

## ORIGINAL RESEARCH

# Relationship Between Recreational Cannabis Use and *Helicobacter pylori* Infection

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### Abstract

**Background:** Cannabis plant extracts suppress gastric acid secretion and inflammation, and promote gastroduodenal ulcer healing, all of which are triggered by *Helicobacter Pylori* infection (HPI). Here, we evaluate the association between cannabis use and HPI among a representative community sample.

**Materials and Methods:** We identified respondents who completed cannabis use questions and were tested for HPI (*H. pylori* IgG antibody seropositivity) from the National Health and Nutrition Examination Survey III dataset ( $n=4556$ ). Cannabis usage was categorized as ever-use (ever, never), cumulative lifetime use (> 10-times, 1–10-times, never), or recent use (> 31-days-ago, within-31-days, never). We calculated the crude and adjusted risk (prevalence rate ratio, cPRR and aPRR) of having HPI with cannabis use using generalized Poisson models (SAS 9.4). The models were adjusted for demographics and risk factors for HPI.

**Results:** The prevalence of HPI was lower among ever versus never cannabis users (18.6% vs. 33%,  $p < 0.0001$ ). Cannabis use was associated with a decreased risk of HPI (cPRR: 0.56 confidence interval [95% CI: 0.47–0.67];  $p < 0.0001$ ), which persisted after adjusting for demographics (aPRR: 0.75 [95% CI: 0.63–0.90];  $p = 0.0016$ ) and comorbidities (aPRR: 0.79 [95% CI: 0.66–0.95];  $p = 0.0145$ ). Further, individuals with > 10-times lifetime cannabis use had a decreased risk of HPI compared with those with 1–10-times lifetime use (aPRR: 0.70 [95% CI: 0.55–0.89];  $p = 0.0011$ ) and never-users (aPRR: 0.65 [95% CI: 0.50–0.84];  $p = 0.0002$ ).

**Conclusion:** Recreational cannabis use is associated with diminished risk of HPI. These observations suggest the need for additional research assessing the effects of medical cannabis formulations on HPI.

**Keywords:** antibiotic resistance; cannabinoids; concomitant; peptic ulcer disease; prevalence

### Introduction

Gastrointestinal infection caused by *Helicobacter pylori* (Hp) bacteria is the most common cause of peptic ulcer disease afflicting more than 80% of the world's population.<sup>1,2</sup> Environmental factors such as food types, household pets, bad hygiene, socioeconomic status, tobacco, and alcohol use are associated with an increased risk of *H. pylori* infection (HPI).<sup>3,4</sup>

After stomach infection by Hp, host factors play a significant modulatory role in determining the pathohistological pattern, as well as the extent and severity of the chronic gastric inflammation induced (antral-predominant, corpus-predominant, or pan-gastritis).<sup>5–7</sup> Without treatment, the characteristic sequelae of HPI

include asymptomatic gastric colonization, duodenal inflammation, ulcerations (gastric and duodenal), pernicious anemia, and gastric adenocarcinoma.<sup>8–10</sup>

The standard clinical treatment for HPI involves the combination of antibiotics and anti-secretory medications (triple or quadruple regimens) for 10 to 14 days. However, treatment failures are being noticed due to antibiotic resistance.<sup>11,12</sup> Cannabis plant extracts contain more than 600 active ingredients and cannabinoids,<sup>13</sup> have been shown to suppress gastric acid secretion, acidic erosion of gastric mucosa, and gastritis, and promote gastric ulcer healing,<sup>14,15</sup> all of which are associated with HPI. Reports have shown that cannabis use can ameliorate duodenal and gastric

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ulcerations via its anti-inflammatory actions.<sup>15–18</sup> In addition, cannabinoids have demonstrated antibacterial activities against *Clostridium difficile*,<sup>19</sup> *Streptococcus pneumoniae*,<sup>20</sup> and *Staphylococcus aureus*,<sup>21</sup> and other pathogens.<sup>22</sup> Finally, cannabis has been shown to modulate colonic microbiota.<sup>23</sup> Taken together, these published observations led us to surmise that cannabis use might have a modulatory effect on gastric pH and microbiota, which can impact HPI. Notwithstanding, no studies have evaluated the effects of cannabis and HPI in humans.

Unlike other countries where initial HPI is primarily among children due to poor hygiene, the majority of HPI in the United States occurs in adults, increasing from 16.7% among the age group of 20–29 years, to 56.9% among the age group of  $\geq 70$  years. Since cannabis usage is primary among adults, there is a potential for interaction between cannabis use and HPI.<sup>24</sup> Further, increased global legalization of recreational cannabis use means that a high proportion of individuals within communities are now using this drug, which can have public health implications for HPI. Delineating any potential associations between cannabis use and HPI will help direct scientific research, and it will shape health policy decisions and recommendations on recreational cannabis use. Therefore, we assessed the association between HPI (defined as positive *H. pylori* IgG antibody test) and the frequency, quantity, and duration of cannabis use among community dwellers in the United States.

