Epidemiology, Clinical Characteristics, and Associations for Rome IV Functional Nausea and Vomiting Disorders in Adults

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BACKGROUND & AIMS: **Functional nausea and vomiting disorders (FNVDs) are classified as chronic nausea and vomiting syndrome (CNVS) or cyclic vomiting syndrome (CVS)—CVS includes cannabinoid hyperemesis syndrome. We investigated the population prevalence of FNVDs, their characteristics, and associated factors.**

METHODS: **In the year 2015, an Internet cross-sectional health survey was completed by 5931 adults in the general populations of 3 English-speaking countries; 2100 participants were in the United States, Canada, or the United Kingdom. Quota-based sampling was used to generate demographically balanced and population-representative samples. The survey collected data on demographics, health care visits, medications, somatic symptom severity, quality of life, and symptom-based diagnostic criteria for Rome IV FNVDs as well as for irritable bowel syndrome and functional dyspepsia. Subsequent comparisons were made between Rome IV FNVD subjects and individuals without FNVDs (controls).**

RESULTS: **Overall, 2.2% of the population (n = 131) fulfilled symptom-based diagnostic criteria for Rome IV FNVDs: the United States (3%) had a greater prevalence than Canada (1.9%) or the United Kingdom (1.8%) ($P = .02$). The prevalence of CNVS was similar among the countries, ranging from 0.8% to 1.2%. However, the prevalence of CVS was higher in the United States (2%) than in Canada (0.7%) or the United Kingdom (1%) ($P = .03$). The proportion of subjects with CVS taking cannabis did not differ significantly among countries ($P = .31$), although the 7 cases of cannabinoid hyperemesis syndrome were in the United States. A significantly higher proportion of subjects with CVS reported a compulsive need for hot water bathing to alleviate emetic symptoms than subjects with CNVS (44% vs 19%; $P = .03$); this behavior was independent of cannabis but augmented by its use. Subjects with FNVDs had significantly greater health impairment and health care utilization than controls. On multivariate analysis, independent factors associated with FNVDs were younger age, increasing somatic symptom severity, lower quality of life, presence of irritable bowel syndrome, and functional dyspepsia. However, on subgroup analysis, somatic symptom severity was associated with CVS but not CNVS, whereas poor quality of life was associated with CNVS but not CVS.**

CONCLUSIONS: **Based on a cross-sectional health survey of adults in the general populations of 3 English-speaking countries, approximately 2% of subjects meet symptom-based criteria for Rome IV FNVDs and have considerable health impairments. Hot water bathing to alleviate emetic symptoms is reported for all FNVDs, and is perpetuated by cannabis use.**

Keywords: IBS; Functional Gastrointestinal Disorders; Nausea and Vomiting; Cannabis.

The Rome IV committee defines functional gastrointestinal disorders as disturbances of the brain–gut axis in the absence of organic pathology to explain the symptoms.[1] Functional nausea and vomiting disorders (FNVDs) are subclassified as either chronic nausea and vomiting syndrome (CNVS) or cyclic vomiting syndrome (CVS) (Table 1).[2] Of late, there has been increasing recognition that in a subset of adults with

Abbreviations used in this paper: **CNVS, chronic nausea and vomiting syndrome; CVS, cyclic vomiting syndrome; FNVD, functional nausea and vomiting disorder; PHQ, Patient Health Questionnaire.**

CVS the symptoms are precipitated by chronic cannabis use, and that its sustained cessation will lead to symptom relief.[3] This variant of CVS has been termed *cannabinoid hyperemesis syndrome* and incorporated within Rome IV.[2,3] However, cannabinoid hyperemesis syndrome can be missed in clinical settings, partly because of physicians' lack of awareness or patients failing to disclose their cannabis history.[4] To improve suspicion and recognition of cannabinoid hyperemesis syndrome, various case series have reported such patients to show the peculiar, and as yet pathophysiologically unexplained, behavioral pattern of repetitive hot water bathing during the active phase of their illness,[3,4] with 1 case also reporting the need for continuous exercise for symptom relief.[5]

However, there are numerous uncertainties regarding FNVDs. First, their population prevalence is not known. Second, although well-recognized conditions such as irritable bowel syndrome and functional dyspepsia have documented associations with increasing psychological distress, somatization, poorer quality of life, overlapping functional gastrointestinal disorders, and greater health care utilization,[6,7] there is a general paucity of data regarding FNVDs. A few studies have evaluated some health-related parameters within FNVD subtypes,[8–11] but no study has concurrently overseen multiple health parameters among all FNVD subtypes while using a non-FNVD control group. Third, the association between cannabis use and repetitive hot water bathing behavior has not been established in FNVDs outside of CVS, such as in CNVS.

