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# Recurrent Acute Pancreatitis Significantly Reduces Quality of Life Even in the Absence of Overt Chronic Pancreatitis

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CONFLICT OF INTEREST

**Guarantor of the article:** Gregory Cote accepts full responsibility for the conduct of the study. He had access to the data and control of the decision to publish.

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## Abstract

**OBJECTIVES:** The impact of recurrent acute pancreatitis (RAP) on quality of life (QOL) is unknown. We hypothesized that RAP would reduce QOL even in the absence of chronic pancreatitis (CP).

**METHODS:** Data were pooled from three prospective, cross-sectional studies conducted across 27 U.S. centers (the North American Pancreatitis Studies); these included subjects with chronic pancreatitis ($n$ = 1086), RAP alone ($n$ = 508), and non-disease controls ($n$ = 1025). QOL was measured using the Short Form 12 (SF-12), generating a Physical Component Summary (PCS) and the Mental Component Summary score (MCS). Multivariable regression models were developed to measure the effect of RAP on QOL, the predictors of lower QOL in those with RAP, and the differential effect QOL predictors between CP and RAP.

**RESULTS:** Compared to controls (51.0 ±9.4), subjects with RAP (41.1 ± 11.4) and CP (37.2 ± 11.8) had lower PCS ($p < 0.01$). Subjects with CP had lower PCS compared to those with RAP ($p < 0.01$). Similarly, MCS was lower among RAP (44.6 ± 11.5) and CP (42.8 ± 12.2) subjects compared to controls (51.7 ± 9.1, $p< 0.01$). Subjects with CP had lower MCS compared to those with RAP ($p < 0.01$). After controlling for independent predictors of PCS, RAP was associated with lower PCS (estimate −8.46, $p < 0.01$) and MCS (estimate −6.45, $p < 0.0001$) compared to controls. The effect of endocrine insufficiency on PCS was differentially greater among RAP subjects (−1.28 for CP vs. −4.9 for RAP, $p = 0.0184$).

**CONCLUSIONS:** Even in the absence of CP, subjects with RAP have lower physical and mental QOL. This underscores the importance of identifying interventions to attenuate RAP before the development of overt CP.

## INTRODUCTION

Acute pancreatitis is among the most common gastrointestinal indications for hospitalization, and those suffering two or more episodes have a high risk of developing chronic pancreatitis [1, 2]. There are ~150,000 incident cases of acute pancreatitis in the U.S. annually, and of these 40–50,000 will suffer recurrent bouts. Unlike most patients with chronic pancreatitis who present with irreversible fibrotic changes in the pancreas, patients with recurrent acute pancreatitis (RAP) are unique in that many do not have morphological changes of chronic pancreatitis at the time of their clinical presentation. However, subjects with RAP have a substantial (10–40%) risk of progressing to chronic pancreatitis and its sequelae: chronic pain, malabsorption, diabetes mellitus, poor quality of life, and/or progression to pancreatic cancer [3]. Many experts believe that “subclinical RAP” is the precursor for individuals who present with overt signs or symptoms of chronic pancreatitis [4–6].

There is substantial variability in the clinical phenotypes of patients with RAP ranging from being asymptomatic between bouts of acute pancreatitis to developing chronic symptoms

between their attacks. Compared to healthy controls and those with overt chronic pancreatitis, little is known about quality of life (QOL) among individuals with RAP. Undoubtedly, QOL is lower among the majority of patients with chronic pancreatitis [7–10]. While less defined, the long-term impact of a single episode of acute pancreatitis on QOL, even following recovery from a severe episode, may be significant [11–20]. A small cohort study of subjects with idiopathic RAP and pancreas divisum, but without objective evidence of chronic pancreatitis, demonstrated lower QOL [21].

The aims of this study were to define QOL among subjects with RAP, and to identify the factors associated with lower QOL in this population.