## Materials and Methods

### Study population

This study was performed using the National Health and Nutrition Examination Survey. Specifically, the Third National Health and Nutrition Examination Survey (NHANES III), which was conducted from 1988 through 1994, was used because these were the only NHANES data that contain information on cannabis use and serologic tests for HPI. Developed by the National Center for Health Statistics, the NHANES III is a nationally representative dataset of noninstitutionalized individuals residing in communities in the United States. The NHANES III is collected through a composite, stratified, and multi-staged methodology. Participating individuals were administered questionnaires on demographics, lifestyle choices, comorbidities, and drug use. Respondents also had physical and laboratory examinations at mobile examination centers. The NHANES III has been used by numerous

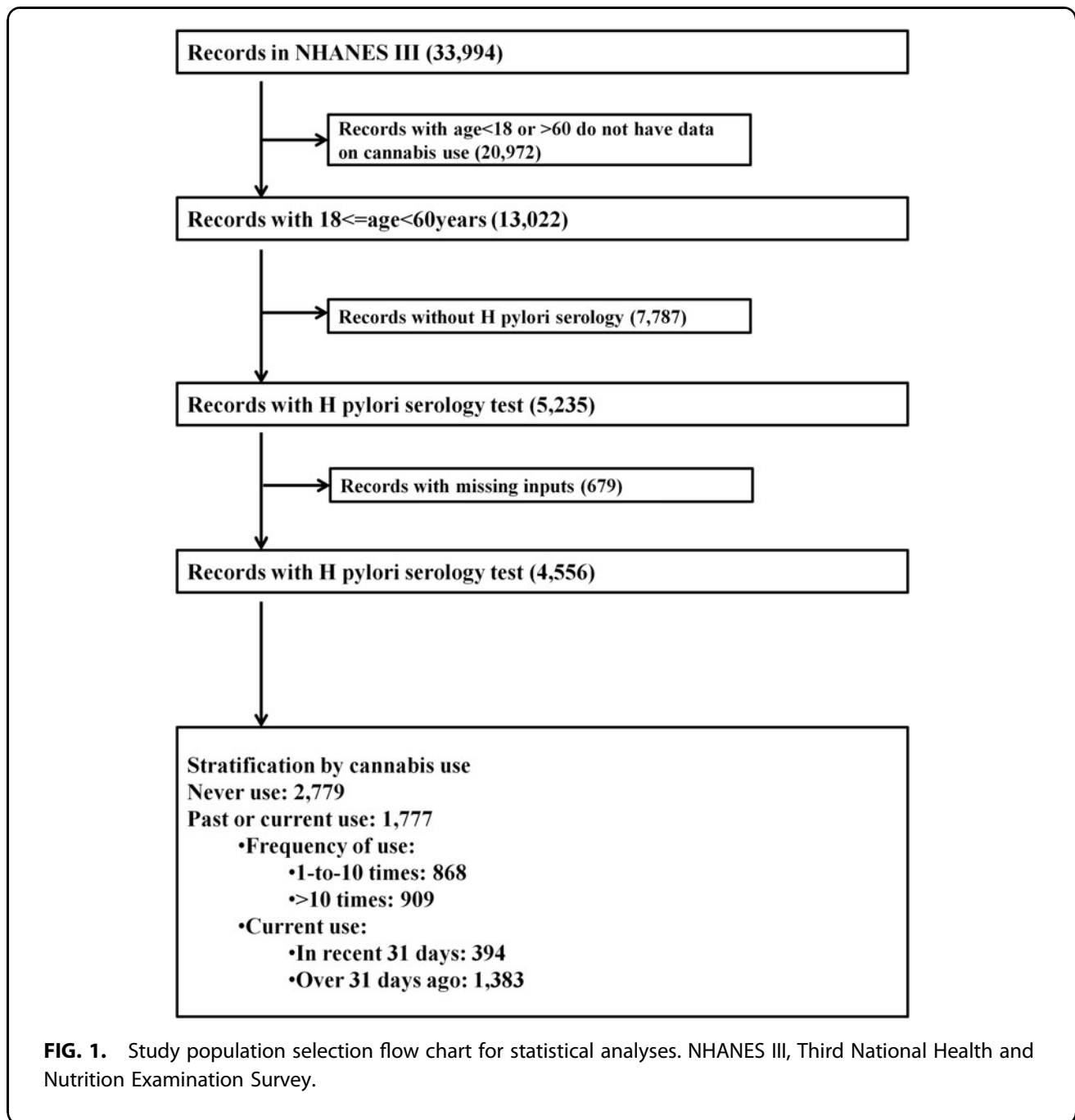
studies to generate national estimates for various disorders, including the serological prevalence of HPI.<sup>24–28</sup> All records with information on cannabis usage (only available for individuals aged 18 to 60 years) and those who had serologic tests for HPI were selected for the analysis before missing records were excluded (Fig. 1). Because the NHANES III is completely de-identified, secondary data analysis employed in this current study did not require any Institutional Review Board Approval.

