Reduced Risk of Alcohol-Induced Pancreatitis With Cannabis Use

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Background: Pancreatitis is an increasingly common clinical condition that causes significant morbidity and mortality. Cannabis use causes conflicting effects on pancreatitis development. We conducted a larger and more detailed assessment of the impact of cannabis use on pancreatitis.

Methods: We analyzed data from 2012 to 2014 of the Healthcare Cost and Utilization Project—Nationwide Inpatient Sample discharge records of patients 18 years and older. We used the International Classification of Disease, Ninth Edition codes, to identify 3 populations: those with gallstones (379,125); abusive alcohol drinkers (762,356); and non-alcohol-non-gallstones users (15,255,464). Each study population was matched for cannabis use record by age, race, and gender, to records without cannabis use. The estimation of the adjusted odds ratio (aOR) of having acute and chronic pancreatitis (AP and CP) made use of conditional logistic models.

Results: Concomitant cannabis and abusive alcohol use were associated with reduced incidence of AP and CP (aOR: 0.50 [0.48 to 0.53] and 0.77 [0.71 to 0.84]). Strikingly, for individuals with gallstones, additional cannabis use did not impact the incidence of AP or CP. Among non-alcohol-non-gallstones users, cannabis use was associated with increased incidence of CP, but not AP (1.28 [1.14 to 1.44] and 0.93 [0.86 to 1.01]).

Conclusions: Our findings suggest a reduced incidence of only alcohol-associated pancreatitis with cannabis use.

Key Words: Cannabis, Pancreatitis, Alcohol Abuse, Gallstones, Incidence.

PANCREATITIS IS AN inflammatory condition of the pancreas, which is a large body organ anatomically located behind the stomach. The pancreas produces digestive enzymes and several hormones that help in digestion and the homeostatic regulation of blood sugar (Röder et al., 2016). Pancreatitis can either be acute or chronic (AP or CP). The major causes of pancreatitis can broadly include abusive alcohol drinking, gallstones, and genetic, autoimmune, and idiopathic origins. Globally, there were about 17 million cases of diagnosed pancreatitis (Lévy et al., 2014). AP is one of the most frequent gastrointestinal causes for hospital admission in the United States. The annual incidence of AP ranges from 13 to 45 cases per 100,000 people (Satoh et al., 2011; Yadav and Whitcomb, 2010). CP from prolonged inflammation resulting in irreversible pancreatic scarring has an incidence and prevalence ranging from 5 to 12 per 100,000 and 26 to 50 cases per 100,000, respectively (Hirota et al., 2012; Yadav et al., 2011). Globally, pancreatitis accounted for over 123,000 deaths in 2013, an alarming rise of over 45.5% from deaths in 1990 (GBD 2013 Mortality and Causes of Death Collaborators, 2015). The high mortality associated with pancreatitis is due to unavailability of early diagnostic tests and the rapidly fatal disease progression or the development of pancreatic cancer in some individuals.

Previously, treatment of severe pancreatitis involved surgical treatment despite overwhelming mortality rates that often exceeded 50% (Bradley and Dexter, 2010; Werner et al., 2005). Recently, a significant paradigm shifts from surgical to early disease management involving analgesia, fluid resuscitation, antibiotics, nutrition, and endoscopic retrograde cholangiopancreatography yielding improved patient outcomes (Banks et al., 2010; Forsmark, 2013; Greenberg et al., 2016; McClave et al., 1998). However, numerous reports have demonstrated no clinical benefits to a range of pharmacological agents used for AP.

Recent reports suggest that cannabinoids (tetrahydrocannabinol [THC] and cannabidiol [CBD]), which constitute the most studied active ingredients found in cannabis (marijuana), might have a modulatory role in the development and progression of pancreatitis (Barkin et al., 2017; Goyal et al., 2017; Li et al., 2013). Although associations between

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cannabinoids and pancreatitis have been reported in case reports (Akkucuk and Erbayrak, 2015; Barkin et al., 2017; Belze et al., 2011; Bournet and Buscail, 2008; Fatma et al., 2013; Howaizi et al., 2012; Nayak et al., 2016), case series (Wargo et al., 2007), and animal experiments (Dembiński et al., 2008; Matsuda et al., 2005; Michalski et al., 2007; Petrella et al., 2010), revelations so far have been divergent and inconclusive. Some studies suggest cannabis use can trigger the development of pancreatitis (Akkucuk and Erbayrak, 2015; Barkin et al., 2017; Belze et al., 2011; Bournet and Buscail, 2008; Fatma et al., 2013; Howaizi et al., 2012; Matsuda et al., 2005; Nayak et al., 2016; Wargo et al., 2007), some reveal an ameliorative effect (Goyal et al., 2017; Michalski et al., 2007), while others conclude on both protective and exacerbating effects (Dembiński et al., 2008; Petrella et al., 2010). Previous studies on cannabis use were limited by small patient populations and lack of detailed assessment of cannabis use in association with known disease risk factors. Given increased cannabis legalization for recreational use, it is expected that an increasing number of individuals will seek cannabis as a treatment for pancreatitis. Therefore, larger population-based studies are urgently needed to elucidate the impact of cannabis use and pancreatitis in association with known disease predisposing factors. Therefore, we conducted this study, to investigate the association between cannabis use and pancreatitis (acute and chronic). To this end, we define 3 mutually exclusive disease-associated risk cohorts: individuals with excessive alcohol use; with gallstones; and with neither alcohol nor gallstones. We then matched cannabis user (cohort) to noncannabis users (controls) within each group and estimated the effects of cannabis use on the prevalence of AP and CP.

Our novel findings revealed that cannabis use had a complex differential effect on the prevalence of pancreatitis in association with known disease etiologic factors.