## METHODS

### Study population

For this analysis, the sampling frame utilized data from the North American Pancreatitis Studies (NAPS): NAPS2, NAPS2-CV (NAPS2-Continuation and Validation), and NAPS2-AS (NAPS2-Ancillary Study) [22–24]. The NAPS2 projects were prospective cohort studies conducted at 27 centers in the United States, collectively enrolling subjects with chronic pancreatitis ($n$ = 1195), RAP ($n$ = 569), and healthy controls ($n$ = 1109) between 2000 and 2014. The methodology of NAPS2 has been detailed previously [22–24]. Subjects with chronic pancreatitis, RAP, and no known pancreatic disease (controls) completed a detailed questionnaire on personal and family history, risk factors, symptoms, and QOL. Control subjects included a spouse, first-degree family member, an accompanying friend of a patient with RAP or chronic pancreatitis, or unrelated subject [24]. All subjects provided written, informed consent prior to the collection of data. The study was approved by the Institutional Review Board of each participating center.

### Subject classification

For the purposes of NAPS2 enrollment, RAP and chronic pancreatitis were diagnosed by the treating physician. Chronic pancreatitis was defined by definitive changes on imaging, including computed tomography, endoscopic retrograde cholangiopancreatography, magnetic resonance imaging with cholangiography, or endoscopic ultrasound; few were diagnosed by histology alone, typically at the time of surgical intervention. RAP was defined by evidence of two or more documented attacks of acute pancreatitis but without imaging or histological evidence of chronic pancreatitis. Non-disease controls (unrelated, spouse or family members) included subjects without signs or symptoms of chronic pancreatitis. The control population was restricted to unrelated and non-cohabitating individuals in a sensitivity analysis, to confirm no changes to the conclusions (data not shown).

### Data collection

Study subjects and their treating physicians completed detailed questionnaires on demographics, personal and family medical history, environmental exposures (e.g., alcohol use and smoking), risk factors, and prior treatments for RAP and chronic pancreatitis. Pain experience, disability related to pain, and quality of life were also queried. Self-reported pain experience in the year prior to enrollment is limited to the NAPS2-CV and NAPS2-AS

studies, since a leading question pertaining to the presence/absence of pain was not included in the original NAPS2 study. QOL was measured using the Short Form 12 (SF-12) (version 1 in original NAPS2, version 2 in NAPS2-CV and NAPS2-AS), a generic health outcomes measure that is useful in surveys of populations to compare the relative burdens of disease as well as the health benefits of different treatments [25]. The SF-12 has been shown to have excellent correlation to the Pancreatitis Quality of Life Instrument, which is an instrument that was developed and validated in patients with chronic pancreatitis [26]. The survey responses allow generation of two component scores, the Physical Component Summary score (PCS) and the Mental Component Summary score (MCS). Higher scores represent better self-perceived physical or mental wellness, respectively. All scores are presented using norm-based comparisons, where 50 is the mean for the U.S. general population and 10 is the standard deviation [27]. A difference of 3 points is considered clinically significant [10].

### Statistical analysis

The PCS and MCS scores were computed based on responses to the questions, and presented as mean ± standard deviation (SD). Descriptive analyses are presented as proportions for categorical data and as mean ± SD for continuous data or median (interquartile range (IQR)) where appropriate. Univariate comparison of each demographic variable and diagnosis category (RAP, chronic pancreatitis, and control) was performed using ANOVA and a *t*-test for each pairwise comparison for continuous variables and Fisher's exact test for categorical variables. All variables with $p < 0.20$ on univariate analysis were considered for potential inclusion in the multivariable models.

Multivariable linear regression models were used to determine the independent predictors of physical and mental QOL among all subjects. A backwards selection technique was used to determine significant independent predictors. Variables selected for initial inclusion based on univariate analysis were removed one by one according to the magnitude of the type III Wald test. A final model was chosen when all remaining variables had a $p$ value < 0.05. Tests for differential effects were done by including significant predictors of chronic pancreatitis and RAP and testing an interaction term between diagnosis and each predictor. The interaction terms were tested one at a time in separate models. A subset analysis was carried out among subjects with RAP and available data regarding pain. This model added pain category to the final model chosen based on the model with all RAP subjects. Data analysis was performed using SAS version 9.4.