The recent publication of the Rome IV criteria for functional gastrointestinal disorders provides an opportunity to address these issues using the most contemporary definition.[1,2] We used data from a large cross-sectional, population-based survey across 3 English-speaking countries to help understand the epidemiology, clinical characteristics, and associations for Rome IV FNVDs (and its subtypes), with non-FNVD subjects serving as comparative controls.

What You Need to Know

Background

The prevalence of functional nausea and vomiting disorders (FNVDs) is not known. This study evaluated the epidemiology, clinical characteristics, and associations for Rome IV FNVDs within the general adult population of the United States, Canada, and the United Kingdom.

Findings

The population prevalence of Rome IV FNVDs is approximately 2%, and is split relatively evenly between chronic nausea and vomiting syndrome and cyclic vomiting syndrome. FNVD subjects incur considerable health impairment and health care utilization.

Implication for patient care

Awareness of the prevalence and implications of FNVDs will help toward clinical service and research provision.

Methods

A comprehensive questionnaire collected data on the following: (1) demographics (age, sex, race, relationship status, country of residence), (2) medications (antiemetics, acid-suppressive drugs, analgesics, psychotropics), (3) health care visits, (4) Patient Health Questionnaire (PHQ)-12 somatic symptom severity,[12] (5) Short Form-8 quality of life,[13] and (6) the presence of Rome IV functional gastrointestinal disorders.[14] The latter was determined using the validated Rome IV diagnostic questionnaire, which has been proposed as a research tool for clinical and epidemiologic purposes.[14] These have been described in detail in a recent publication.[15]

In this study we focused on identifying those subjects fulfilling symptom-based criteria for FNVDs, and its

Table 1. Rome IV Criteria for Functional Nausea and Vomiting Disorders[2]

CNVS	CVS[a]
Must include all of the following: 1) Bothersome nausea occurring at least 1 day per week and/or ≥1 vomiting episodes per week 2) Self-induced vomiting, eating disorders, regurgitation, or rumination are excluded 3) No evidence of organic, systemic, or metabolic diseases that is likely to explain the symptoms on routine investigations (including at upper endoscopy) 4) The symptoms have to be present for the past 3 months with onset at least 6 months prior	Must include all of the following: 1) Stereotypical episodes of acute-onset vomiting lasting < 1 wk 2) At least 3 discrete episodes in the prior year and 2 episodes in the past 6 months, occurring at least 1 week apart 3) Absence of vomiting between episodes, although milder symptoms can be present 4) The symptoms have to be present for the past 3 months with onset at least 6 months prior

CNVS, chronic nausea and vomiting syndrome; CVS, cyclic vomiting syndrome.
[a]Cannibinoid hyperemesis syndrome is a variant of CVS, in which the symptoms are attributed to chronic cannabis use and resolve after stopping cannabis.

CNVS and CVS subtypes (Table 1).[2] Moreover, the Rome IV diagnostic questionnaire directly proceeds to enquire for the following only in those who fulfill criteria for FNVDs: (1) cannabis use (never/occasional/regular); (2) where appropriate, symptom relief after stopping cannabis for several weeks (yes/no/not tried); and (3) the need for hot baths or showers to relieve vomiting (yes/no).[14] From this, a diagnosis of cannabinoid hyperemesis syndrome would be made in a subset of CVS subjects who take cannabis and experience clinical remission after its sustained abstinence. All individuals in the population who did not meet the criteria for Rome IV FNVDs were used as control subjects in the analyses.