### Measurement of cannabis use and explanatory variables

The primary predictor was cannabis use, which was captured in the NHANES III dataset in three ways, and has been used in previous studies.<sup>29,30</sup> The first is the question, “Have you ever used marijuana?” with the responses “Yes” or “No” encoded as “Ever-users” and “Never-users” of cannabis respectively. Respondents who had used marijuana were subsequently evaluated for frequency and quantity of use captured in the second question: “About how many times in your life have you used marijuana?” Responses were grouped into “> 10-times” and “1-to-10-times.” Third, cannabis users were questioned on recent usage, “During the past month, on how many days did you use marijuana?” Responses were encoded as “past-31-days” and “> 31-days-ago.” Our secondary predictors were the factors associated with HPI. These associated factors were identified from published literature<sup>24,25</sup> and subsequently correlated with information from the NHANES III dataset. These factors include age, gender (male and female), body mass index (BMI), household size, Race (Whites, Blacks, Hispanics, and others), region of residence (Northeast, Midwest, South, and West), urbanization (metropolitan and nonmetropolitan), income status ( $\geq \$40,000$ ,  $\$20,000$  to  $\$40,000$ , and  $< \$20,000$ ), highest educational level ( $> 12$ th grade, 12th grade, and  $< 12$ th grade), household pets (yes, no), current smoking (yes, no), alcohol use (excessive use, modest use, and nonuse), use of tap water (yes, no), place of birth (outside the United States, within the United States), and marital status (married, separated, and single).<sup>1–4,24,25</sup>

### Measurement of HPI

The outcome was HPI, which was quantified with Hp serologic testing, using commercial IgG ELISA (Wampole Laboratory, Cranbury, NJ). The analytic test details have been extensively described in other previous



studies.<sup>24,25</sup> Briefly, an immune status ratio (ISR) was calculated for each patient, by dividing the patient's sample optical density with the mean optical density of the cutoff controls. Samples with ISR between 0 and 0.90 were deemed negative, whereas those with ISR > 0.9 were positive. Using optimal cutoffs, serologic IgG for HPI laboratory diagnosis has a 72.% sensitivity and 74.3% specificity for individuals aged  $\geq 18$  years.<sup>31</sup>

#### Statistical analysis

All statistical analysis was performed using the Statistical Analysis System (SAS V.9.4; SAS Institute Inc., Cary, NC). We plotted the estimated prevalence and confidence intervals (CI) using GraphPad Prism 8.1.2 (GraphPad Software, La Jolla, CA). The strata, clusters, and weights provided in the NHANES were used to generate national estimates. We summarized categorical variables with percentages and compared them

with the chi-square test. Numerical variables were reported as means and compared with Student's *T*-tests. We estimated the prevalence rate and risk of HPI seropositivity with cannabis use by using generalized estimating equations with Poisson regression model and robust modification of the error variances.<sup>32</sup> Three models were built to measure the risk of HPI with cannabis use. The base model was the crude model (model 1). Model 2 adjusted for demographic variables by including age, sex, race, BMI, household size, region, urbanization, income status, and education level in the base model. Model 3 additionally adjusted for risk factors of HPI, including household pets, current smoking, use of tap water, place of birth, alcohol use, and marital status in model 2. Each of these three statistical models was designed for each of the three different measurements of cannabis use (ever use, cumulative use, and recent use) as a predictor, to make nine models in total.

## Results

### Study characteristics

From the NHANES III dataset, we evaluated records from 4556 individuals, among whom 1777 had a history of cannabis use (current or past) (Fig. 1). The frequency of HPI was about half among individuals with a history of cannabis use (18.62% vs. 32.95%;  $p < 0.0001$ ) compared with noncannabis users. Cannabis users were more likely to be among individuals who were young, of the male sex, of a white racial group, who reside in the Northeastern region of the United States, but less likely to reside in the Southern region of the United States (Table 1). In addition, cannabis users more often had income earnings of less than \$20,000 per year, and paradoxically were more likely to have attained an education level at or above the 12th grade. Further, cannabis users were more frequently from households with pets, to be born within the United States, to have excessive alcohol use and current tobacco use, and to be single (vs. married or separated).