## RESULTS

### Characteristics of individuals with RAP

The cohort included 2,618 individuals with RAP ($n$ = 508, 19.4%), chronic pancreatitis ($n$ = 1086, 41.4%), and healthy controls ($n$ = 1025, 39.2%). Compared to subjects with chronic pancreatitis and healthy controls, those with RAP were younger at the time of enrollment, more likely to be female, and had undergone a previous cholecystectomy (Table 1). Compared to healthy controls, subjects with RAP and chronic pancreatitis were more commonly past or current smokers; current smoking was most prevalent among subjects

with chronic pancreatitis. Similarly, heavy and very heavy alcohol use were most commonly reported among subjects with chronic pancreatitis (47.6%, $p < 0.0001$).

### Quality of life

Compared to controls (51.0 ± 9.4), subjects with RAP (41.1 ± 11.4) and chronic pancreatitis (37.2 ± 11.8) had a lower PCS score ($p < 0.0001$). Similarly, the MCS score was lower among subjects with RAP (44.6 ± 11.5) and chronic pancreatitis (42.8 ± 12.2) compared to controls (51.7 ± 9.1, $p < 0.0001$). Still, subjects with RAP had significantly higher PCS ($p < 0.0001$) and MCS scores (p = 0.0072) compared to those with chronic pancreatitis.

### Determinants of lower physical component summary scores

A multivariable linear regression model was constructed using data from all three NAPS2 studies ($n = 2335$ of 2619 (89%) potential subjects, see appendix Table 4). After adjusting for significant predictors of PCS including age, sex, race, body-mass index, smoking, and alcohol use, past medical history (specifically diabetes mellitus, heart disease, cancer, liver disease, or kidney disease), and previous cholecystectomy, individuals with RAP had a significant reduction in PCS (mean 8.5 ± 0.6, $p < 0.001$) compared to healthy controls. The magnitude of reduction in PCS was even greater among those having chronic pancreatitis (11.0 ± 0.6, $p < 0.001$) and was significantly different than RAP subjects ($p < 0.001$).

Among subjects with RAP and available data ($n = 504/508$), factors associated with lower PCS were female sex (4.4 ± 0.9, $p < 0.001$), endocrine insufficiency (4.6 ± 1.4, $p = 0.0008$), past smoking (2.5 ± 1.2, $p = 0.034$), current smoking (3.6 ± 1.2, $p = 0.0039$), and self-reported disability (9.6 ± 1.4, $p < 0.001$) (Table 2). In the model limited to RAP subjects with available pain data ($n = 105$), self-reported constant pain (versus no or intermittent pain), was also associated with a significant reduction in PCS (5.5 ± 2.2, $p = 0.0137$) (see appendix Table 5 for complete model data).

### Determinants of lower mental component summary scores

A similar multivariable regression model was constructed to determine the association between RAP and MCS ($n = 2572$ of 2619 (98.2%) subjects with available data (see appendix Table 6 for complete model). After adjusting, subjects with RAP had lower MCS scores (6.5 ± 0.6, $p < 0.001$) compared to healthy controls; the magnitude of reduction was greater for those with chronic pancreatitis (7.6 ± 0.5, $p < 0.001$). Among subjects with RAP ($n = 504/508$ with available data), factors associated with lower MCS scores included current smoking, self-reported disability, and a physician suspicion for underlying chronic pancreatitis (despite no objective evidence on cross sectional imaging) (Table 3). Among subjects having RAP and available data on pain characteristics ($n = 105$), the presence of pain was not independently associated with lower MCS scores (see appendix Tables 6, 7) for complete model data).

### Differential effects

A model was constructed using the significant predictors of QOL for both RAP and chronic pancreatitis [28] to test whether the common predictor of lower QOL among subjects with RAP and chronic pancreatitis had differential effects based on diagnosis (i.e., to determine if

the impact of a given predictor was greater for RAP or chronic pancreatitis). The only differential effect noted was for endocrine insufficiency on reducing the PCS score: the effect of endocrine insufficiency on PCS score was significantly greater among RAP subjects than chronic pancreatitis subjects (−4.9 vs. −1.28, $p = 0.0184$). Stated alternatively, the impact of diabetes mellitus on QOL was greater for subjects with RAP when compared to chronic pancreatitis. No other differential effects were found for PCS or MCS scores.

