of AP (given as a rate of event) AND/OR all-cause mortality.

2.4.2. Secondary outcome measures
Secondary outcome measures will be the following: (1) Pancreas-specific mortality; (2) Cardiovascular cause mortality, (3) newly diagnosed CP, (4) changes in BMI compared to baseline (both total and percentage), serum lipid parameters (values and change from baseline), including: (5) total cholesterol, (6) TG, (7) HDL-cholesterol and (8) LDL-cholesterol; (9) serum albumin value and change from baseline, levels of (10–13) vitamins A, D, E and K (value and change from baseline); (14) blood pressure (systolic and diastolic) values and change compared to baseline. We will also assess (15) current smoking at the time of each visit, (16) adherence to dietary recommendations (as determined by the results of a food frequency questionnaire); (17) adverse events (given as rate of events). We will also assess (18) quality of life with the EQ-5D-5L questionnaire (see in supplementary material) and (19) muscle strength using a handgrip dynamometer (value and change from baseline for both).

2.4.3. Additional data collected at baseline
The index visit will entail an additional patient questionnaire and retrospective chart review collecting data on: comorbidities (diabetes, hypertension, chronic heart disease, chronic kidney disease, chronic liver disease, stroke, etc.), socioeconomic status (education, occupation, income, subjective social status) and past pancreatic history: how many episodes of AP, etiology of former episodes, is CP present. In case the patient has a new episode of AP during the study period, its etiology will also be recorded.

Data collection forms are available in our supplementary material.

2.4.4. Biologic sample collection
At enrollment and every visit, basic laboratory tests from blood will be carried out and participants will provide blood for storage in the biobank.

Laboratory parameters measured are shown on the data collection forms in our supplementary material. In case of alarming laboratory results, a physician will be notified, who will decide whether further medical attention is necessary. All patients will receive the results of their laboratory tests in written form.

The samples in the biobank will be stored at −80 °C and identified by the personal identification number (PIN) given at study entry. All samples will be collected and sent together to the laboratory when the patient number reached the pre-set goal for analysis.

From the collected biological samples, we will — for not diagnostic, but research purposes — conduct genetic analyses. In case the result of these analyses contains information that impacts the health of either the participant or their relatives, we will inform them via one of the provided methods of availability.

2.4.5. Participant timeline

All participants will appear at the study site according to the study schedule (Table 2).

To determine eligibility, physical examination, BMI measurement, laboratory testing and a review of the individuals' medical history and documentation in order to rule out AP with an established etiology will be performed. At the time of allocation and before receivable of the intervention baseline values for outcomes (4—15, 18, 19) will be collected and participants will be physically examined as well as a FFQ will be completed with the help of a study administrator, all in an outpatient setting. All outcomes will be assessed at 3, 6, 12, 18 and 24 month visits. Participants will receive a repeated dietary intervention at months 3, 6, 12 and 18.

2.4.6. Sample size

As there are no similar studies to date, we will employ a two-stage trial design — we estimated a likely accurate participant number of 384 accounting for drop-outs, equally allocated (192-192) to both intervention groups which we will refine according to the results of an interim analysis performed at the time of reaching 50% (n = 192) of the planned participant number. We based this preliminary estimate on (1) recurrence rates among patients with at least 2 episodes of AP within 2 years from the Hungarian Pancreatic Study Group's (HPSG) AP registry and (2) an RCT conducted by Nordback et al. [17] examining the effect of two types of alcohol-intervention on pancreatitis recurrence.

2.4.7. Recruitment

Recruitment will be performed in 2 distinct ways: (1) patients can be asked to participate during their pancreatitis-associated hospital stay, or (2) eligible patients identified through medical database search can be contacted with a proposal of participation. The planned start of recruitment is 2021.07.01. with a proposed end of 2026.07.01.

2.5. Assignment of interventions

2.5.1. Sequence generation and allocation concealment mechanism

Central randomization will be used with randomly permuted block size and allocation ratio of 1:1 using a computer-generated random sequence. Participants will be stratified based on (1) the presence of CP and (2) the presence of DM. Inclusion criteria and exclusion criteria will be checked prior to computer-aided randomization via an online platform to ensure that only eligible patients are included in the trial. The platform generates a PIN. The computer-aided randomization ensures allocation concealment. The randomization procedure will be performed by the same person who screened and consented the patient.

