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Chronic pancreatitis: Pediatric and adult cohorts show similarities in disease progress despite different risk factors

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Abstract

Objectives: To investigate the natural history of chronic pancreatitis (CP), patients in the North American Pancreatitis Study2 (NAPS2, adults) and INternational Study group of Pediatric Pancreatitis: In search for a cuRE (INSPPIRE, pediatric) were compared.

Methods: Demographics, risk factors, disease duration, management and outcomes of 224 children and 1,063 adults were compared using appropriate statistical tests for categorical and continuous variables.

Results: Alcohol was a risk in 53% of adults and 1% of children ($p<0.0001$); tobacco in 50% of adults and 7% of children ($p<0.0001$). Obstructive factors were more common in children (29% vs 19% in adults, $p=0.001$). Genetic risk factors were found more often in children. Exocrine pancreatic insufficiency was similar (children 26% vs adult 33%, $p=0.107$). Diabetes was more common in adults than children (36% vs 4% respectively, $p<0.0001$). Median emergency room visits, hospitalizations, and missed days of work/school were similar across the cohorts. As a secondary analysis, NAPS2 subjects with childhood onset (NAPS2-CO) were compared to INSPPIRE subjects. These two cohorts were more similar than the total INSPPIRE and NAPS2 cohorts, including for genetic risk factors. The only risk factor significantly more common in the NAPS2-CO cohort compared with the INSPPIRE cohort was alcohol (9% NAPS2-CO vs 1% INSPPIRE cohorts, $p=0.011$).

Conclusions: Despite disparity in age of onset, children and adults with CP exhibit similarity in demographics, CP treatment, and pain. Differences between groups in radiographic findings and diabetes prevalence may be related to differences in risk factors associated with disease and length of time of CP.

Keywords

Children; pain; genetic; environmental; endoscopy; diabetes

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Conflicts of Interest

Dr. Mark Lowe is on the Board of Directors of the National Pancreas Foundation; he receives royalties from Millipore Inc and UpToDate. Drs. Tanja Gonska and Michael Wilschanski received a research grant from Vertex Pharmaceuticals. Dr. Sohail Husain owns equity in PrevCon. Dr. John Pohl is on the speaker's bureau for Medical Education Resources, Inc.; Dr. Melena Bellin is a consultant for AbbVie Inc and ARIEL Precision Medicine. Dr. Sarah Jane Schwarzenberg is a consultant for AbbVie, Inc. Dr. Aliye Uc is a member of American Board of Pediatrics, Subboard of Pediatric Gastroenterology. The other authors declare no conflicts of interest.

Introduction

Chronic pancreatitis (CP) is a fibro-inflammatory disease of the pancreatic parenchyma with variable and complex etiologies, features and severity [1]. Episodic and chronic pain, which is frequently intractable, leads to loss of work and school time [2–5], and increased utilization of healthcare resulting in high medical costs [6, 7]. CP is most commonly described in adults as associated with excessive use of alcohol and tobacco [8]. CP is increasingly recognized as a disease of children, [2, 9–12], although the prevalence of disease is lower than in adults [13]. This may represent a true rise in prevalence in children or improved ascertainment.

Two large, multicenter studies have described the characteristics of individuals with CP: The North American Pancreatitis Study 2 (NAPS2, adults) [14–16] and the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE, children) [2, 17, 18]. Both groups recruited individuals from secondary and tertiary referral centers. Each examined demographic and risk factors for CP, and disease-related outcomes in a cross-sectional manner.

The separate analyses of pediatric and adult CP cohorts hamper investigation of the full clinical course of CP. Genetic risk factors are reported to be more common in children than in adults with CP [2]. However, this difference may represent true differences in the genesis of CP in children compared with adults or may represent differences in clinical practice; that is, providers treating adults are less likely to order genetic testing. Adults and children may have differences in the progression of CP, or it may be that reports in adults and children represent an ongoing disease examined at different stages. Recent guideline publications by both adult and pediatric pancreas experts highlight the need to understand the full spectrum of disease [19, 20].