### Prevalence of HPI with cannabis use

We observed reduced prevalence of HPI among cannabis users both before (Fig. 2A) and after stratification by the quantity of lifetime use (Fig. 2B) but not recency of use (Fig. 2C). Individuals with >10-times lifetime use had a lower prevalence of HPI compared with those with 1–10-times lifetime cannabis use (14.95% vs. 23.14%;  $p < 0.0001$ ) (Fig. 2B). However, the prevalence of HPI was similar among individuals with recent

**Table 1. Baseline Characteristics of Study Participant by Cannabis Use, National Health and Nutrition Examination Survey III**

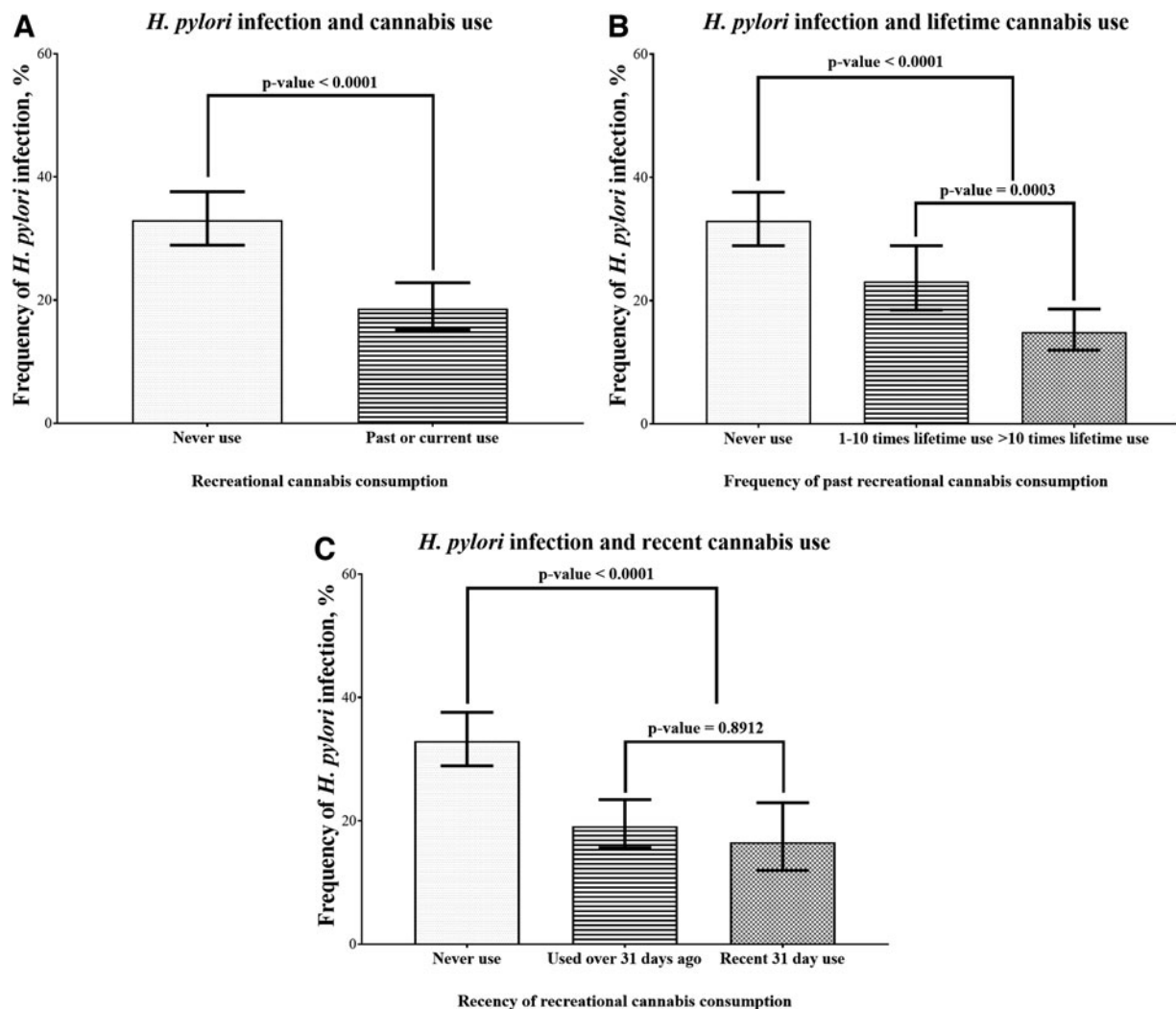
N	Cannabis use		p
	Never used 2779 (~ 32,253,074)	Ever used 1777 (26,483,091)	
Frequency of <i>H. helicobacter pylori</i> infection, %	32.9748	18.6201	<0.0001
Age (SD), years	38.44 (12.45)	32.07 (8.92)	<0.0001
Gender, %			
Male	43.46	56.60	<0.0001
Female	56.54	43.40	
BMI, median (IQR)	25.9 [22.8–29.9]	25 [22.2–28.9]	<0.0001
Household size, median (IQR)	4 [2–5]	3 [2–5]	<0.0001
Race, %			
Whites	73.94	81.45	<0.0001
Blacks	10.26	10.84	
Hispanics	6.35	3.59	
Others	9.44	4.12	
Hospital region, %			
Northeast	19.01	23.76	<0.0001
Midwest	24.90	24.84	
South	37.76	29.07	
West	18.33	22.33	
Urbanization, %			
Metropolitan	46.30	52.29	<0.0001
Non-Metropolitan	53.70	47.71	
Income status, %			
≥\$40,000	39.06	35.19	<0.0001
\$20,000–40,000	34.82	34.15	
Less than \$20,000	26.12	30.66	
Educational level, %			
Above grade 12	44.41	47.39	<0.0001
Grade 12	31.30	34.13	
Below grade 12	24.29	18.48	
Household pets, %	45.26	52.55	<0.0001
Current smoking, %	37.94	52.07	<0.0001
Tap water, %	89.19	89.91	0.3897
Place of birth, %			
Outside the United States	17.57	4.81	<0.0001
Within United States	82.43	95.19	
Alcohol use, %			
Excessive use	7.14	18.49	<0.0001
Modest use	75.19	80.04	
Nonuse	17.67	1.47	
Marital status, %			
Married	68.06	59.74	<0.0001
Separated	12.80	11.83	
Single	19.15	28.43	