2.5.2. Blinding

Due to their role in delivering the individualized dietary intervention, study dieticians cannot be blinded to the group of the participants. Since they complete the FFQs with the participants, the assessment of dietary habits will not be blinded. Doctors caring for the participants and assessors of all other outcomes (laboratory parameters, BMI, blood pressure, adverse events) as well as statisticians handling the data will be blinded to the participants' allocated group. Participants will also be blinded — they will be informed of the trial structure and that they will be randomized to one of two diets with different dietary fat contents but they will be warned in advance that dieticians will not reveal to them whether they are in the 'reduced fat diet' arm or the 'standard healthy diet' arm. Naturally, they will be informed and allowed to ask in detail regarding the composition of these two diets, but it is our firm belief, that based only on this information and the meal-plan that the dietician will give to the participants, the vast majority will not know which arm they are on.

2.6. Data management, analysis and monitoring

2.6.1. Data management and monitoring

Investigators will be responsible for the accuracy, reliability and quality of the collected data. Detailed data flow will be described in a Data Management Plan. Data from completed electronic case report forms (eCRFs) will be validated under the direction of the Data Manager on the DMC according to a Data Cleaning Plan. Any missing, implausible, or inconsistent recordings in the eCRFs will be referred back to the Investigator using a data query form and will be

Table 2
SPIRIT schedule outlining timing of interventions and assessments.

STUDY PERIOD	Screening	Allocation	Visit 2	Visit 3	Visit 4	Visit 5	Close-out
	−4 − 0 weeks	0 week	3 months	6 months	12 months	18 months	24 months
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS (dietary consultation)							
Reduced-fat group		X	X	X	X	X	
WHO-diet group		X	X	X	X	X	
ASSESSMENTS:							
Physical examination	X	X	X	X	X	X	X
BP, HR measurement		X	X	X	X	X	X
BMI measurement	X	X	X	X	X	X	X
Laboratory testing	X	X	X	X	X	X	X
Handgrip test		X	X	X	X	X	X
Food Frequency Questionnaire		X	X	X	X	X	X
Quality of life		X	X	X	X	X	X
Comorbidities, socioeconomic status, pancreatic history	X						

WHO: World Health Organization; BP: blood pressure; HR: heart rate; BMI: body mass index.

documented for each subject before clean file status is declared. All changes to eCRFs will be recorded.

The DMC will perform an independent assessment of trial-related documents and activities to ensure respect for subjects' rights, safety and well-being and to guarantee the plausibility of clinical data. The similarity of groups at baseline will also be checked.

After written consent of the subjects, data will be recorded by the investigators. Clinical research data will be processed separately from participants' personal data. Data may only be accessed by persons acting under the authority of the controller and in accordance with the authorization system established within the controller's organizational structure, only to the extent and in the manner necessary for the performance of tasks. Personal data will not be made accessible to third parties.

2.6.2. Statistical analysis plan

In the final analysis, the intention-to-treat analysis will be favored over per-protocol (or "as-treated") analysis. We expect there will be no missing data for the primary outcome. In case there is, we will use available case analysis. The "last observation carried forward" strategy will be followed to impute missing data for other outcomes measured during the study, including data from the National Health Insurance Fund (or similar organizations in case of foreign centers).

In descriptive statistics, the count and percentage will be provided for each treatment arm for binary outcomes. For continuous outcomes, n, mean, median, interquartile (Q3—Q1), standard deviation, minimum, and maximum values will be provided for each treatment arm. In a univariate comparative analysis, we will calculate relative risk with 95% confidence interval (CI) when comparing the primary endpoint between two groups (alpha $= 5\%$) with a reference arm using non-repeated intervention complemented with chi-square or Fisher's exact test (the same strategy will be followed for binary secondary outcomes). For continuous variables, we will use *t*-test assuming unequal variances or the Mann-Whitney test. We will perform univariate (Kaplan-Meier and Cox-regression) and multivariate (Cox-regression) survival analysis for binary outcomes. An adjustment will be carried out at least for age, sex, BMI, smoking and education.