This study compares the NAPS2 and INSPPIRE CP cohorts, examining demographics, risk factors, disease duration, management and outcomes. Our goals are to better understand the natural history of CP and to initiate a dialog on protocols for care across age groups to improve outcomes across the age spectrum.

Methods

Study design and participants

INSPPIRE is a cross-sectional, multi-national study from 19 institutions, collecting demographic and clinical data by means of two sets of questionnaires: one completed by the patient or parent and the other completed by the physician on children who fulfilled the criteria for CP and were <19 years old at the time of enrollment [18]. Diagnosis of CP required at least 1 of the following: (1) abdominal pain plus imaging suggestive of changes associated with chronic pancreatic; (2) exocrine pancreatic insufficiency and imaging findings suggestive of chronic pancreatic damage; or (3) endocrine pancreatic insufficiency and imaging findings suggestive of chronic pancreatic damage [21]. Data for this analysis was entered into the Research Electronic Data Capture (REDCap, hosted at University of Iowa) database between August 22, 2012 to March 20, 2017 and represents baseline information from the cohort. All centers had institutional review board approval or the equivalent for

their country. All centers obtained written informed consent and assent, when required, from parents and children. Some of the pediatric patients included in this study have been previously reported [2, 17, 22–24].

The NAPS2 is a series of three sequential cross-sectional studies (original NAPS2 study [14], NAPS2 continuation and validation and NAPS2 Ancillary Study) [14–16] involving 26 US centers that prospectively recruited CP patients 2000–2014. CP was defined as definitive evidence of CP on either (1) endoscopic retrograde cholangiopancreatography using the Cambridge classification or magnetic resonance cholangiopancreatography (MRCP), (2) computed tomography (CT) scan, or endoscopic ultrasound (EUS) (≥5 criteria or calcifications), or 3) histologic evidence of CP [14]. Data in this study was also collected by sets of questionnaires completed by the patient and the physician. Some adult patients included in this study have been previously reported [14–16].

Questionnaires for INSPPIRE were modeled after those for NAPS2, adapted for children. Both studies collected similar information on demographics, family and personal history, environmental history including smoking and alcohol consumption, and clinical questions related to pancreatitis, medication use, and disability. The similarity in study methodology allows comparison of these two cohorts. Physician questionnaires included documentation of risk factors and medical or surgical therapies prior to enrollment [14, 18]. Risk factors for CP were by physician report, using the physicians' determination for the significance of alcohol or tobacco use, hypertriglyceridemia and hypercalcemia. Duration of disease was calculated from the time of first diagnosis of acute pancreatitis (AP), CP, or symptoms of pancreatitis (whichever came first) to entry into either NAPS2 or INSPPIRE.

In INSPPIRE, genetic risk factors were extracted from the physician report; the number of CP risk factor genes tested was variable. For the NAPS2 cohort, results reported here are based on *post hoc* testing for mutations in four genes (*PRSS1* (cationic trypsinogen gene), *CFTR* (cystic fibrosis transmembrane conductance regulator gene), *SPINK1* (serine protease inhibitor Kazal type 1 gene), *CTRC* (chymotrypsin C gene)) that all subjects underwent as part of a research study [25]. Analysis was done in a single laboratory by a combination of sequencing and Taq-man® assays (Thermo-Fischer, Waltham MA).

Statistical analysis

Demographic, clinical, and treatment variables were compared between pediatric and adult patients using t-test or Wilcoxon rank-sum test for continuous variables, Pearson chi-square test or Fisher's exact test for categorical variables, and Wilcoxon rank-sum test for ordinal variables. Summary statistics are presented as mean (standard deviation) or median (interquartile range, IQR) for continuous variables, frequency count (percent) or median (IQR) for ordinal variables, and frequency count (percent) for categorical variables. All statistical analyses were performed using SAS (version 9.4).