MATERIALS AND METHODS

Data Source

We evaluated data from the Nationwide Inpatient Sample (NIS) Database from 2012 to 2014. The NIS is the largest all-payer database, containing approximately 8 million hospitalization records, and represents 20% of a stratified multilevel random sample of nonfederal acute-care hospitals in the United States of America. This data set contains demographic and hospital characteristics, and up to 25 discharge conditions and 15 medical procedures. These data are coded with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (World Health Organization, 2004), and provides nationwide estimates and associations of many gastrointestinal conditions. As the NIS data are completely de-identified and publicly available, our study did not require an Institutional Review Board approval.

Study Population

We evaluated adult records of individuals 18 years and over from the NIS for 2012, 2013, and 2014. We used the ICD-9-CM codes (Table S1) to identify records with abusive alcohol consumption disorder and evidence of gallstones disease. We then created 3 mutually exclusive groups: abusive alcohol consumption (alcohol group), clinical evidence of gallstones (gallstones group), and non-abusive alcohol consumers and non-gallstones diagnosis (other group). The alcohol group contained records with abusive alcohol consumption disorder (ICD-9-CM: 303.x, 305.0x) and without any past or current diagnosis of gallstones (symptomatic or asymptomatic) (Fig. 1). The gallstones group contained records with a diagnosis of gallstones disease (ICD-9-CM code for gallstones [574.x] or cholecystectomy [512.x]), but without any concomitant diagnosis of abusive alcohol drinking disorder. The non-alcohol-non-gallstones contained all the other records, without any diagnosis of abusive alcohol drinking and/or gallstones disease. From each group, we eliminated records with missing variables and those using other illicit drugs besides cannabis. Furthermore, we identified records with cannabis use (ICD-9-CM: 305.2x, 304.3x) and matched these individuals by age, gender, and race to noncannabis users (1:5 for gallstones group and 1:1 for the 2 others). The codes used in this study have been extensively described in previous studies (Adejumo et al., 2017, 2018; Bollom et al., 2017; Setiawan et al., 2017). Furthermore, as defined by the DSM-IV (American Psychiatric Association, 1994), which guides the use of ICD-9-CM codes, cannabis use was segregated into 2 groups: cannabis abuse (non-dependent use) and cannabis dependence (Hasin et al., 2013). Non-dependent use was the use of cannabis with significant problems such as inability to meet essential responsibilities or engaging in risky activities under the influence of cannabis. Cannabis dependence (dependent use) included exhibition of physical/mental symptoms of dependence. Dependent users have consumed cannabis more frequently than nondependent user, allowing us to loosely approximate a dose–response (Grant and Pickering, 1998).

Variables

Our primary evaluation group was cannabis users. Individual variables evaluated included age, gender (male and females), race (Whites, Blacks, Hispanics, and others), health insurance (Medicaid, Medicare, private, and others), and income status (categorized into 4 quartiles based on average income in the zip code of residence). We then used the ICD-9-CM code to identify risk factors for pancreatitis such as tobacco use, hyperlipidemia, obesity, diabetes mellitus, hypercalcemia, autoimmune disorders, and family history of digestive diseases. We also identified over 40 other comorbidities to compute the Charlson–Deyo comorbidity index, which was grouped into 3 categories (0, 1 to 3, and >3) (Quan et al., 2005). Our primary outcomes of interest were having AP and/or CP (ICD-9-CM: 577.0 and 577.1, respectively).

Statistical Analyses

Continuous and categorical variables were respectively compared using the Student *t*-test and Rao–Scott chi-square within the unmatched population, and paired Student *t*-test and McNemar's test within matched pairs. We analyzed each of the 3 groups independently. After cohort matching of cannabis to noncannabis users, we developed multivariate conditional logistic regression models to estimate the adjusted odds ratio (aOR) of having AP and CP. For each of the 3-multivariate model analyses performed, we accounted for confounding variables including race, tobacco use, hyperlipidemia, diabetes mellitus, hypercalcemia, autoimmune diseases, and family history of pancreatitis.

All the analyses were performed using Statistical Analysis System (SAS V.9.4; SAS Institute Inc, Cary, NC). We accounted for stratified clustered sampling frameworks and included the recommended strata, cluster, and discharge weights variables. All tests were 2-sided, considering a p-value of <0.05 as statistically significant and 95% confidence interval (CI). Graphical results are presented as aORs and CI using GraphPad Prism 7 software (San Diego, CA).