Finally, in those with and without FNVDs, we also determined the presence of symptom-based irritable bowel syndrome and functional dyspepsia using the Rome IV criteria.[2,16]

Questionnaire Distribution and Completion

Qualtrics, Inc (Provo, UT), a global market survey company, was commissioned in 2015 to provide a nationally representative general population sample of adults from 3 English-speaking countries: the United States, Canada, and the United Kingdom. Quota-based sampling was used to generate demographically balanced and population-representative samples with regard to age, sex, and education level. This has been detailed elsewhere.[15]

Statistics

Statistical analysis was performed using SPSS version 21.0 software (SPSS, Inc, Chicago, IL), with significance set at a P value of .05. There were no missing data because the online questionnaire required participants to complete each applicable question before being allowed to move onto the next step. The prevalence and characteristics of the overall population, those with and without FNVDs, and the FNVD subtypes, were determined. Categoric variables were summarized by descriptive statistics, including total numbers and percentages, with comparisons between groups performed using the chi-square test. Continuous variables were summarized by means and SD, with differences between 2 independent groups compared using the unpaired Student t test.

We also performed binary logistic regression to identify independent associations for FNVDs (and its CNVS and CVS subtype) against controls. The variables considered for selection were those deemed to be potentially associated with FNVDs, and comprised demographic data, somatic symptoms, quality of life, and the presence of irritable bowel syndrome and functional dyspepsia. Before their entry we assessed for multicollinearity using linear regression and checked for a variance inflation factor greater than 3. This showed a strong multicollinearity between the number of somatic symptoms and the PHQ-12 somatic symptom severity score (variance inflation factor, >10), and so we excluded the former from entering the binary logistic regression model. These data were presented using adjusted odds ratio and 95% CIs.

Ethics

Before data collection started, the study was reviewed by the Institutional Review Board at the University of North Carolina and deemed Institutional Review Board–exempt because all study participants were unidentifiable to the investigators.

Results

General Population Characteristics

The survey was completed by 6300 individuals, of whom there were 2100 from each of the 3 countries. After excluding 369 (5.9%) inconsistent responders, data were analyzed from 5931 individuals; 1949 from the United States, 1988 from Canada, and 1994 from the United Kingdom. The mean age was 47.4 years, 49.2% were female, and 72% were white. Further details on nationally representative demographic profiles within the countries are provided elsewhere.[15]

The Prevalence of Rome IV Functional Nausea and Vomiting Disorders and Its Subtypes

From the 5931 subjects available for evaluation, 97.8% (n = 5800) did not meet symptom-based criteria for Rome IV FNVDs and were classed as non-FNVD controls (Figure 1). The remaining 2.2% (n = 131) of subjects did fulfill symptom-based criteria for Rome IV FNVDs: 1% (n = 58) had CNVS, and 1.2% (n = 73) had CVS. Of the 73 subjects with CVS, 30 (41%) declared occasional or regular cannabis use, of whom 7 stated relief in symptoms on stopping cannabis, with 14 having no relief, and 9 not having tried to stop cannabis. Therefore, the overall prevalence of cannabinoid hyperemesis syndrome across the 3 countries was 0.1% (n = 7 of 5931), or, alternatively, the proportion of cannabinoid hyperemesis syndrome accounted for within CVS was 9.6% (n = 7 of 73), or 23.3% (n = 7 of 30) within cannabis-consuming CVS.

With regard to the prevalence of FNVDs according to country, the United States (3%) had a significantly greater prevalence than Canada (1.9%) and the United Kingdom (1.8%) (P = .02) (Figure 1). There was no difference in the prevalence of CNVS between the United States (1%), Canada (1.2%), and the United Kingdom (0.8%) (P = .6). However, the United States had a greater prevalence of CVS (2%; n = 39) compared with Canada (0.7%; n = 15) and the United Kingdom (1%; n = 19) (P = .03). The proportion of cannabis use in the CVS cohort was similar between the United States (46.2%; n = 18 of 39), Canada (46.7%; n = 7 of 15), and the United Kingdom (26.3%; n = 5 of 19) (P = .31). However, all 7 subjects with