Results

Population

The NAPS2 cohort included 1,195 subjects. Of these, 1,063 had age at onset of symptoms or diagnosis of AP or CP (whichever came first) as adults (>18 years); 76 reported onset of symptoms or diagnosis of AP or CP at <18 years of age; age at onset of symptoms could not be determined in the remaining 56 patients. The INSPPIRE cohort included 224 childhood-onset CP subjects. None were in the NAPS2 cohort. All subjects included in the study met criteria for CP at enrollment in the study.

In the primary analysis, the 1,063 NAPS2 subjects with adult onset of disease were compared with the 224 INSPPIRE subjects with childhood onset. As a secondary analysis, the NAPS2 subjects with childhood onset were compared with the INSPPIRE subjects. In the secondary analysis, only the subjects specifying white race were compared (158 INSPPIRE, 69 NAPS2) because of the small size of the non-white population (n=7) in this NAPS2 subset.

Demographics

Demographic data for the primary analysis from the two cohorts are presented in Table 1. Age at presentation of CP was, by definition, divergent. Children presented at a mean age of 11.9±3.9 years, while adults presented at a mean age of 52.7±13.3 years. The cohorts were similar with respect to race. Female sex was more common in the pediatric cohort (56% female in pediatric cohort vs 45% in adult cohort, p=0.003). Adults with CP were more likely to be overweight or underweight, compared with children (adult cohort 10% underweight and 27% overweight vs pediatric cohort 5% underweight and 13% overweight, p=0.001 and p<0.0001, respectively). History of acute or acute recurrent pancreatitis was reported in pediatric CP 92% and 83%, respectively versus 71% and 66% of adult CP (p<0.0001 for each). Family history of CP was significantly more common in children with CP (23% in children vs 8% in adults, p<0.0001). This may reflect the difference in risk factors for the two groups, discussed below.

The pediatric cohort had a mean period of 3.6±3.3 years from patient or physician-reported presentation of disease to enrollment in INSPPIRE while adults had a 6.9±7.1 year period between disease onset and enrollment (p<0.0001).

Risk factors

Risk factors for CP in the two populations are presented in Table 2. Adults reported environmental risk factors significantly more than children. Alcohol exposure was a risk in 53% of adults and 1% of children (p<0.0001), and tobacco exposure was a risk in 50% of adults and 7% of children (p<0.0001). Hypertriglyceridemia was also more common in adults (11%) vs. children (4%) (p=0.007). Medications were more frequently identified as risk factors in children compared with adults (7% vs 3%, p=0.0007). Children were more likely to be diagnosed with autoimmune pancreatitis than adults (6% vs 2%, p=0.039). Obstructive factors were found more commonly in children (29%) compared with adults (19%), p=0.001).

Analysis of four genetic risk factors for CP, *PRSS1, SPINK1, CFTR and CTRC*, was done in every adult. As children were tested as part of clinical care, and often for a more limited group of genes, all four genetic risk factor results are not available for all children. Despite the more complete testing in adults, all four genetic risk factors were significantly more common in children than adults ($p<0.0001$ for each gene, Table 2).

Morphologic features

Morphologic features of the pancreas and biliary tree are important in the diagnosis of CP. Few differences were found between imaging features of the pancreas and biliary tree in adults and children (Table 3). Pancreatic calcifications, cysts and pseudocysts were significantly more common in adults (calcifications, 15% in children vs 57% in adults, $p <0.0001$; cysts/pseudocysts 22% in children vs 31% in adults, $p =0.007$). Pancreatic atrophy (fatty or fibrous replacement of the pancreas), which has been reported as more common in children with CP [2] was equal in occurrence in children and adults in this head-on comparison ($p = 0.063$).

Disease impact

The impact of CP was measured as frequency and intensity of pain, frequency of complications (exocrine pancreatic insufficiency or diabetes), and frequency of interference with daily life (Table 3). Pain was common in both adults and children, in both groups only 13–14% reported being always or usually pain-free. Adults reported more pain overall, with a higher percentage of adults reporting constant mild-moderate pain with episodes of severe pain. However, prevalence of constant severe pain was similar between the two groups (5% of children, 6% of adults). Adults were more likely to use pain medication of any kind (57% of children vs 70% of adults, $p=0.0006$), and more commonly used opioids either alone or in combination with non-opioids (children 42% vs adults 62%, $p<0.0001$).