## DISCUSSION

There is wide variability in the clinical presentation of patients with RAP, ranging from those with mild and infrequent episodes to those with a high incidence density that often evolves to a syndrome of chronic, daily pain even in the absence of overt changes of chronic pancreatitis. Population-based studies examining the distribution of individuals with RAP across this spectrum of disability are lacking. However, this analysis of the NAPS2 cohorts confirms that RAP—even in the absence of overt chronic pancreatitis—reduces physical and mental components of quality of life. This observation underscores the importance of identifying viable treatments for RAP. Since RAP is a disease that usually presents with sporadic symptoms, prophylactic pharmacological interventions are suboptimal. Therefore, a careful evaluation for acute pancreatitis risk factors and aggressive pursuits to modify them remain paramount to the treatment approach. These include occult gallstone disease, alcohol and smoking, metabolic risk factors such as hypertriglyceridemia, and genetic factors [29–32].

Although histological data are limited, many individuals with RAP who report chronic, daily pain are suspected to have chronic pancreatitis. This analysis of the NAPS2 cohorts confirms that the magnitude of reduction in quality of life is intermediate between healthy controls and chronic pancreatitis, which is consistent with longitudinal studies that RAP is an intermediate stage in the pathogenesis of chronic pancreatitis, and a clinical marker for risk of progressing from RAP to overt chronic pancreatitis over time [30, 33]. In a cohort of 49 subjects who underwent total pancreatectomy with autoislet cell transplantation for RAP without overt chronic pancreatitis, 37 (76%) had histological evidence based on the presence of fibrosis with or without inflammation and/or acinar atrophy [34]. This may illustrate the suboptimal sensitivity of cross sectional imaging studies such as computed tomography, magnetic resonance imaging, and endoscopic ultrasound, the latter of which also lacks specificity [35]. Furthermore, the impact of prior treatments for RAP on pancreatic histology, most notably ERCP with pancreatic sphincterotomy and stent placement, is unknown. Even in the absence of prior interventions, RAP may be associated with a high prevalence of periampullary inflammation and fibrosis [36]. This phenomenon—and whether or not it is a cause, consequence, or both vis à vis acute pancreatitis—requires further investigation. In the NAPS2-CV and -AA studies, among subjects with available data on pain characteristics, 41/105 subjects (39%) with RAP reported constant pain, suggestive of underlying processes akin to chronic pancreatitis even though pathologic fibrosis was not seen on imaging. Therefore, we believe that the definition and diagnostic criteria of chronic pancreatitis, which focuses on morphological abnormalities identified by imaging, may be inadequate. Indeed, a new mechanistic definition of chronic pancreatitis has been proposed that addresses the underlying inflammatory processes and their consequences, with or

without fibrosis [37]. Longitudinal, population-based cohort studies of RAP are needed to determine the proportion of subjects who present with or develop constant pain, and relate this to the probability of developing overt changes of chronic pancreatitis over time.

Among subjects with RAP in NAPS2, self-perceived disability, smoking, diabetes mellitus, and female sex were associated independently with lower PCS. Current alcohol use was associated with higher PCS, perhaps since those continuing to consume alcohol have not associated drinking with their pancreatitis, consume alcohol at low volume, or both. The same covariates were associated independently with lower MCS, except for female sex. In a subgroup analysis of those with available data on pain character, pain significantly impacted PCS but not MCS. For patients with acute and chronic pancreatitis, most clinicians would immediately associate lower QOL with pain. These data illustrate that QOL among individuals with RAP is more nuanced. While pain is undoubtedly a critical component of the disorder, risk factors such as smoking and pancreatitis sequelae (e.g., diabetes mellitus and exocrine pancreas insufficiency) have an important role. We suspect that diabetes was associated with a greater impact on QOL among individuals with RAP because the effect of pain is less prominent in this population compared to those with chronic pancreatitis. Self-perceived disability was the single most important factor associated with lower PCS. This subjective measure integrates pancreatitis-related symptoms, availability of subject support systems, psychosomatic comorbidities, and coping—an understudied qualitative metric that is probably influenced by many factors in its own right [38]. Self-perceived disability influences clinician's assessment of the risk:benefit ratio for many interventions; thus, surgery is usually reserved for those who develop the most disabling symptoms.