BMI, body mass index.

31-day cannabis use compared with those who had taken cannabis over 31 days in the past (16.57% vs. 19.15%;  $p = 0.8912$ ) (Fig. 2C).

### Association between cannabis use and HPI

There was a 44% lower risk of HPI among individuals who had previously used cannabis compared with



**FIG. 2.** Cannabis use is associated with a decreased prevalence of *Helicobacter pylori* infection. There was a decreased prevalence of *H. pylori* infection with past/current cannabis use (**A**), with increasing lifetime usage (**B**), but not with recency of use (**C**).

never users (adjusted risk prevalence rate ratio [aPRR]: 0.56 [95% CI: 0.47–0.67];  $p < 0.0001$ ) (“A” in Table 2). This lower risk of HPI was diminished, respectively, to 25% and 21% after adjusting for demographic (aPRR: 0.75 [95% CI: 0.63–0.90];  $p = 0.0016$ ) and other risk factors of HPI (aPRR: 0.79 [95% CI: 0.66–0.95];  $p = 0.0145$ ) (“B” and “C” in Table 2).

When cannabis use was measured by cumulative lifetime usage, individuals with greater than 10-times lifetime use were associated with a significantly lower risk of HPI when compared with those who had taken cannabis 1 to 10 times or never-users (aPRR:

0.65 [95% CI: 0.52–0.8] and 0.45 [95% CI: 0.37–0.55];  $p < 0.001$ ) (“A” in Table 2). These relationships were moderately diminished but remained significant after adjustment for demographics and other risk factors for HPI (“B” and “C” in Table 2). However, respondents with 1-to-10-times lifetime cannabis use were only associated with a decreased risk of HPI when compared with never-users in the crude model (aPRR: 0.70 [95% CI: 0.58–0.86],  $p = 0.0013$ ) (“A” in Table 2), but not after adjustments for demographics (“B” in Table 2) and other risk factors for HPI (“C” in Table 2).

**Table 2. Crude and Adjusted Risk (Prevalence Rate Ratio) of *Helicobacter pylori* Infection with Cannabis Use, National Health and Nutrition Examination Survey III**