Prevalence of exocrine pancreatic insufficiency was similar between the adult and pediatric cohorts (children 26% vs adult 33%, $p=0.107$). Diabetes was more commonly reported in adults than in children (36% vs 4% respectively, $p<0.0001$). Median number of emergency room visits and hospitalizations, as well as missed days of work and school in the year preceding enrollment were similar across both cohorts.

Medical and surgical treatment

Suppl Table 1 includes therapies used for CP in the children and adults. Adults were more likely to use pancreatic enzymes (children 55% vs adults 66%, $p=0.004$). Children were more likely to have undergone pancreatic duct sphincterotomy ($p<0.0001$) and pancreatic duct stone removal ($p<0.0001$) compared with adults and less likely to have undergone cholecystectomy ($p=0.0002$).

Secondary population analysis

Table 4 compares demographic and risk factors of 69 white adults from NAPS2 who reported their CP began in childhood and 158 white subjects from the INSPPIRE cohort. These two cohorts were much more similar than the entire INSPPIRE and NAPS2 cohorts. Percent female sex was similar in these two groups, with the INSPPIRE cohort 51% female

and the NAPS2 childhood onset cohort at 54% female. Prevalence of family history of CP and presence of genetic risk factors were similar between the two groups, as was the presence of pancreas divisum. The only risk factor significantly more common in the NAPS2 childhood onset cohort compared to the INSPPIRE cohort was alcohol as a risk factor (9% in NAPS2 and 1% in INSPPIRE cohorts, p=0.011). Disease duration for the two cohorts was different; however, comparison was not made as the difference may be due to the study start periods.

Discussion

The NAPS2 and INSPPIRE cohorts allow large studies of demographics, risk factors, clinical course and therapies in adults and children, respectively, with CP. Our comparison of these two large databases shows that children have few differences and many similarities in demographics, complications and therapies. In contrast, marked differences exist in risk factors between children and adults.

In studies of children with CP, the most common physician-reported risk factors are genetic variants associated with CP [2, 10–12, 17, 26]. Adults more commonly have environmental risk factors, particularly alcohol and smoking [3, 8, 27, 28]. Even when adults with CP were tested *post hoc*, the presence of known genetic risk factors was significantly lower than in children. This difference may account for the difference in age of presentation of disease. It is likely that genetic risk factors with significant penetrance lead to onset of CP in childhood, whereas the older age when alcohol and tobacco use begins and the length of use contributes to adult-onset CP. The finding that adults with CP in the NAPS2 study who presented during childhood have a similar frequency of genetic risk factors compared with the INSPPIRE cohort supports this hypothesis. It is also possible that adults with CP have less penetrant genetic risk factors and thus manifest later in life or when an environmental risk factor is introduced. It should be noted that the degree to which second-hand smoke might contribute to childhood CP is undetermined, as unbiased analysis of the risk of second-hand smoke (for example, using urine or blood cotinine levels) has not been done.

When comparing the INSPPIRE cohort with the patients in NAPS2 who presented as children, we did not find significant differences in the prevalence of genetic variants between the groups. Although a previous report found that *PRSS1* and *CTRC* mutations are more prevalent in early childhood CP [22], only *PRSS1* approached significance (p = 0.059) in our analysis. The average age of initial presentation of CP is older in the adults in NAPS2 who presented as children compared to the INSPPIRE cohort. This may explain the difference in the prevalence of *PRSS1* and *CTRC* mutations.

Of great clinical significance, our data shows that children and adults report similar pain patterns in terms of severity and frequency of daily pain. Pain is one of the most severe complications of CP, and the factor most likely to lead to disability. Pain intensity is a subjective measure; thus, it is striking that both groups describe their pain patterns so similarly. Despite comparable reports of pain frequency and intensity, children report less pain medication use than adults. Our study cannot determine what level of pain management is appropriate, but these data suggest that investigation of the adequacy of pain management

in adults and children is crucial to limit the long-term effects of too little or too much pain control. Increased use of pain scales and protocol medication management may improve control and outcome for both adults and children.