This study is limited by its cross-sectional design and amalgamation of three related NAPS2 cohorts which were conducted at pancreatitis referral centers across the United States over a 15-year time span. There is a risk for selection bias, where NAPS2 subjects could reflect a more disabled subgroup that required referral to major health centers. Enrolled subjects were mostly similar across NAPS2 sites, so it is unlikely that such a phenomenon could explain these observations. In addition, since NAPS2 studies were cross sectional in design, subjects were enrolled at variable times during their disease course: some after multiple medical, endoscopic, and surgical interventions had been performed. Other covariates including number of acute pancreatitis episodes, time since last episode, and opiate utilization were not available for inclusion. Subjects with late stage disease may skew quality of life measures lower or higher depending on their response to treatments. Finally, the SF-12 is a widely utilized and validated generic QOL instrument which reflects patient responses over the past four weeks; it has not been specifically validated in a population with RAP. In view of the recurrent episodes of pancreatitis, it is possible that responses to QOL questionnaires vary over time, with worse scores nearer an episode of pancreatitis. Thus, the results should be interpreted in light of the timing of the QOL instrument's administration in relation to illness-related variables during the past 4 weeks.

## CONCLUSIONS

RAP leads to a reduction in physical and mental components of quality of life, even in the absence of overt changes of chronic pancreatitis. These findings underscore the importance

of detecting and managing risk factors early in the disease course, and identifying treatments that can attenuate the disease before its progression to chronic symptoms.

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## APPENDIX

**Table 4**

Multivariable linear regression model evaluating factors associated with lower Physical Component Summary Scores

| Parameter | Estimate | Standard error | *P* value |
|---|---|---|---|
| Intercept | 53.79 | 0.78 | <0001 |
| Chronic pancreatitis vs. control | −11.05 | 0.56 | <0001 |
| Recurrent acute pancreatitis vs. control | −8.47 | 0.63 | <0001 |
| Age between 45-65 vs. age < 45 years | −0.73 | 0.47 | 0.1236 |
| Age > 65 years vs. age < 45 years | 0.54 | 0.58 | 0.3533 |
| BMI > 25 to 30 vs. ≤ 25 kg/m$^2$ | 0.07 | 0.49 | 0.8807 |
| BMI ≥ 30 vs. ≤ 25kg/m$^2$ | −2.07 | 0.54 | 0.0001 |
| Female sex vs. male sex | −1.74 | 0.43 | <0001 |
| Current drinking vs. never drinking | 3.62 | 0.62 | <0001 |
| Prior drinking vs. never drinking | 0.79 | 0.60 | 0.1867 |
| Past smoker vs. never smoker | −1.64 | 0.55 | 0.0029 |
| Current smoker vs. never smoker | −4.38 | 0.53 | <0001 |
| History of diabetes mellitus | −2.49 | 0.54 | <0001 |
| History of heart disease, heart attack, or stroke | −3.56 | 0.75 | <0001 |
| History of cancer | −2.69 | 1.10 | 0.0139 |
| Black vs. White race | −2.18 | 0.52 | <0001 |
| Other race vs. White race | −0.83 | 1.11 | 0.4561 |
| History of liver disease vs. no history | −2.23 | 0.91 | 0.0146 |
| History of cholecystectomy vs. no prior cholecystectomy | −2.0 | 0.48 | <0001 |
| History of kidney disease vs. no history | −2.72 | 1.04 | 0.0087 |

Past medical history variables are derived from patient responses R-squared=0.342144. 2572/2619 subjects with full data used *BMI* body mass index

**Table 5**

Determinants of lower physical component scores in RAP

| Parameter | Estimate | Standard Error | P value |
|---|---|---|---|
| Intercept | 54.88 | 2.83 | <0001 |
| Age (centered at 50 years)[a] | 0.01 | 0.07 | 0.8596 |

| Parameter | Estimate | Standard Error | P value |
|---|---|---|---|
| Female sex vs. male sex | −7.19 | 20.56 | 0.0007 |
| Current drinking vs. no drinking | −4.21 | 2.93 | 0.1546 |
| Prior drinking vs. no drinking | −4.96 | 2.85 | 0.0856 |
| Prior pancreatic surgery vs. no | −7.39 | 4.39 | 0.0956 |
| Endocrine insufficiency vs. no | −6.28 | 2.42 | 0.0110 |
| Past smoker vs. never smoker | −4.17 | 2.61 | 0.1136 |
| Current smoker vs. never smoker | −6.15 | 2.64 | 0.0220 |
| Self-reported disability vs. no | −6.04 | 2.83 | 0.0351 |
| Self-reported constant pain vs. no | −5.53 | 2.20 | 0.0137 |