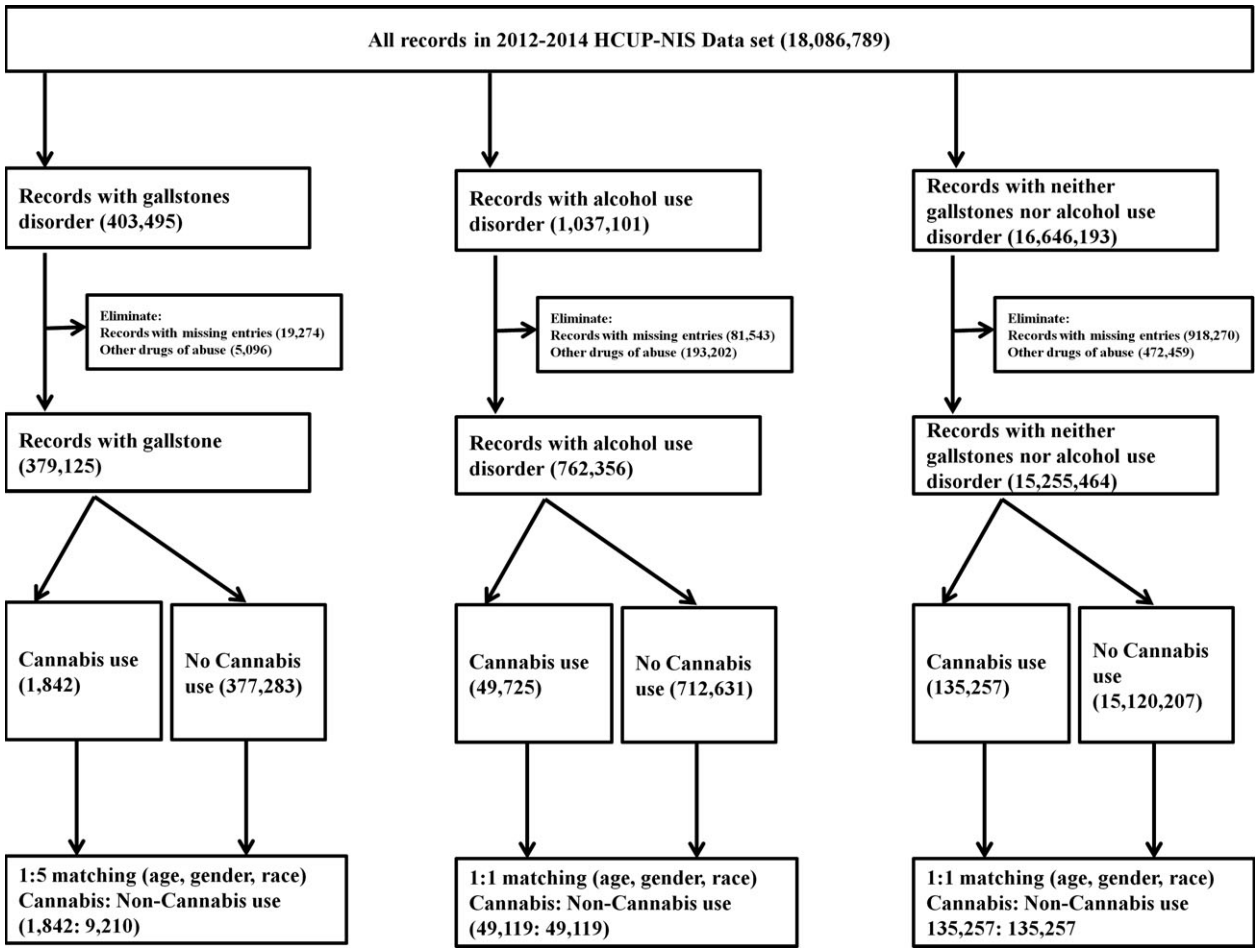

Fig. 1. Selection flowchart. Illustrated flow diagram of the study selection process of various populations investigated.

RESULTS

Characteristics of the Study Populations with Regard to Cannabis Usage

Among the 18,086,789 patient discharge records from 2012 to 2014, our final evaluated populations with pancreatitis (individuals with gallstones, abusive alcohol drinking, and neither) were, respectively, 379,125, 762,356, and 15,255,464 (Fig. 1). Before matching our cohorts by age, gender, and race, cannabis users were more likely to be younger Black males, on Medicare (government health insurance), self-payer/other health insurance, and from the lowest income quartile (Table S2). We found no difference in the prevalence of pancreatitis among individuals with gallstones with and without additional cannabis use. Strikingly, the incidence of AP and CP was significantly lower in alcoholics who additionally use cannabis compared to alcoholics who do not use cannabis. Furthermore, cannabis use was associated with higher prevalence of AP and CP in the non-alcohol-non-gallstones group compared to noncannabis users. Across all 3 pancreatitis risk groups, cannabis users had fewer comorbidities (Charlson–Deyo index) such as hyperlipidemia, obesity, diabetes mellitus, and pancreatic cancer, but a higher frequency of tobacco use.

After matching, age, gender, and racial distribution became identical between cannabis users and nonusers across the 3 groups (Table 1 and Fig. 1). Cannabis users were more likely to have nonprivate health insurance and to come from the lowest income quartile. Among gallstones and alcohol-use cohort, there is no difference in the frequency of most comorbidities between cannabis use and nonuse groups. However, cannabis users had decreased frequency of these comorbid conditions within the non-alcohol-non-gallstones cohort. Individuals who additionally consume cannabis have a lower frequency of AP among the alcohol-use group, unlike the other groups where there was no difference (Table 1). Respectively, the frequency of CP was lower, not different, and higher among alcohol, gallstones, and non-alcohol-non-gallstones cohort (Table 1).

No Difference in the Incidence of AP and CP Among Individuals with Gallstones with and without Concomitant Cannabis Use

After eliminating age-, gender-, and race-related cofounding factors by matching, and additionally adjusting for other risk factors for AP, cannabis usage had no impact on the