Overall children and adults have a similar incidence of complications with a few exceptions. Adults have more pancreatic calcifications on imaging and are more likely to develop diabetes. American adults in general have a high background risk of diabetes (12.2% in people in America > 18 years of age [29]), but adults with CP have >2 times the baseline risk. The differences in pancreatic calcifications and diabetes between adults and children may, in part, result from the differing risk factors associated with CP, or possibly disease duration, rather than the age of the patient at disease onset [30]. In the group of adult subjects with disease onset in childhood there was also a higher frequency of pancreatic calcification and diabetes in adulthood compared to the pediatric population (data not shown). This suggests that endocrine (but not exocrine) insufficiency is dependent on longer disease duration, as both groups have similar risk factors for CP. The NAPS2 childhood onset cohort was close to the same age as the INSPPIRE cohort at their first episode of pancreatitis, but older at the age of diagnosis of pancreatitis. It is possible that environmental factors, such as alcohol or tobacco become risks as children with a previous episode of pancreatitis age into their teens.

In our cohorts, the most common risk factors in adults were alcohol and tobacco use; in children genetic and obstructive risk factors were more common. Alcoholic pancreatitis has a more rapid progression than genetic or idiopathic pancreatitis [31–33], and cigarette smoking has a high prevalence of pancreatic calcifications and increases risk for exocrine pancreatic insufficiency [34, 35]. Additionally, cigarette smoking often correlates with alcohol use [36]. Both alcohol use and tobacco use are independently associated with development of insulin resistance [37, 38]. Thus, in children and adults with similar length of CP, adults with CP would be more likely to exhibit advanced radiographic disease and be more likely to have diabetes. In this respect, children are more similar to adult women with CP, whose pancreatic morphology is different from men, likely reflecting different risk factors associated with their CP [27].

Our study has limitations. Both the NAPS2 and the INSPPIRE recruited subjects from secondary and tertiary treatment centers; individuals with milder forms of CP may not present at these centers and be underrepresented. The NAPS2 study is limited to the USA while the INSPPIRE cohort includes subjects from sites outside the USA Environmental risk factors or clinical management may differ between countries. The discrepancy in size of cohorts may also affect statistical analysis.

In conclusion, despite the disparity in age of onset of disease, children and adults with CP exhibit remarkable similarity in demographics, treatment of CP, and experience of pain. Differences between the groups with respect to radiographic findings and prevalence of diabetes may be related to the differences found in the risk factors associated with disease and the length of time they have had CP. Typically, children and adults with CP are diagnosed and managed by separate medical teams. Our study suggests that to understand the natural history of CP we need to include both children and adults in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is known

- Chronic pancreatitis (CP) is a devastating disease leading to pain and lost school/work time.
- Understanding the similarities and differences in CP between these groups is critical to providing appropriate care to children in transition from pediatric to adult providers.

What is new

- Children and adults with CP exhibit remarkable similarity in demographics, treatment of CP, and pain experience.
- Adults and children with CP have different risk factors for their disease: genetic factors in children versus alcohol and smoking in adults. This may explain the variations in disease progression in these two populations.

Table 1.

Demographic characteristics of pediatric and adult subjects with chronic pancreatitis in the INSPPIRE and NAPS2 cohorts