Results derived from the FFQs of the patients will give ground for subgroup analyses based on dietary factors. Pre-planned subgroup analyses will be based on: dietary adherence, alcohol consumption, daily calorie intake, true fat consumption, unsaturated and saturated fat consumption, *trans*-fat consumption and processed food consumption. We are also planning to conduct subgroup analyses based on the presence of known genetic variants in AP.

All analyses will be carried out with SPSS version 26 and Stata version 15.

2.6.3. Trial organization, committees and boards

The corresponding center of the EFFORT study is the Center for Translational Medicine at the University of Pécs Medical School (www.tm-centre.org), whereas the coordinator and designer research team is the HPSG (https://tm-centre.org/en/study-groups/hungarian-pancreatic-study-group/). The Centre for Translational Medicine and the HPSG have been running high-quality international, multicentre clinical trials together since 2014 [18—21] and have published relevant guidelines for pancreatic diseases with the aim of improving patient care [22—24].

The Steering Committee (SC) will be led by PH (principal investigator, gastroenterologist, specialist in internal medicine and clinical pharmacology). SC members will be MFJ (study coordinator), NF (biostatistician); ZsV (dietician coordinator); FI, LCza, MP,

AP (center representatives). There will be independent members as well, and the SC will include a patient representative. The SC will supervise the trial primarily and will make decisions regarding all critical questions (e.g., premature termination of the study, drop-outs, etc.).

All data gathered for research purposes will be handled confidentially and anonymously, which will be ensured by the Data Monitoring Committee (DMC). For each participant, a PIN will be generated that will be present on all forms and documents of each individual.

The International Advisory Board (ITAB) will include MW, SJP, FJ and GC.

The study was designed by the SC and was supported by the University of Pécs, Medical School. The sponsor had no role in the design of the trial and will have no access to the randomization codes or the data.

Five eligible patients were invited to review the protocol and to discuss any concerns or doubts that emerged. Remarks made during this meeting were incorporated into the final version of the protocol. The participant prospects positively responded to the concept of the study and highlighted its importance, agreed that the primary outcome was crucial. They deemed the forms and questionnaires understandable and appropriate. We originally planned only 2 follow-ups at months 12 and 24, but upon discussing it with the participant prospects they highlighted the importance of frequent controls in supporting dietary adherence, thus we modified the study schedule to include more visits. We also added the option of calling for dietary advice and for relatives to attend the dietary consultation to augment adherence, as described in the 'Adherence' and 'Description of interventions' sections of the protocol. The participant prospects described no negative feelings or ethical concerns regarding blood sample tests and the two interventions used in the study.

The independent Safety Monitor will be LCzo. The monitor will ensure the safety of the patients.

2.6.4. Interim analyses

(1) Upon reaching 10% of the target sample size an interim safety analysis will be performed wherein the Safety Monitoring Board will review data of the patients and determine whether the occurrence of any negative effects can be linked to any of the interventions and if needed the given intervention or the trial will be terminated for the safety of the patients.

At the point of the safety analysis, patient data will only be made available to the Safety Monitoring Board and they will make the final decision whether or not to terminate the trial.

(2) Upon reaching 50% of the target sample size an interim analysis will be performed in order the refine the number of participants necessary to complete the trial (see 'Sample size').

2.6.5. Safety

As our primary interest was the safety of participants, we did not overstep the WHO recommended maximum 30% fat intake (which already qualifies as a low-fat diet) just to better observe differences in AP recurrence. Maintaining such a balanced diet or a diet with an added reduction in fat content similar to what we aim to assess poses no health risks whatsoever. Adverse events in these cases might be due to a formerly excessive eater attempting controlled intake, such as irritation, fatigue, maybe headache. Other

minor and moderate events may occur, but we expect no serious side effects with either of the interventions. In case a potentially serious health problem is detected by the investigators related to the intervention, the Safety Monitoring Board will be notified. To avoid detection bias in assessing adverse events doctors conducting patient examination will be advised to ask all patients about the presence of nausea, abdominal pain and changes in stool.

The frequent dietary monitoring will also allow for the prompt recognition and treatment of malnourished participants.