[a]The variable of age is centered at 50 years

This model restricts data from NAPS2-CV and NAPS2-AA only, where data regarding pain character were collected

**Table 6**

Multivariable Linear regression model evaluating factors associated with lower Mental Component Summary Scores

| Parameter | Estimate | Standard error | *P* value |
|---|---|---|---|
| Intercept | 52.23 | 0.71 | <0001 |
| Chronic pancreatitis vs. control | −7.56 | 0.52 | <0001 |
| Recurrent acute pancreatitis vs. control | −6.45 | 0.61 | <0001 |
| Age between 45 and 65 vs. < 45 years | 0.83 | 0.48 | 0.0847 |
| Age > 65 years vs. < 45 years | 4.73 | 0.59 | <0001 |
| Female sex vs. male sex | −1.42 | 0.43 | 0.0010 |
| Current drinking vs. never drinking | 0.98 | 0.64 | 0.1252 |
| Prior drinking vs. never drinking | −0.41 | 0.61 | 0.4983 |

**Table 7**

Determinants of lower mental component scores among subjects with RAP

| Parameter | Estimate | Standard error | *P* value |
|---|---|---|---|
| Intercept | 48.72 | 2.42 | <0001 |
| Age (centered at 50 years) | 0.02 | 0.08 | 0.7860 |
| Female sex vs. male sex | −2.29 | 2.31 | 0.3238 |
| Suspected chronic pancreatitis vs. no suspicion | −5.83 | 3.2 | 0.0698 |
| Past smoker vs. never smoker | −3.42 | 2.89 | 0.2390 |
| Current smoker vs. never smoker | −3.55 | 2.77 | 0.2020 |
| Self-reported disability vs. no | −5.57 | 3.13 | 0.0781 |
| Self-reported constant pain vs. no | −2.20 | 2.51 | 0.3828 |

This model restricts data from NAPS2-CV and NAPS2-AA cohorts only, where data regarding pain character were collected

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**Study Highlights**

**WHAT IS CURRENT KNOWLEDGE**

- ✓ Quality of life is significantly reduced among patients with chronic pancreatitis.
- ✓ Patients with recurrent acute pancreatitis are at high risk for developing overt chronic pancreatitis.
- ✓ Pain, smoking, co-morbidities, and self-perceived disability are significantly associated with lower quality of life in chronic pancreatitis.

**WHAT IS NEW HERE**

- ✓ In the absence of overt changes of chronic pancreatitis, recurrent acute pancreatitis causes a significant reduction in physical and mental quality of life.
- ✓ The magnitude of reduction in quality of life with recurrent acute pancreatitis is intermediate between healthy controls and those with chronic pancreatitis.
- ✓ Determinants of lower quality of life in recurrent acute pancreatitis are similar to those for chronic pancreatitis, and include smoking, self-perceived disability, and pain.
- ✓ Endocrine insufficiency has a greater effect on reducing quality of life in recurrent acute pancreatitis compared to chronic pancreatitis.