	All CP			
	Pediatric (n=224)	**Adult (n=1063)**	**Odds Ratio (95% CI) Pediatric/Adult**	**p-value**
Age at enrollment	(n=214)	(n=1063)		
Mean±SD	11.9±3.9	52.5±13.3		
Median (IQR)	12.6 (9.7–15.2)	52.7 (43.2–61.5)		
Age at first diagnosis AP	(n=157)	(n=633)		
Mean±SD	8.1±4.3	43.0±14.0		
Median (IQR)	7.7 (4.5–11.6)	43.0 (32.0–52.0)		
Age at diagnosis CP	(n=172)	(n=1035)		
Mean±SD	9.8±4.1	49.1±13.4		
Median (IQR)	9.9 (6.7–12.8)	49.0 (39.0–58.0)		
Sex (Female)	125/223 (56%)	479 (45%)	1.56 (1.16, 2.08)	0.003
Race (White)	158/192 (82%)	813/1062 (77%)	1.42 (0.96, 2.12)	0.080
BMI *	(n=216)	(n=1050)		
Underweight	10 (5%)	102 (10%)	0.33 (0.17, 0.65)	0.001
Normal	146 (68%)	496 (47%)	(ref)#	
Overweight	29 (13%)	289 (27%)	0.34 (0.22, 0.52)	<0.0001
Obese	31 (14%)	163 (16%)	0.65 (0.42, 0.99)	0.046
History of acute pancreatitis	180/196 (92%)	662/930 (71%) ***	4.55 (2.68, 7.74)	<0.0001
History of ARP	161/195 (83%)	457/690 (66%)	2.41 (1.61, 3.61)	<0.0001
Family history of CP **	42/185 (23%)	81 (8%)	3.56 (2.36, 5.38)	<0.0001
Family history of AP	52/177 (29%)	71 (7%)	5.81 (3.88, 8.70)	<0.0001
Disease duration	(n=170)			
Mean±SD	3.6±3.3	6.9±7.1		
Median (IQR)	2.7 (0.9–5.4)	4.3 (2.0–9.4)		<0.0001

N, number of patients, is noted for an individual variable if fewer patients or physicians completed the appropriate question in the questionnaires. Where no “n” is noted for a variable the “n” is the whole cohort.

AP: Acute Pancreatitis; ARP: acute recurrent pancreatitis; CP: Chronic Pancreatitis

* BMI categories for pediatric patients based on percentile rankings using CDC data; underweight is <5th percentile, normal is 5th–85th percentile, overweight is ≥85th percentile, obese is ≥95th percentile, for age and gender. BMI categories for adults: underweight <18; normal 18-<25; overweight 25-≤30; obese >30.

** Family history of CP is for first degree relatives.

*** In 133 adult patients, the enrolling physician indicated a history of acute pancreatitis to be unclear or unknown, or the information was missing.

Normal weight was the reference category

Table 2.

Distribution of risk factors in pediatric and adult subjects with chronic pancreatitis according to the TIGAR-O classification in the INSPPIRE and NAPS2 cohorts

	All CP			
	Pediatric (n=224)	**Adult (n=1063)**	**Odds Ratio (95% CI) Pediatric/Adult**	**p-value**
Toxic/Metabolic Factors				
Alcohol	3/220 (1%)	562 (53%)	0.01 (0.004, 0.04)	<0.0001
Tobacco (Active or Passive)	15/212 (7%)	536 (50%)	0.07 (0.04, 0.13)	<0.0001
Hypertryglyceridemia	7/173 (4%)	113 (11%)	0.35 (0.16, 0.77)	0.007
Hypercalcemia	0/180 (0%)	9 (1%)	--	0.373
Medications	14/188 (7%)	28 (3%)	2.97 (1.54, 5.76)	0.0007
Chronic renal failure	1/191 (1%)	19 (2%)	0.29 (0.01, 1.84)	0.343
Genetic mutations*				
PRSS1	69/156 (44%)	20/1028 (2%)	39.97 (23.21, 68.85)	<0.0001
SPINK1	32/142 (23%)	69/1005 (7%)	3.95 (2.48, 6.27)	<0.0001
CFTR	42/149 (28%)	151/1017 (15%)	2.25 (1.51, 3.35)	<0.0001
CTRC	8/96 (8%)	10/1030 (1%)	9.27 (3.08, 26.74)	<0.0001
Autoimmune				
Autoimmune pancreatitis	9/162 (6%)	26 (2%)	2.35 (1.08, 5.10)	0.039
Other autoimmune diseases	13/189 (7%)	29 (3%)	2.63 (1.34, 5.16)	0.004
Obstructive Factors	58/200 (29%)	200 (19%)	1.76 (1.25, 2.48)	0.001
Pancreas divisum	25/195 (13%)	91 (9%)	1.57 (0.99, 2.27)	0.059
Sphincter of oddi dysfunction	3/191 (2%)	57 (5%)	0.28 (0.09, 0.91)	0.024
Gallstones	7/195 (4%)	54 (5%)	0.70 (0.31, 1.55)	0.373
Duct obstruction	6/195 (3%)	54 (5%)	0.59 (0.25, 1.40)	0.228

n, number of patients, is noted for an individual variable if fewer patients or physicians completed the appropriate question in the questionnaires. Where no “n” is noted for a variable the “n” is the whole cohort.