Table 1. Baseline Characteristics of the 3 Study Groups

	Gallstones			Abusive alcohol use			Non-alcohol-non-gallstones		
	Noncannabis users n = 9,210 ~ 46,050	Cannabis users n = 1,842 ~ 9,210	p-Value	Noncannabis users n = 49,119 ~ 245,595	Cannabis users n = 49,179 ~ 245,595	p-Value	Noncannabis users n = 135,257 ~ 676,285	Cannabis users n = 135,257 ~ 676,285	p-Value
Age, years (SD)	39.14 (14.44)	39.14 (14.44)	1	40.74 (13.65)	40.74 (13.65)	0.2204	36.39 (14.14)	36.39 (14.14)	0.2958
Gender			1			1			1
Male	49.51	49.51		74.31	74.31		57.22	57.22	
Female	50.49	50.49		25.69	25.69		42.78	42.78	
Race			1			1			1
White	54.78	54.78		61.11	61.11		51.32	51.32	
Black	26.44	26.44		24.38	24.38		34.47	34.47	
Hispanic	13.25	13.25		8.82	8.82		9.45	9.45	
Asian and others	5.54	5.54		5.69	5.69		4.76	4.76	
Insurance			<0.0001			<0.0001			<0.0001
Medicaid	13.68	15.31		14.12	17.67		15.17	17.38	
Medicare	25.14	36.59		27.89	33.00		29.39	39.80	
Private	42.42	21.44		28.96	22.04		39.15	21.81	
Self-pay and others	18.76	26.66		29.03	27.29		16.29	21.02	
Household median income			<0.0001			<0.0001			<0.0001
First quartile	33.56	42.19		34.51	38.73		34.79	42.78	
Second quartile	25.09	24.83		25.78	25.82		25.56	25.42	
Third quartile	23.73	21.82		21.76	20.32		22.14	19.37	
Fourth quartile	17.62	11.16		17.96	15.13		17.51	12.43	
Charlson–Deyo comorbidity score			<0.0001			<0.0001			<0.0001
0	64.81	58.90		59.01	61.14		60.09	59.07	
1, 2, 3	26.10	30.51		29.94	31.07		28.93	32.30	
>3	9.09	10.59		11.05	7.79		10.98	8.62	
Acute pancreatitis	15.17	14.39	0.3961	9.25	4.83	<0.0001	1.09	1.12	0.4145
Chronic pancreatitis	0.99	1.09	0.7021	3.70	2.42	<0.0001	0.47	0.69	<0.0001
Tobacco use	24.95	65.04	<0.0001	49.59	63.00	<0.0001	23.62	53.74	<0.0001
Hyperlipidemia	13.25	13.25	1	11.56	11.84	0.1758	13.49	12.99	0.0011
Obesity	22.32	21.34	0.3517	7.00	7.26	0.1094	12.70	10.88	<0.0001
Diabetes mellitus	15.33	15.36	0.972	12.28	10.26	<0.0001	16.37	14.15	<0.0001
Family history of pancreatitis	0.25	0.43	0.1741	0.05	0.04	0.7629	0.04	0.07	0.0014
Hypercalcemia	0.38	0.33	0.7259	0.35	0.34	0.8697	0.35	0.40	0.0226
Pancreatic malignancy	0.36	0.49	0.4087	0.11	0.09	0.3019	0.15	0.09	<0.0001
Cystic fibrosis	0.08	0.05	0.7517	0.06	0.02	0.0037	0.31	0.08	<0.0001
Autoimmune disease	0.66	0.65	0.9581	0.30	0.26	0.3341	0.88	0.70	<0.0001

prevalence of AP (aOR: 0.96 [0.83 to 1.13], p-value: 0.6433) or CP: (0.87 [0.50 to 1.52], p-value: 0.6268) among individuals with gallstones (Tables 2 and 3). Additionally, age, gender, race, tobacco use, hypercalcemia, autoimmune disease, and having a family history of pancreatitis had no impact on the prevalence of gallstones-related AP (Table 2). However, CP, hyperlipidemia, and obesity (aOR: 3.63 [2.43 to 5.41], 1.31 [1.10 to 1.55], and 1.26 [1.11 to 1.43]) were significantly associated with gallstones-related AP (Table 3 and Fig. 1). Female gender, and having AP and obesity significantly increased the likelihood of developing CP (0.56 [0.37 to 0. 78], 3.66 [2.44 to 5.48], and 0.24 [0.12 to 0.49]).

Among the gallstone group, 58.52% (5,506 of 11,052) had cholecystectomy. After adjusting for cholecystectomy in the models, there remained no association of cannabis use with AP and CP (aOR: 0.94 [0.80 to 1.1] and 0.83 [0.47 to 1.44]). Cholecystectomy was associated with decreased odds for both AP and CP (aOR: 0.73 [0.66 to 0.82] and 0.42 [0.28 to 0.64]).

Decreased Odds of AP and CP Among Individuals with Abusive Alcohol Consumption with Concomitant Cannabis Use

After confounder matching by eliminating age-, gender- and race-related variables, cannabis use was associated with approximately 50 and 20% reduced odds for developing AP and CP, respectively, among patients with abusive alcohol consumption (aOR: 0.50 [0.48 to 0.53] and 0.77 [0.71 to 0.84]) (Tables 2 and 3). For every 10-year increase in age, there was 13% decreased odds for AP. Other factors associated with increased odds for alcohol-related AP include race (non-White racial groups), income (lower quartiles), region (non-northeastern regions of the United States), rural areas, having CP, tobacco use, hyperlipidemia, diabetes mellitus, having a family history of pancreatitis, and hypercalcemia. Obesity and autoimmune disorders were inversely associated with alcoholic AP (Table 2). These findings were similar for alcoholic CP. The difference was that the odds for CP were

Table 2. Adjusted Odds of Acute Pancreatitis Among Individuals with Gallstones, Abusive Alcohol Use, and No-Alcohol–No-Gallstones