Upon reaching 10% of the target sample size an interim safety analysis will be performed wherein the Safety Monitoring Board will review data of the patients and determine whether the occurrence of any negative effects can be linked to any of the interventions and if needed the given intervention or the trial will be terminated for the safety of the patients.

2.6.6. Ethics, dissemination

This trial is registered on clinicaltrials.gov (NCT04761523).

This study was approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (40304-11/2020/EÜIG), on 2020.08.17.

Planned start of patient recruitment: 2021.07.01.

Anticipated study duration: 5–6 years.

Study results will be published in an international scientific journal. Study sponsors have no role in writing the publication, deciding to publish and choosing the target journal.

2.6.7. Protocol amendments

In case of any changes and deviations from the original protocol, investigators and past participants will be contacted via email, letter, or phone; future participants will be notified in person during inclusion; deviations from the original protocol will be indicated on clinicaltrials.gov and in any and all publications originating from the acquired data.

Consent

Informed consent for participation in the study and providing biological samples will be collected by medical doctors. For a model adult consent form see our supplementary material. Consent forms are tailored to the age of the participant, each having received ethical approval.

3. Discussion

It has been a long-standing conviction that dietary fat content, even in the absence of immoderate calorie intake and putting biliary factors aside, can influence pancreatic pathogenesis. This study is the first to test this hypothesis in a randomized, controlled setting.

The results of our study will determine the effect of modifying the dietary fat content on AP recurrence, mortality, serum lipids and weight loss in idiopathic ARP cases ie. the patient group in which there is a dire need for interventions to positively influence the course and progression of the disease.

4. Strengths and limitations

The main strength of this study is that it is the first RCT to test the effect of dietary fat content on pancreatitis recurrence, thus providing high quality evidence for one of the central questions of pancreatology.

4.1. Limitations

As we tried to counteract the expected low event rate and finer

differences between interventions with a select population of frequent relapsers and a larger estimated sample size it is likely that enrolment will be slow. This could be ameliorated by multiple centers joining and supplying eligible participants already in their care. While it will provide insight on the effect of dietary fat content on recurrence, this comparison in itself is unsuitable to determine the effect of a low-fat diet compared to not dieting/excessive eating. We did not include such an arm as we found it unethical to not provide an individual with dietary recommendations after AP. However, we plan to estimate this effect, by comparing the groups with the best and worst dietary adherence based on the result of FFQs.

5. Implication for research: ketogenic diet

Originally, we planned to include a 3rd arm in our trial: a ketogenic diet arm. Several meta-analyses of RCTs compare such a diet to a low-fat diet in healthy individuals, or patients with malignancies, observing a favorable effect on diastolic blood pressure (DBP), serum TG and HDL-cholesterol levels [25–28]. However, issues regarding feasibility emerged. A ketogenic diet arm would have significantly raised the required patient number while introducing additional exclusion criteria to an already select patient population. Interview of participant prospects (see 'Roles and responsibilities) also revealed a low willingness to adhere with this diet. However, we encourage fellow researchers to pursue the possibility of the beneficial effect of ketosis on disorders of the pancreas.

Declaration of competing interest

Authors declare no conflicts of interest.

Acknowledgements

None

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2021.10.002.

Authors' contributions

Authorship was determined according to International Committee of Medical Journal Editors (ICMJE) recommendations. All authors participated in either drafting the study or providing critical revisions; all authors have read and approved the final manuscript version and are in agreement to be accountable for all aspects of the work.

Apart from above mentioned responsibilities, MFJ, KO, LS, NF, ZS, NZ, AP and PH made substantial contributions to the concept and design of the trial. Data collection was carried out by MFJ. NF performed the sample size estimation, based on data provided by MFJ and AP. MFJ wrote the majority of the manuscript. LCzo will also act as an independent Safety Monitor for the study. MW, SJP, FJ, GC, PGA, FI, LCza, MP, AP and PH will play a key role in participant enrolment and data acquisition. Every involved center can name coauthors for later publications for every 15 enrolled participant. Further roles are detailed in the 'Trial organization, committees and boards' section of the protocol.

Role of study sponsor in study

Study sponsors have no role in the planning, executing, analyzing and interpreting results of the study, nor in the decision to write and submit the report.

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