Note that some patients had more than one risk factor.

CP: Chronic Pancreatitis

*Genetic mutations reported in children based on physician report (not all genes tested in all children); genetic mutations in adults is based on *post hoc* testing of all four genes in number noted in denominator.

Table 3.

Select morphological features, exocrine and endocrine insufficiency, pain, resource utilization, and disability in pediatric and adult subjects with chronic pancreatitis in the INSPPIRE and NAPS2 cohorts

	All CP			
	Pediatric (n=224)	**Adult (n=1063)**	**Odds Ratio (95% CI) Pediatric/Adult**	**p-value**
Pattern of abdominal pain *	(n=203)	(n=572)	(significantly greater	0.030
- No abdominal pain	28 (14%)	79 (14%)	pain level in adults)	
- Usually pain free; episodes of mild-moderate pain	28 (14%)	73 (13%)		
- Constant mild-moderate pain	12 (6%)	24 (8%)		
- Usually pain free; episodes of severe pain	60 (30%)	104 (18%)		
- Constant mild-moderate pain; episodes of severe pain	63 (31%)	257 (45%)		
- Constant severe pain	12 (6%)	35 (6%)		
Pain medications	125/219 (57%)	398/569 (70%)	0.57 (0.41, 0.79)	0.0006
Narcotics	89/210 (42%)	353/569 (62%)	0.45 (0.33, 0.81)	<0.0001
Non-narcotics **	27/210 (13%)	45/569 (8)	1.72 (1.04, 2.85)	0.034
ER visits last year	(n=186)	(n=470)		
Median (IQR)	2 (0–3)	2 (0–5)		0.091
ER visits lifelong (av/yr of those dx duration>1yr)	(n=98)	(n=413)		
Median (IQR)	1.4 (0.4–2.8)	1.4 (0.6–3.6)		0.133
Hospitalizations last year	(n=188)	(n=679)		
Median (IQR)	1 (0–3)	1 (0–3)		0.667
Hospitalizations lifelong (av/yr of those dx duration >1yr)	(n=98)	(n=625)		
Median (IQR)	1.3 (0.5–2.8)	0.9 (0.4–2.5)		0.499
Days missed school/work last month	(n=153)	(n=532)		
Median (IQR)	2 (0–8)	0 (0–5)		0.0006
Calcifications	25/169 (15%)	608 (57%)	0.13 (0.08, 0.20)	<0.0001
Cysts/Pseudocysts	43/200 (22%)	330 (31%)	0.61 (0.42, 0.87)	0.007
Pancreatic Atrophy	71/170 (42%)	366 (34%)	1.37 (0.98, 1.90)	0.063
Exocrine insufficiency ***	48/185 (26%)	339 (33%)	0.75 (0.53, 1.07)	0.107
Endocrine insufficiency ***	8/189 (4%)	384 (36%)	0.08 (0.04, 0.16)	<0.0001

n, number of patients, is noted for an individual variable if fewer patients or physicians completed the appropriate question in the questionnaires. Where no “n” is noted for a variable the “n” is the whole cohort.

CP: Chronic Pancreatitis

* Data for pattern of pain in Adults is shown for NAPS2-CV/AS only

** Pain medication use in adult patients reported by physicians was organized in a hierarchical question: patients who were taking non-narcotics along with narcotics are assigned into the narcotic group; Pain medication use in INSPPIRE are based on physician or patient report

*** Omits subjects who had total pancreatectomy

Table 4.