	Crude prevalence rate ratio	Lower confidence limit	Upper confidence limit	<i>p</i>
A: Crude model				
Ever cannabis use				
Ever vs. never	0.56	0.47	0.67	<0.0001
Cumulative lifetime cannabis use				
Greater than 10 times vs. never	0.45	0.37	0.55	<0.0001
One to ten times vs. never	0.70	0.58	0.86	0.0013
Greater than 10 times vs. 1 to 10 times	0.65	0.52	0.80	0.0003
Recent cannabis use				
Used within the past 31 days vs. never	0.50	0.37	0.68	<0.0001
Used over 31 days ago vs. never	0.58	0.49	0.69	<0.0001
Used over 31 days ago vs. used over 31 days ago	0.87	0.66	1.14	0.8912
	Adjusted prevalence rate ratio	Lower confidence limit	Upper confidence limit	<i>p</i>
B: Adjusted for demographic factors				
Ever cannabis use				
Ever vs. never	0.75	0.63	0.90	0.0016
Cumulative lifetime cannabis use				
Greater than 10 times vs. never	0.62	0.48	0.79	<0.0001
One to 10 times vs. never	0.90	0.70	1.14	0.8248
Greater than 10 times vs. 1 to 10 times	0.69	0.54	0.88	0.0006
Recent cannabis use				
Used within the past 31 days vs. never	0.61	0.42	0.89	0.0048
Used over 31 days ago vs. never	0.79	0.64	0.97	0.0181
Used over 31 days ago vs. used over 31 days ago	0.78	0.58	1.06	0.1544
	Adjusted prevalence rate ratio	Lower confidence limit	Upper confidence limit	<i>p</i>
C: Adjusted for demographic and risk factors for <i>H. pylori</i> infection				
Ever cannabis use				
Ever vs. never	0.79	0.66	0.95	0.0145
Cumulative lifetime cannabis use				
Greater than 10 times vs. never	0.65	0.50	0.84	0.0002
One to 10 times vs. never	0.93	0.72	1.20	1
Greater than 10 times vs. 1 to 10 times	0.70	0.55	0.89	0.0011
Recent cannabis use				
Used within the past 31 days vs. never	0.67	0.46	0.98	0.0369
Used over 31 days ago vs. never	0.82	0.65	1.02	0.0916
Used over 31 days ago vs. used over 31 days ago	0.82	0.61	1.12	0.3782

A, crude model; B, model adjusted for age, sex, race, BMI, house-hold size, income status, geographic region, rural versus urban location, and education level; C, model adjusted for model B and other risk factors for *H. pylori* infection including household pets, smoking, alcohol, tap water use, country of birth, and marital status.

Finally, when cannabis use was categorized by the timing of use, recent 31-day cannabis use was associated with a 50% decreased risk of HPI when compared with never-users (aPPR: 0.50 [95% CI: 0.37–0.68];  $p < 0.0001$ ), which persisted after adjustments for demographics (“B” in Table 2) and other risk factors for HPI (“C” in Table 2). However, there was no difference in HPI among recent 31-day use versus cannabis use over 31 days in the past before or after adjustments (“A–C” in Table 2).

In the fully adjusted model, other factors associated with HPI were increasing age, male sex, increasing household size, race (any other race compared with

Whites), lower-income status (less than \$20,000 vs.  $\geq$  \$40,000), lower educational level, and being born outside the United States (Table 3).

## Discussion

Using a well-characterized dataset of community dwellers in the United States, we reveal for the first time, to the best of our knowledge, that recreational cannabis use is associated with a reduced risk of HPI. Notably, our results unveiled that longer-term usage of cannabis was associated with the lowest risk for HPI. The reasons for these observations remain ill-defined.

**Table 3. Factors Associated with *Helicobacter Pylori* Infection in a Multivariate Model, National Health and Nutrition Examination Survey III**

Characteristics associated with <i>H. pylori</i> infection	Adjusted prevalence rate ratio	Lower confidence limit	Upper confidence limit	<i>p</i>
Cannabis ever use vs. never use	0.79	0.66	0.95	0.0145
Age, per 10 year increase	1.26	1.20	1.33	< 0.0001
Sex, female vs. male	0.86	0.77	0.96	0.0082
BMI, per 5 increase	1.00	1.00	1.00	0.4126
Household size, per 2 increase	1.08	1.02	1.14	0.0108
Race				
Black vs. White	2.26	1.83	2.79	< 0.0001
Hispanics vs. Whites	1.73	1.20	2.51	0.0005
Others vs. Whites	1.72	1.08	2.75	0.0134
Hospital region				
Midwest vs. Northeast	1.07	0.75	1.52	1
South vs. Northeast	1.29	0.92	1.82	0.2623
West vs. Northeast	1.13	0.77	1.67	1
Rural vs. urban location	1.02	0.83	1.25	0.88
Income status				
\$20,000–40,000 vs. less than \$40,000	1.16	0.96	1.40	0.1959
Less than \$20,000 vs. \$40,000	1.26	1.01	1.57	0.0319
Educational level				
Below grade 12 vs. above grade 12	1.79	1.42	2.26	< 0.0001
Grade 12 vs. above grade 12	1.59	1.21	2.09	0.0001
Household pets	0.96	0.85	1.07	0.4456
Current smoking	0.97	0.87	1.09	0.6505
Tap water	1.07	0.83	1.38	0.6188
Place of birth, outside the United States vs. within United States	1.62	1.20	2.18	0.0015
Alcohol use				
Modest use vs. nonuse	1.05	0.85	1.29	1
Excessive use vs. nonuse	0.96	0.69	1.33	1
Marital status				
Married vs. single	1.09	0.88	1.35	0.985
Separated vs. single	1.19	0.98	1.46	0.0951