	Gallstones				Abusive alcohol use				Non-alcohol-non-gallstones			
	[a]OR	95% CI		*p*-Value	[a]OR	95% CI		*p*-Value	[a]OR	95% CI		*p*-Value
Cannabis use versus nonuse	0.964	0.825	1.126	0.6433	0.503	0.477	0.531	<0.0001	0.93	0.857	1.009	0.0802
Age	0.996	0.992	1.001	0.1319	0.987	0.985	0.989	<0.0001	0.995	0.992	0.999	0.0055
Females versus males	1.081	0.967	1.207	0.17	0.969	0.912	1.029	0.2784	0.639	0.586	0.697	<0.0001
Race				0.2277				<0.0001				0.0033
Black versus White	0.898	0.783	1.029		1.619	1.52	1.723		0.992	0.907	1.086	
Hispanic versus White	1.081	0.912	1.282		1.201	1.092	1.322		1.235	1.085	1.406	
Asian and others versus White	1.031	0.807	1.317		1.218	1.086	1.366		0.885	0.727	1.077	
Health insurance				0.0014				<0.0001				<0.0001
Medicare versus private	1.225	0.998	1.504		1.614	1.464	1.778		1.139	1.001	1.296	
Medicaid versus private	1.42	1.174	1.717		1.716	1.551	1.899		1.302	1.147	1.477	
Self-pay and others versus private	1.39	1.126	1.717		2.13	1.934	2.346		1.632	1.434	1.857	
Income status				0.7389				<0.0001				0.0155
Lowest versus highest quartile	0.959	0.833	1.104		1.071	1.001	1.146		1.017	0.923	1.121	
Second versus highest quartile	0.919	0.792	1.066		1.182	1.098	1.272		0.95	0.851	1.06	
Third versus highest quartile	0.966	0.814	1.145		1.145	1.054	1.244		1.167	1.034	1.316	
Hospital region				0.7431				<0.0001				<0.0001
Midwest versus northeast	1.075	0.896	1.29		1.178	1.086	1.279		1.173	1.032	1.333	
South versus northeast	1.096	0.932	1.29		1.284	1.19	1.385		1.326	1.182	1.488	
West versus northeast	1.062	0.89	1.268		1.52	1.398	1.654		1.399	1.23	1.591	
Hospital teaching status				0.657				<0.0001				<0.0001
Urban nonteaching versus rural	0.922	0.755	1.125		0.793	0.722	0.871		0.744	0.65	0.85	
Urban teaching versus rural	0.96	0.791	1.166		0.59	0.539	0.645		0.589	0.518	0.67	
Chronic pancreatitis	3.625	2.429	5.41	<0.0001	16.298	14.99	17.722	<0.0001	64.014	56.64	72.35	<0.0001
Tobacco use	0.996	0.88	1.128	0.9558	1.402	1.328	1.48	<0.0001	1.278	1.174	1.391	<0.0001
Hyperlipidemia	1.305	1.103	1.545	0.002	1.524	1.401	1.657	<0.0001	1.577	1.409	1.766	<0.0001
Obesity	1.262	1.113	1.431	0.0003	0.897	0.805	0.999	0.047	1.004	0.892	1.13	0.9481
Diabetes mellitus	1.027	0.874	1.207	0.7478	1.043	0.956	1.138	0.3424	1.707	1.545	1.886	<0.0001
Family history of pancreatitis	2.129	0.998	4.544	0.0507	2.301	1.026	5.162	0.0432	1.018	0.31	3.335	0.9771
Hypercalcemia	1.928	0.918	4.051	0.0831	3.108	2.311	4.18	<0.0001	2.283	1.479	3.522	0.0002
Pancreatic malignancy	0.594	0.203	1.742	0.3428	1.267	0.524	3.061	0.599	3.074	1.362	6.938	0.0068
Cystic fibrosis	0.875	0.109	7.004	0.9001	0.439	0.09	2.138	0.3082	1.522	0.793	2.921	0.2065
Autoimmune disease	0.448	0.178	1.128	0.0884	0.564	0.319	0.996	0.0483	1.609	1.077	2.405	0.0203

[a]OR, adjusted odds ratio.

higher by 19% for every 10-year increase in age. Odds for CP were also higher among Black race, midwest and southern regions, having cystic fibrosis. The odds for alcoholic CP were decreased with among the Hispanic race and those with hyperlipidemia (Table 3 and Fig. 1).

Increased Odds for CP But Not AP Among Individuals with Neither Gallstones Nor Abusive Alcohol Consumption Disorders

Among the non-alcohol-non-gallstones population, cannabis use had no impact on the incidence of AP but increased the odds for developing CP (aOR: 0.93 [0.86 to 1.01] and 1.28 [1.14 to 1.44]) (Tables 2 and 3). Odds for AP were decreased by 5% for every 10-year increase in age. Other risk factors for AP in this group included male gender, Hispanic race, nonprivate health insurance, lower income, region (non-northeastern regions of the United States), rural residence, CP, tobacco use, hyperlipidemia, obesity, diabetes, family history of pancreatitis, hypercalcemia, pancreatic malignancies, and autoimmune disorders (Table 2). Risk factors for CP among this group were increased by 17% for every 10-year increase in age. In addition, White race background, private health insurance, AP, tobacco use, diabetes, history of pancreatitis, pancreatic malignancies, cystic fibrosis, and autoimmune disorders were also associated with CP (Table 3 and Fig. 2).