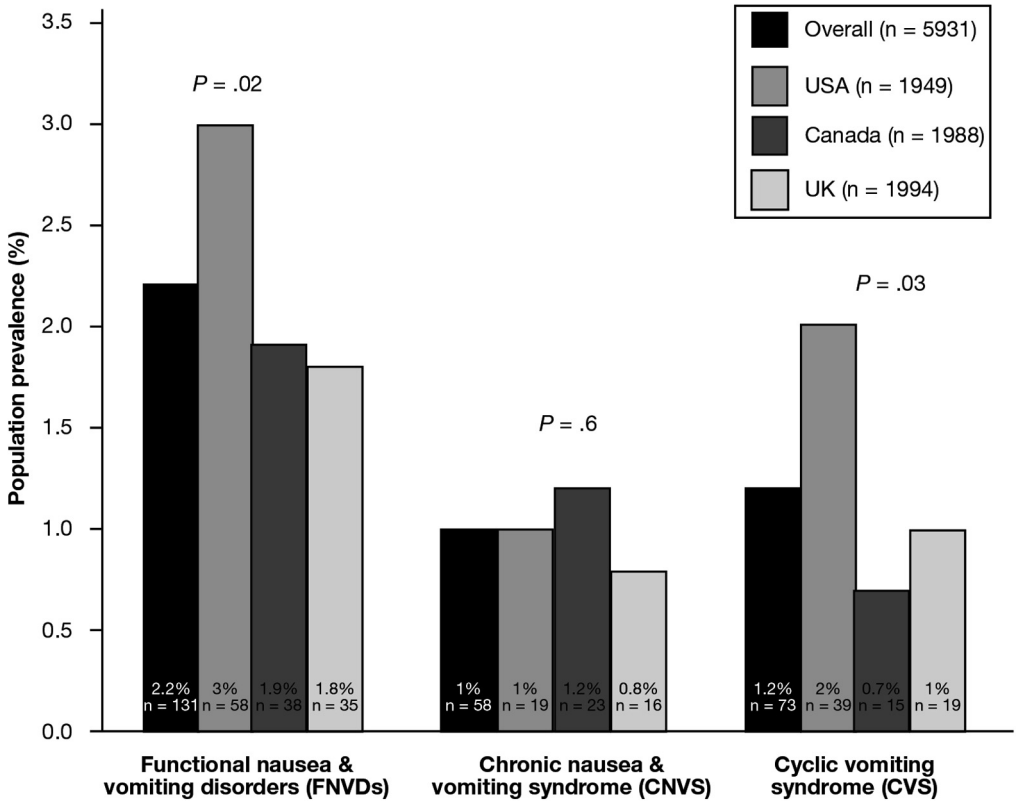

Figure 1. The prevalence of symptom-based functional nausea and vomiting subtypes in adults. *P* values are between the countries. Within the CVS cohort, there were 7 cases of cannabinoid hyperemesis syndrome, all of whom originated from the United States.

cannabinoid hyperemesis syndrome came from the United States, with none from Canada or the United Kingdom ($P = .001$). Therefore, the prevalence of cannabinoid hyperemesis syndrome within the United States was 0.4% (n = 7 of 1949), or, alternatively, accounted for 18% (n = 7 of 39) of its CVS cohort, or, alternatively, 39% (n = 7 of 18) of its cannabis-consuming CVS cohort.

Comparison Between Rome IV Functional Nausea and Vomiting Disorders Against Non–Functional Nausea and Vomiting Disorders Controls

Those with FNVDs were significantly younger and female predominant, but had a similar prevalence of white race and single relationship status, compared with controls (Table 2). Furthermore, individuals with FNVDs had significantly higher PHQ-12 somatic symptom severity scores and number of somatic symptoms, poorer mental and physical quality of life, and a greater prevalence of irritable bowel syndrome and functional dyspepsia compared with controls. Finally, subjects with FNVDs had significantly increased health care utilization.

Comparison Between Chronic Nausea and Vomiting Syndrome and Cyclic Vomiting Syndrome

There was no difference in age, sex, white race, relationship status, quality of life, presence of overlapping irritable bowel syndrome and functional dyspepsia, or health care utilization between the CNVS and CVS subgroups. However, subjects with CVS showed greater somatic symptom severity and an increased number of somatic symptoms than CNVS (Table 3).

There were no differences between the CNVS and CVS groups with regard to the use of cannabis ($P = .23$) or symptom relief after its cessation ($P = .9$). Furthermore, both groups reported that hot baths were helpful in relieving the symptoms of vomiting, although this was significantly greater for CVS than CNVS (44% vs 19%; $P = .03$). We also assessed whether there was a relationship between cannabis use and the need for hot baths to relieve vomiting symptoms; for both groups, this showed that hot water bathing for symptom relief was independent of cannabis, but augmented by its use (Figure 2).