Demographic characteristics and risk factors for chronic pancreatitis in white subjects with chronic pancreatitis among pediatric patients (INSPPIRE cohort) and those presenting as children in the NAPS2 cohort

	Pediatric (n=158)	Adult (n=69)	Odds Ratio (95% CI) Pediatric/Adult	p-value
Age at enrollment	(n=152)	(n=69)		
Mean±SD	12.1±3.8	24.7+12.0		
Median (IQR)	12.8 (10.3–15.1)	21.8 (16.3–30.6)		
Age at first diagnosis AP	(n=111)	(n=52)		
Mean±SD	8.2±4.3	9.4+4.9		
Median (IQR)	8.1 (4.9–11.8)	9.0 (5.0–14.0)		
Age at diagnosis CP	(n=121)	(n=61)		
Mean±SD	9.9±4.0	19.5+10.9		
Median (IQR)	10.0 (7.0–12.8)	18.0 (10.9–23.0)		
Sex (Female)	81 (51%)	37/76 (54%)	1.11 (0.64, 1.92)	0.712
Family history of CP	50/141 (35%)	16 (23%)	1.82 (0.94, 3.51)	0.072
Family history of AP	41/132 (31%)	17 (25%)	1.38 (0.71, 2.67)	0.340
Disease Duration	(n=123)			
Mean±SD	3.6±3.5	15.6+11.9		
Median (IQR)	2.6 (1.0–6.1)	13 (6–22)		
Toxic/Metabolic Factors				
Alcohol	2 (1%)	6 (9%)	0.13 (0.01, 0.79)	0.011
Tobacco (Active or Passive)	10/155 (6%)	9 (13%)	0.46 (0.18, 1.19)	0.102
Hyperlipidemia	5/126 (4%)	0 (0%)	--	0.163
Hypercalcemia	0/129 (0%)	0 (0%)	--	--
Medications	10/135 (7%)	3 (4%)	1.76 (0.43, 10.26)	0.549
Chronic renal failure	1/137 (1%)	0 (0%)	--	1.00
Genetic mutations^				
PRSS1	56/118 (47%)	23 (33%)	1.81 (0.97, 3.35)	0.059
SPINK1	22/105 (21%)	15 (22%)	0.95 (0.46, 2.00)	0.901
CFTR	30/109 (28%)	18 (27%)	1.08 (0.54, 2.13)	0.833
CTRC	4/73 (5%)	1 (2%)	3.94 (0.37, 196.93)	0.367
Autoimmune				
Autoimmune pancreatitis	9/116 (8%)	1 (2%)	5.72 (0.76, 254.3)	0.093
Other autoimmune diseases	10/134 (7%)	2 (3%)	2.70 (0.55, 25.96)	0.228
SAP associated CP	6/86 (7%)	1 (2%)	5.10 (0.59, 238.0)	0.132
Obstructive Factors	39/143 (27%)	15 (22%)	1.35 (0.68, 2.67)	0.386
Pancreas divisum	15/141 (11%)	9 (13%)	0.79 (0.33, 1.92)	0.607
Sphincter of oddi dysfunction	2/137 (1%)	3 (4%)	0.33 (0.03, 2.93)	0.337
Gallstones	6/139 (4%)	0/43 (0%)	--	0.338
Pancreaticobiliary malunion	3/139 (2%)	NA		--
Traumatic PD stricture	0/138 (0%)	0 (0%)	--	--

	Pediatric (n=158)	Adult (n=69)	Odds Ratio (95% CI) Pediatric/Adult	p-value
Duct obstruction	5/141 (4%)	4 (6%)	--	0.480
Biliary cyst	2/141 (1%)	NA		--

n, number of patients, is noted for an individual variable if fewer patients or physicians completed the appropriate question in the questionnaires. Where no “n” is noted for a variable the “n” is the whole cohort.

Note that some patients had more than one risk factor.

AP: Acute Pancreatitis; CP: Chronic Pancreatitis; SAP: Severe Acute Pancreatitis; PD: Pancreatic Duct

* Results of genetic mutations in adults is based on *post hoc* testing