Dependent Cannabis Use Was Associated with a Reduced Likelihood for Developing AP and CP Among Individuals Who Abusively Consumed Alcohol

Given that cannabis use significantly impacted, by reducing the incidence of AP and CP among individuals who abusively consumed alcohol, we studied this group further. We performed a subgroup analysis and substratified the cannabis usage among this into dependent and nondependent users. We found that compared to noncannabis users, nondependent and dependent cannabis users, respectively, had approximately 45 and 85% decreased odds for alcohol-related AP (aOR: 0.55 [0.52 to 0.59] and 0.14 [0.11 to 0.18]) (Table 4). Strikingly, dependent cannabis use was associated with a 75% decreased odds of AP compared to nondependent cannabis use (0.25 [0.19 to 0.33]). Further, the odds of having CP in individuals who abusively consumed alcohol were significantly reduced in concomitant cannabis users

Table 3. Adjusted Odds of Chronic Pancreatitis Among Individuals with Gallstones, Abusive Alcohol Use, and No-Alcohol–No-Gallstones

	Gallstones				Abusive alcohol use				Non-alcohol-non-gallstones			
	[a]OR	95% CI		*p*-Value	[a]OR	95% CI		*p*-Value	[a]OR	95% CI		*p*-Value
Cannabis use versus nonuse	0.87	0.50	1.52	0.6268	0.77	0.71	0.84	<0.0001	1.28	1.14	1.44	<0.0001
Age	1.01	0.99	1.03	0.2851	1.02	1.01	1.02	<0.0001	1.02	1.01	1.02	<0.0001
Females versus males	0.56	0.37	0.87	0.0096	1.08	0.99	1.18	0.0989	0.93	0.83	1.04	0.2048
Race				0.3666				<0.0001				0.0129
Black versus White	1.25	0.81	1.92		1.26	1.15	1.37		0.85	0.75	0.97	
Hispanic versus White	0.65	0.31	1.37		0.66	0.55	0.78		0.83	0.67	1.01	
Asian and others versus White	1.14	0.51	2.56		0.79	0.65	0.96		0.71	0.53	0.97	
Health insurance				0.0136				<0.0001				<0.0001
Medicare versus private	0.90	0.45	1.76		1.26	1.11	1.42		0.82	0.70	0.96	
Medicaid versus private	0.45	0.24	0.83		0.57	0.50	0.66		0.53	0.45	0.63	
Self-pay and others versus private	1.03	0.55	1.94		0.87	0.76	0.99		0.64	0.54	0.76	
Income status				0.4317				0.603				0.5013
Lowest versus highest quartile	0.81	0.48	1.37		1.04	0.94	1.14		0.93	0.81	1.06	
Second versus highest quartile	1.31	0.82	2.09		0.96	0.86	1.07		0.90	0.77	1.05	
Third versus highest quartile	1.08	0.59	1.97		0.97	0.85	1.11		0.93	0.78	1.11	
Hospital region				0.9845				<0.0001				0.1037
Midwest versus northeast	0.89	0.47	1.69		1.21	1.07	1.36		1.18	0.99	1.39	
South versus northeast	0.96	0.54	1.70		1.20	1.07	1.34		1.09	0.93	1.27	
West versus northeast	0.94	0.51	1.75		0.86	0.75	0.98		0.97	0.81	1.17	
Hospital teaching status				0.0293				<0.0001				0.0047
Urban nonteaching versus rural	1.66	0.64	4.35		1.26	1.07	1.47		1.11	0.89	1.38	
Urban teaching versus rural	2.59	1.02	6.60		1.47	1.26	1.71		1.30	1.06	1.60	
Acute pancreatitis	3.66	2.44	5.48	<0.0001	16.65	15.31	18.11	<0.0001	64.66	57.34	72.91	<0.0001
Tobacco use	1.31	0.85	2.03	0.2178	1.32	1.22	1.44	<0.0001	1.55	1.38	1.74	<0.0001
Hyperlipidemia	1.02	0.59	1.75	0.9556	0.85	0.75	0.96	0.0088	0.88	0.76	1.02	0.0902
Obesity	0.24	0.12	0.49	<0.0001	0.42	0.35	0.52	<0.0001	0.50	0.41	0.61	<0.0001
Diabetes mellitus	2.38	1.43	3.98	0.0009	2.68	2.41	2.98	<0.0001	2.42	2.12	2.76	<0.0001
Family history of pancreatitis	4.56	0.64	32.27	0.1288	1.51	0.47	4.89	0.49	6.97	2.45	19.86	0.0003
Hypercalcemia	3.79	0.77	18.61	0.1012	0.68	0.39	1.20	0.1833	1.15	0.57	2.30	0.6975
Malignancy	3.87	0.73	20.41	0.1113	3.78	1.83	7.82	0.0003	2.95	1.29	6.75	0.0106
Cystic fibrosis					4.29	1.09	16.92	0.0377	9.05	5.22	15.69	<0.0001
Autoimmune disease	1.78	0.23	13.94	0.5849	1.52	0.85	2.73	0.1566	1.76	1.09	2.86	0.0216

[a]OR, adjusted odds ratio.

compared to alcoholics who did not use cannabis (0.79 [0.71 to 0.87] and 0.58 [0.43 to 0.79]). Among abusive alcohol plus cannabis consumers, dependent cannabis users were less likely to develop CP compared to nondependent cannabis users (0.74 [0.54 to 1.00]) (Table 4).

DISCUSSION

Using the largest publicly available data set that covers the entire United States, we conducted a detailed population study evaluating the effects of cannabis use and the incidence of pancreatitis. We focused on all the major etiologies ranging from alcohol abuse, gallstones, and pancreatitis from other causes. Our findings revealed cannabis use had no effect or increased the incidence of pancreatitis due to gallstones and other (genetic, drugs, infection, etc.) causes. Strikingly, cannabis use was associated with significantly reduced odds for developing pancreatitis among individuals who abusively consumed alcohol and use cannabis.