Associations With Rome IV Functional Nausea and Vomiting Disorders and Its Subtypes

After binary logistic regression, independent factors associated with FNVDs were younger age, increasing somatic symptom severity, poorer quality of life, presence of irritable bowel syndrome, and functional dyspepsia (Table 4). However, on subgroup analysis, somatic symptom severity was associated with CVS but not CNVS, whereas poor quality of life was associated with CNVS and not CVS. We did not analyze factors associated independently with cannabinoid hyperemesis syndrome because of the small number of subjects in this group.

Table 2. Characteristics of Adult Population Subjects With and Without Symptom-Based Diagnostic Criteria for Rome IV FNVDs

	Non-FNVD controls (n = 5800; 97.8%)	Rome IV FNVDs (n = 131; 2.2%)	*P* value
Demographics			
Mean age, *y* (SD)	47.7 (17.1)	37.2 (14.4)	<.0001
Female	2829 (48.8%)	89 (67.9%)	<.0001
White race	4177 (72%)	94 (71.8%)	.95
Single relationship status	1704 (29.4%)	48 (36.6%)	.07
Symptom scores			
PHQ-12 somatic symptom severity score (SD)	4.6 (3.7)	11 (4.4)	<.0001
Number of somatic symptoms (SD)	3.7 (2.5)	7.5 (2.5)	<.0001
Short Form-8 quality of life (SD)			
Physical component score	49.4 (9.6)	38.7 (11.3)	<.0001
Mental component score	49.3 (10.7)	35.5 (12.3)	<.0001
Overlapping FGIDs			
Irritable bowel syndrome	284 (4.9%)	57 (43.5%)	<.0001
Functional dyspepsia	470 (8.1%)	81 (61.8%)	<.0001
Health care utilization			
Seen doctor for GI health	1300 (22.4%)	71 (54.2%)	<.0001
More than once-yearly health care visits	3294 (56.8%)	113 (86.3%)	<.0001
Medication taken at least once/wk, n			
Antiemetic	152 (2.6%)	53 (40.5%)	<.0001
Acid-suppressing drug	1094 (18.9%)	61 (46.6%)	<.0001
Analgesic	1664 (28.7%)	73 (55.7%)	<.0001
Psychotropics	936 (16.1%)	57 (43.5%)	<.0001
Any of the above medications	2523 (43.5%)	100 (76.3%)	<.0001

FGID, functional gastrointestinal disorder; FNVD, functional nausea and vomiting disorder; GI, gastrointestinal.

Discussion

Having used the Rome IV criteria, this study evaluated the prevalence and characteristics of symptom-based FNVDs within the general adult population of the United States, Canada, and the United Kingdom.

First, we showed that 2.2% of the adult population fulfilled symptom-based criteria for Rome IV FNVDs. The highest prevalence of FNVDs was in those from the United States (3%), compared with Canada (1.9%) and the United Kingdom (1.8%). This was accounted for by a greater representation of CVS, but not CNVS, within the United States compared with Canada and the United Kingdom. Within the CVS subset there was a greater prevalence of cannabinoid hyperemesis syndrome in the United States, although the proportional use of cannabis was similar between the countries. The reasons for differences between the countries were not elicited in this study but future studies should establish the role of pathophysiological and environmental factors, including variations in the potency of cannabis.[17] It also is worth noting that since March 2017, 8 US States have legalized cannabis for recreational use. This may lead to an increase in FNVDs, such as CVS and its cannabinoid hyperemesis syndrome variant, akin to what already has been seen after the liberalization of medical marijuana in some regions.[18] Hence, awareness of FNVDs is paramount, particularly because they frequently are underrecognized despite accounting for more than 10% of adult outpatient gastroenterology cases.[9] Moreover, there are no randomized controlled trials evaluating therapeutic options for FNVDs in adults.[19] Our findings hopefully will stimulate increased awareness and research efforts for these debilitating conditions.