Given our novel observations, the potential mechanisms by which cannabis can impact HPI need to be examined. Consequently, from published reports, we surmise that cannabis use may impact HPI through: (1) direct antibacterial action of cannabis on Hp; (2) suppression of gastric acidity; (3) anti-inflammatory and healing properties of cannabis in the gut; (4) modulation of a diversity of gastric microbiome; (5) modulation of the immune system; (6) and avoidance of cannabis consumption by individuals with HPI due to symptom exacerbation.<sup>14–18,20,22,23,33–35</sup>

First, cannabis may have direct antibacterial effects on Hp. Although studies on the direct action of cannabis on Hp are not available, cannabis has been reported to have antibacterial activities against *S. aureus*<sup>21</sup> and *Clostridoides difficile*.<sup>19</sup> Second, cannabis suppresses gastric acid production and increases gastric pH,<sup>15</sup> thereby improving the healing of duodenal ulcers.<sup>16</sup> These direct actions of cannabis might decrease duodenal Hp colonization and infection that may account for our observed decrease in the prevalence of HPI among recreational cannabis users.

Third, cannabis plant extracts have demonstrated anti-inflammatory and ulcer healing properties.<sup>14–18</sup> Many studies have shown that intestinal mucosal CB2 receptor agonists can decrease gastric acidity, gastritis, and gastric ulcerations.<sup>15,17</sup> The anti-inflammatory properties of cannabis suppress gastritis and gastric ulcer formation.<sup>16,18</sup> Specifically, murine models have shown that CB2 agonists can promote the healing of gastric and duodenal ulcers, protecting mice from adverse gastric effects of nonsteroidal anti-inflammatory agents and alcohol.<sup>17,18</sup> By promoting healing during/after infection, cannabis may decrease the severity and duration of HPI. As such, cannabis can reduce the intensity of HPI-induced inflammation characterized by increased inflammatory cytokines and Hp antibodies, which are revealed in our study. Fourth, infection by Hp can severely alter the gastric microbiome. Hp stomach colonization can severely decimate the population of three (Firmicutes, Actinobacteria, and Bacteroides) of the four most abundant gut bacteria flora, with concomitant amplification of the quantity of Proteobacteria from <20% to more than

90%.<sup>33</sup> The ensuing dysbiosis with HPI correlates strongly with adverse disease progression in the stomach, increased gastric metaplasia, and adenocarcinoma.<sup>33</sup> Although there are no studies of the impact of cannabis on the gastric microbiome, cannabis had been reported to maintain a healthy balance of the gut microbiome and prevent obesity when administered together with a fatty diet to mice.<sup>23</sup> Cannabis might exert a similar effect on the stomach, countering the dysbiosis from HPI<sup>33</sup> and limiting disease progression.

Alternative mechanisms may additionally explain our novel findings. A fifth possible explanation may be that cannabis use suppresses immune system functions<sup>34</sup> and its production of optimal levels of IgG against HPI. This is especially possible, because our results reveal that after full adjustments when compared with never users, individuals with recent 31-day cannabis use had a diminished risk of HPI when compared with individuals with a history of last cannabis use being more than 31 days ("C" in Table 2). It may be that such individuals with recent cannabis use have HPI but do not produce adequate IgG and, therefore, tested negative to the serologic test; however, those with past (> 31 days ago) cannabis use have recovered from cannabis suppression of IgG production against HPI and, therefore, were similar to individuals who never took cannabis. However, such patients will be expected to test positive for stool Hp antigen test and/or to show more symptoms. Unfortunately, the stool antigen tests were not available in the NHANES III dataset, and we are unable to assess this potential mechanism. Finally (sixth), it may be that cannabis use exacerbated symptoms of HPI, resulting in patients with HPI, avoiding cannabis use. By inhibiting gastric acid production, a major gastrointestinal antimicrobial defense mechanism, cannabis may predispose to some bacterial infections, including HPI. For example, heavy cannabis use has been associated with more voluminous diarrhea due to *Vibrio* and *Escherichia* spp. infections.<sup>35</sup> However, this possibility is less likely given that preclinical studies have reported the suppressive actions of cannabis on gastroduodenal acidity, inflammation, and ulcerations.<sup>15–18</sup>

Our findings on the risk of HPI with demographic factors are consistent with other studies in the literature,<sup>1–4,24,25</sup> including increasing age, male sex, household size, non-White races, insufficient education (at or below 12th grade), and place of birth outside the United States. However, unlike some of the previous studies, we did not find any association of alcohol

and tobacco use, tap water, marital status, and household pets with HPI.<sup>4</sup> Also, the average BMI was lower among subjects with cannabis use in our frequency table, which is similar to recent findings.<sup>36</sup> The consistency of our findings with most other studies,<sup>1–4,24,25</sup> the large sample size of our study subjects, and multiple adjustments modeling employed by our study offer strong reliability of our novel findings.