## Table 1

Subject characteristics

| Variable | Group (*n*) | | | *p*-value | | |
|---|---|---|---|---|---|---|
| | CP (*n*=1086) | RAP (*n*=508) | Control (*n*=1024) | CP vs. control | RAP vs. control | CP vs. RAP |
| Mean age (±SD) | 50.8 (14.7) | 45.3 (15.5) | 49.1 (14.2) | 0.0072 | <0.0001 | <0.0001 |
| Median age of pancreatitis symptom onset (IQR) | 44.0 (32.0, 54.0) | 40.2 (27.0, 51.0) | N/A | N/A | N/A | <0.001 |
| Male sex | 598 (55.1) | 235 (46.3) | 393 (38.3) | <0.0001 | <0.0001 | <0.0001 |
| Race[a] | | | | N/A | N/A | N/A |
| White | 819 (75.5) | 445 (87.6) | 714 (87.8) | | | |
| Black | 234 (21.6) | 46 (9.1) | 264 (9.1) | | | |
| Other | 32 (3.0) | 16 (3.2) | 45 (3.2) | | | |
| Prior cholecystectomy | 480 (44.2) | 277 (54.5) | 129 (12.6) | <0.0001 | | |
| Alcohol use category | | | | <0.0001 | 0.0282 | <0.0001 |
| Abstainer | 182 (17.2) | 124 (24.9) | 175 (21.3) | | | |
| Light | 182 (17.2) | 140 (28.1) | 267 (32.5) | | | |
| Moderate | 178 (16.8) | 114 (22.9) | 181 (22.1) | | | |
| Heavy | 161 (15.2) | 60 (12.0) | 128 (15.6) | | | |
| Very heavy | 356 (33.6) | 61 (12.2) | 70 (8.5) | | | |
| Smoking status | | | | <0.0001 | 0.041 | <0.0001 |
| Never smoker | 269 (24.8) | 225 (44.6) | 510 (50.0) | | | |
| Past smoker | 282 (26.0) | 160 (31.8) | 263 (25.8) | | | |
| Current smoker | 532 (49.1) | 119 (23.6) | 247 (24.2) | | | |
| Maximum BMI | | | | | | |
| Current BMI | 24.7 (5.6) | 27.1 (6.5) | 28.5 (6.1) | <0.0001 | <0.0001 | <0.0001 |
| Past medical history | | | | | | |
| Diabetes mellitus | 347 (32.0) | 84 (16.5) | 101 (9.9) | <0.0001 | 0.0002 | <0.0001 |
| Renal disease or failure | 66 (6.1) | 24 (4.7) | 18 (1.8) | <0.0001 | 0.0008 | 0.2755 |
| Heart disease | 132 (12.2) | 33 (6.5) | 62 (6.1) | <0.0001 | 0.7324 | 0.0005 |
| Liver disease | 95 (8.8) | 19 (3.7) | 28 (2.7) | <0.0001 | 0.281 | 0.0003 |

Proportions account for missing data on some variables, and may not add up to 100.0 due to rounding CP chronic pancreatitis, RAP recurrent acute pancreatitis, BMI body-mass index, IQR interquartile range

[a]Race is not compared between groups since NAPS2-AA deliberately enrolled subjects from minority races

**Table 2**

Determinants of lower physical component scores among subjects with RAP

| Variable | Estimate | Standard error | *P* value |
|---|---|---|---|
| Intercept | 46.78 | 1.22 | <0.001 |
| Age (centered at 50) | 0.003 | 0.03 | 0.9100 |
| Female vs. male sex | −4.42 | 0.95 | <0.001 |
| Current alcohol use vs. no alcohol use | 3.96 | 1.42 | 0.0055 |
| Previous alcohol use vs. no alcohol use | −0.69 | 1.22 | 0.5744 |
| Previous pancreatic surgery vs. no prior surgery | −3.34 | 2.02 | 0.0992 |
| Endocrine insufficiency vs. no endocrine insufficiency | −4.58 | 1.35 | 0.0008 |
| Past smoker vs. never smoker | −2.49 | 1.17 | 0.0343 |
| Current smoker vs. never smoker | −3.63 | 1.25 | 0.0039 |
| Self-reported disability vs. no self-reported disability | −9.56 | 1.44 | <0.0001 |

**Table 3**

Determinants of lower mental component scores among subjects with RAP

| Variable | Estimate | Standard error | *P* value |
|---|---|---|---|
| Intercept | 48.70 | 1.00 | <0.0001 |
| Age (centered at 50) | −0.06 | 0.03 | 0.0680 |
| Female sex vs. male sex | −1.42 | 0.99 | 0.1522 |
| Suspected chronic pancreatitis (vs. not suspected) | −2.92 | 1.27 | 0.0225 |
| Past smoker vs. never smoker | −2.54 | 1.19 | 0.0338 |
| Current smoker vs. never smoker | −4.62 | 1.29 | 0.0004 |
| Self-reported disability vs. no self-reported disability | −5.37 | 1.54 | 0.0005 |