Cannabis has been used for medicinal purposes for virtually every disease condition (Röder et al., 2016). The effects of cannabis use on pancreatitis from both population and experimental mice studies have been conflicting. Reports have shown that cannabinoids (THC and CBD) can suppress pro-inflammatory cytokine production associated with inflammatory disease due to abusive alcohol consumption or other causes (Klein, 2005; Nair et al., 2015). Notwithstanding, other findings have advanced that cannabis use can induce or have no effect on inflammatory diseases including pancreatitis (Klumpers et al., 2012; Nagarkatti et al., 2009). To the best of our knowledge, our study is the first to address the simultaneous effects of cannabis use and pancreatitis from known etiologic factors. The functional effects of cannabinoids either endogenously produced or from the cannabis plant are mediated by their interaction on specific cannabinoid receptors. There are 2 main G protein-coupled cannabinoid receptors: CB1R and CB2R which show differential body expressions in both health and disease states. CB1R has been shown to be highly expressed in the nervous system while CB2R is primarily present in immune cells and the gut (Petrella et al., 2010). CB1R and CB2R show low but functional expression in the pancreas which significantly increases during inflammation (Bermúdez-Silva et al., 2008; Linari et al., 2009; Miller and Devi, 2011). Activation of CB1R in the pancreas has been linked to increased inflammation and fibrosis. On the contrary, CB2R activation has

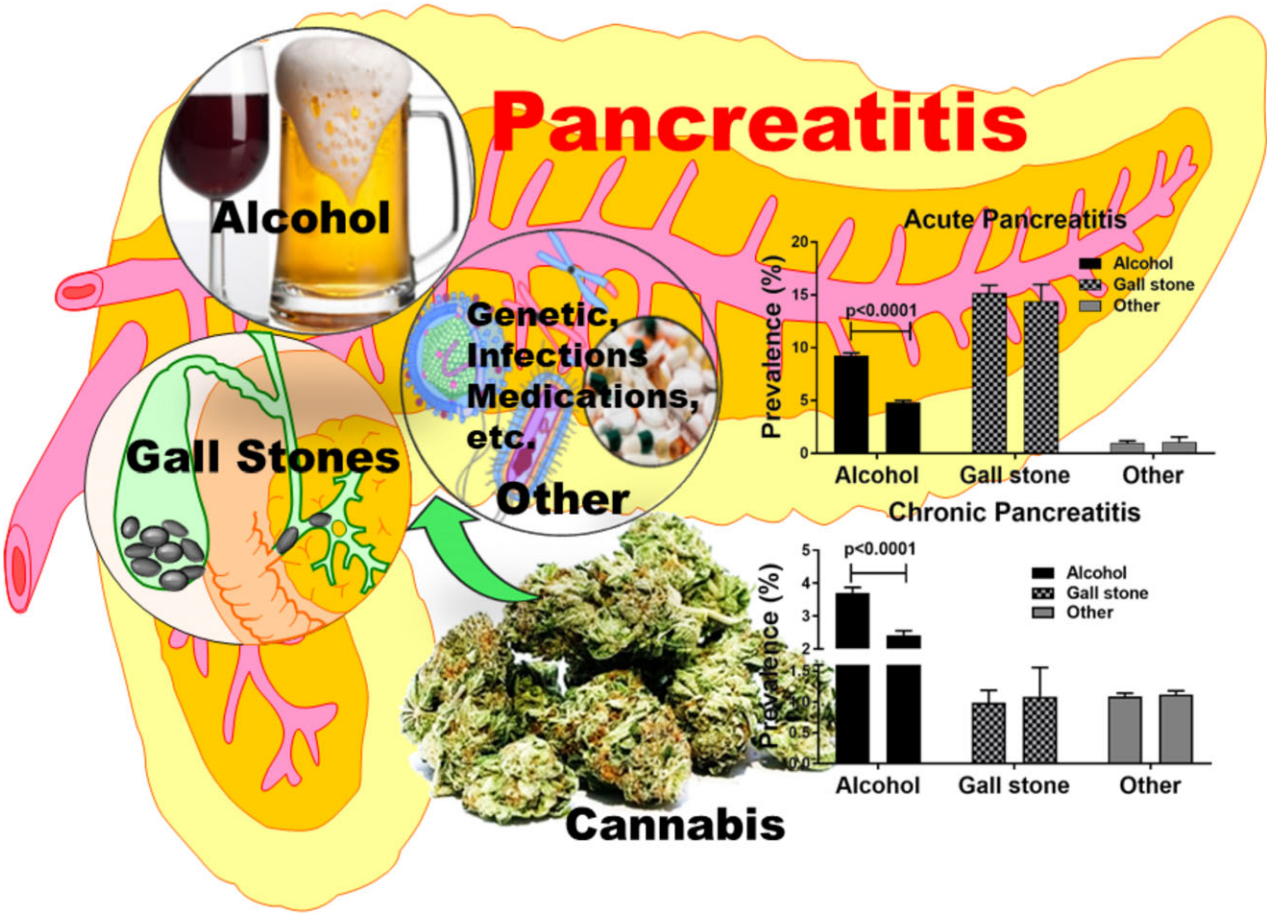

Fig. 2. Effects of cannabis use and the incidence of pancreatitis from diverse causes. Impact of cannabis on the prevalence of pancreatitis, acute (**upper** figure) and chronic (**lower** figure), was examined within 3 groups: abusive alcohol use, gallstones disease, and neither alcohol nor gallstones [other]. Our studies revealed reduced prevalence of acute pancreatitis among abusive alcohol users (cannabis nonuse: 9.25% vs. cannabis use: 4.83%, *p*-value: <0.0001), but not among individuals with gallstones (15.17% vs. 14.31%, 0.3981) nor with other risk factors (1.09% vs. 1.12%, 0.4145). With concomitant cannabis use, the prevalence of chronic pancreatitis was lower among abusive alcohol users (cannabis nonuse: 3.7% vs. cannabis use: 2.42%, *p*-value: <0.0001), similar among individuals with gallstones (0.99% vs. 1.09%, 0.7021), but higher among those with other risk factors (0.47% vs. 0.69%, <0.0001). Illustrated schematics made use of some motifolio templates (www.motifolio.com).