The NHANES III datasets are, however, limited by their cross-sectional study design<sup>37</sup> Therefore, direct causal and temporal relationships cannot be ascertained by just statistical analysis. In addition, errors in recalling the frequency or quantity of cannabis use; imperfect accuracies for the serologic marker of HPI, paucity of data on the specific type, or mode of consuming cannabis; and the possibility of residual confounding can all potentially affect the validity of our study. However, these errors are likely to be nondifferential across exposure and outcome groups and are more likely to diminish our measured effect. These shortcomings of the NHANES dataset are outweighed by the fact that our analysis incorporates multiple confounding factors in the statistical models. Also, the NHANES III (collected from 1988 to 1996) is quite old, and the HPI serologic tests performed during this period might be less accurate compared with more recent tests that have increased sensitivity and specificity. These drawbacks might potentially impact the validity of our results using the indicated dataset. Unfortunately, the NHANES III is the only cycle of NHANES to contain both cannabis use and HPI serologic tests. There are currently no recent NHANES datasets that capture cannabis use and HPI. Given our observations, it will be helpful if the NHANES and other datasets capture new information to strengthen similar future research on this important subject. Further, the NHANES III only samples noninstitutionalized members of the population and excludes homeless and incarcerated individuals, who may have a high risk of both HPI and cannabis use. Also, only about 40% (5235 of 13,022, Fig. 1) of eligible respondents had a serologic test for HPI, which may potentially result in sampling bias. However, we incorporated the recommended weighing methodologies in our statistical analysis to account for non-response. The NHANES III dataset does not have information on the strains/formulation of cannabis used or mode of consumption (oral vs. vaping vs. inhalation), which might impact interactions with Hp in the stomach. Finally, our



measurement of HPI in the community assesses for evidence of infection (past or present) and does not specify whether the individual has active HPI.

Our current study has many strengths. First, the use of a large, nationally representative database, with detailed racial and sociodemographic information, allowed us to study the relationship between cannabis and HPI at a population level. Second, cannabis consumption was captured in different ways, providing us separate perspectives and deeper understanding. Third, our analysis built on previous studies on the NHANES,<sup>24</sup> where a majority of HPI occurred in adulthood, coinciding most likely during periods of cannabis use, allowing for an opportunity to study the effect of cannabis on HPI. Finally, cannabis use history was collected using a confidentially completed questionnaire, providing reliable estimates.

In the past few years, there has been increased legalization of cannabis use for recreational purposes, especially in North America.<sup>38,39</sup> Canada has legalized cannabis use for recreational use for individuals  $\geq 18$  years.<sup>39</sup> Our current article analyzed data, which are several years old when cannabis was illegal in North America. As such, our observations from the data might not currently reflect the situation. This is because more individuals are now more regularly using a wide range of full-spectrum cannabis formulations. Cannabis is legal in Canada and an increasing number of states in the United States<sup>40</sup>; as such, most individuals do readily disclose their cannabis use status without fear of adverse legal implications. Therefore, it will be very beneficial for future research if population datasets that incorporate cannabis use habits additionally capture more extensive/comprehensive clinical and laboratory information on all disease conditions, including HPI. This is because cannabis contains more than 400 active chemicals that are shown to have numerous and diverse anti-pathogenic and physiological chemical regulatory properties that will most certainly affect numerous disease prevalence, progression, and clinical outcomes.<sup>41–43</sup>

In conclusion, our novel findings reveal that cannabis use was associated with a lower prevalence of HPI among noninstitutionalized residents of the United States. Further, individuals with recent use and those with larger lifetime cannabis use were less likely to test positive for HPI. Our interesting observations suggest the need for additional molecular studies to delineate the direct impact of cannabis use and HPI. Specifically, future studies evaluating how the active

ingredients in cannabis exert potential antibacterial effects on Hp and immunomodulatory activities in humans are highly needed.

### Authors' Contributions

A.C.A., P.L., and T.N.B. conceived and designed the study; acquired, analyzed, and interpreted the data; and wrote the article. T.N.B. supervised the project.

### Author Disclosure Statement

No competing financial interests exist.

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#### Abbreviations Used

aPRR = adjusted risk prevalence rate ratio  
 cPRR = crude risk prevalence rate ratio  
 BMI = body mass index  
 CI = confidence intervals  
 Hp = *Helicobacter pylori*  
 HPI = *Helicobacter pylori* infection  
 ISR = immune status ratio  
 NHANES III = Third National Health and Nutrition Examination Survey