Table 4. Subgroup Analysis of Cannabis Use (Dependent and Nondependent) with Acute and Chronic Pancreatitis

	Abusive alcohol use							
	Acute pancreatitis				Chronic pancreatitis			
	[a]OR	95% CI		*p*-Value	[a]OR	95% CI		*p*-Value
Cannabis use versus nonuse	0.50	0.48	0.53	<0.0001	0.77	0.71	0.84	<0.0001
Nondependent cannabis use versus nonuse	0.55	0.52	0.59	<0.0001	0.79	0.71	0.87	<0.0001
Dependent cannabis use versus nonuse	0.14	0.11	0.18	<0.0001	0.58	0.43	0.79	<0.0001
Dependent cannabis use versus nondependent use	0.25	0.19	0.33	<0.0001	0.74	0.54	1.00	0.0531

[a]OR, adjusted odds ratio.

been shown to be anti-inflammatory/fibrotic on diverse body organs including pancreas (Burstein, 2015; Gerich et al., 2015; Matsuda et al., 2005). Studies have demonstrated that a synthetic CB1R and CB2R agonist can significantly improve survival, attenuate abdominal pain, and decrease disease severity in experimental models of pancreatitis (Dembiński et al., 2006; Li et al., 2013; Matsuda et al., 2005). More recent findings have revealed that cannabinoid receptor activation induces a quiescent phenotype of CP-derived pancreatic stellate cell by down-regulating production of extracellular matrix proteins and inflammatory cytokines (Michalski et al., 2008). The reasons for these

contradictory findings from basic and even in population-based studies could because of differences in experimental methods/models, the diversity of the study populations assessed, and the type and dose of cannabinoids used. Additionally, striking the precise therapeutic timing, dose, and balance between CB1R and CB2R activation or inhibition seems to be crucial in harnessing the health benefits of cannabis for pancreatitis.

This study is our effort to determine the effect of cannabis use on the clinical incidence of pancreatitis from known distinct etiologies given conflicting data from experimental and population-based studies. Our novel findings reveal that cannabis use might possibly impact the development of alcoholic pancreatitis (both AP and CP). Our results are consistent with a recent single-center study where among patients hospitalized for alcoholic pancreatitis, and those with concomitant history of cannabis use had less severe inflammation, lower BUN, and need for ICU care (Goyal et al., 2017). In our study, dependent cannabis use provided the stronger association with lower odds of AP and CP in alcoholics. However, pancreatitis from nonabusive alcohol consumption or gallstones induced was not affected or exacerbated with cannabis use. Because the effects of cannabis on pancreatitis are primary among abusive alcohol users, our results suggest that cannabis might be interacting with alcohol in the pancreas through unknown mechanisms. These observations highlight the need to conduct more detailed studies on different actions of cannabinoid formulations, dosage, and timing on alcoholic pancreatitis. Furthermore, studies are needed to assess the potential role of cannabis in modulating the development and course of pancreatitis with a detailed focus on specific underlying disease etiology.

Our result revealed a higher odds of AP among privately insured versus noninsured individuals. Often employer sponsored or individually purchased, private health insurance in the United States typically infers a better level of health care compared to the nonprivate insurance (uninsured or governmental insurance) (Davis, 2004). Nonprivate health insurance has been shown by many studies to be related to poorer access to health care and poorer outcomes (Brooks et al., 2010). Our result reflects this general trend by revealing that individuals across the 3 groups generally had a higher odds of AP compared to those with nonprivate insurance. In contrast, nonprivate health insurance was also related to decreased odds of CP in our study across all the 3 groups, which was an unexpected finding. Further studies are needed to clarify the relationship between health insurance status and pancreatitis (acute and chronic).

We must also underscore some potential limitations of our study. Given its cross-sectional design, it is impossible to make a precise link between cannabis use and the direct impact of pancreatitis development. For individuals who used cannabis and consumed alcohol abusively, we cannot have ascertained whether cannabis and alcohol were consumed at the same time or not, as well as the frequency of consumption. We stratified our cannabis-use group into dependent and nondependent categories (Chen et al., 1997), assuming that dependent cannabis users consumed more cannabis than occasional users. Also, our data are only among hospitalized patients, which are <10% of the U.S. population. This group might be different from the nonhospitalized U.S. population. Underreporting of cannabis use and validity of the cannabis use using the ICD-9-CM codes would diminish the size of our cannabis-use groups. However, both events would likely result in misclassification errors, which would decrease our observed effect size. Other limitations include residual confounders, including the strain of cannabis consumed, and the duration and route of usage (Piomelli and Russo, 2016). Finally, the accuracy of the ICD-9-CM codes for AP and CP in the NIS is unknown, although some studies have reported accuracy of 83 and 49%, respectively, for AP and CP in other data (Razavi et al., 2011; Reddy et al., 2016).

In conclusion, despite the shortcomings of cross-sectional studies, our novel revelations of a strong dose-dependent decrease in the odds of both AP and CP among alcohol users and increased odds of CP among non-alcohol-non-gallstones users are remarkable (Fig. 2). We believe that more translational and longitudinal studies are warranted to clarify the relationship between cannabis and pancreatitis due to increasing decriminalization and legalization of cannabis globally. Studies are needed to identify the best cannabis strains and the right strategies of striking the adequate balance of CB1/2R agonism and antagonism to achieve maximum therapeutic benefits.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Adjusted odds of acute pancreatitis among individuals ICD-9-CM codes used in the study.

Table S2. Baseline characteristics of the 3 studied groups (unmatched).