Second, as another novel finding, we showed that subjects with Rome IV FNVDs have greater health impairment and health care utilization than non-FNVD controls. On multivariate analysis, independent factors associated with FNVDs were younger age, increasing somatic symptom severity, poorer quality of life, and the presence of irritable bowel syndrome and functional dyspepsia. This is consistent with disorders of brain–gut interaction and indeed previous studies have shown abnormalities in psychological status, visceral hypersensitivity, autonomic dysfunction, and gastric emptying in FNVDs.[20–23] The physiologic features of gastric emptying vary in FNVDs, and irrespective of CNVS or CNVS, are largely either normal (~27%–45%) or accelerated (~36%–59%), and delayed in approximately 4% to 17%.[10,24] However, on subgroup analysis, we noted that somatic symptom severity was associated independently with CVS but not CNVS, whereas poor quality of life was associated with CNVS but not CVS. Recent studies in CVS have shown high levels of psychological distress in subjects with CVS,[9,25] with somatization being the most severe symptom domain.[25] Moreover, psychological stressors commonly predispose to attacks of CVS. Other documented associations for CVS include a history

Table 3. Characteristics of Patients Fulfilling Rome IV Diagnostic Criteria for CNVS and CVS

	CNVS (n = 58)	CVS (n = 73)	*P* value
Demographics			
Mean age, *y* (SD)	37.1 (15.1)	37.3 (13.9)	.9
Female sex	41 (70.7%)	48 (65.8%)	.6
White race	39 (67.2%)	55 (75.3%)	.3
Single relationship status	24 (41.4%)	24 (32.9%)	.3
Behavior			
Marijuana use			.2
Never	41 (70.7%)	43 (58.9%)	
Occasional	7 (12.1%)	17 (23.3%)	
Regular	10 (17.2%)	13 (17.8%)	
Relief of vomiting after stopping marijuana			.9
No	9/17 (52.9%)	14/30 (46.7%)	
Yes	3/17 (17.6%)	7/30 (23.3%)	
Not tried	5/17 (29.4%)	9/30 (30%)	
Hot baths to relieve vomiting	11 (19%)	32 (44%)	.03
Symptom scores			
PHQ-12 somatic symptom severity score (SD)	9.9 (4)	11.8 (4.5)	.02
Number of somatic symptoms (SD)	6.9 (2.3)	7.9 (2.5)	.02
Short Form-8 quality of life, (SD)			
Physical component score	38.1 (11.2)	39.3 (11.5)	.5
Mental component score	34.5 (12.9)	36.3 (11.8)	.4
Overlapping FGIDs			
Irritable bowel syndrome	24 (41.4%)	33 (45.2%)	.7
Functional dyspepsia	32 (55.2%)	49 (67.1%)	.2
Health care utilization			
Seen doctor for GI health	29 (50%)	42 (57.5%)	.4
More than once-yearly health care visits	50 (86.2%)	63 (86.3%)	1.0
Medication taken at least once/wk, n			
Antiemetic	27 (46.6%)	26 (35.6%)	.2
Acid-suppressing drug	26 (44.8%)	35 (47.9%)	.7
Analgesic	31 (53.4%)	42 (57.5%)	.6
Psychotropics	23 (39.7%)	34 (46.6%)	.4
Any of the above medications	47 (81%)	53 (72.6%)	.3

CNVS, chronic nausea and vomiting syndrome; CVS, cyclic vomiting syndrome; FGID, functional gastrointestinal disorder; GI, gastrointestinal; PHQ, patient health questionnaire.

of migraines, particularly in pediatric cases, although between 24% and 70% of adults will report a personal or family history of migraines.[26] Mitochondrial DNA mutations also have been reported in the pediatric literature, although no such association has been found in adult-onset CVS.[27] Finally, recent insights have shown that polymorphisms in the cannabinoid receptor type 1 and μ-opioid receptor genes are associated with CVS.[28]

The description of cannabinoid hyperemesis syndrome, a variant of CVS, is intriguing given that cannabis traditionally has been used as an anti-emetic and appetite stimulant. The major psychoactive component in cannabis is 9-tetrahydrocannabinol, which after binding to cannabinoid type-1 receptors in the brain and gut activates the endocannabinoid system, an integral component in regulating nausea, vomiting, and gastrointestinal motility. Hence, the paradox of cannabinoid hyperemesis syndrome is poorly understood, with various mechanisms having been proposed, relating to potency, accumulation, and interaction of 9-tetrahydrocannabinol or alternate metabolites with cannabinoid type-1 receptors.[29] One suggested manifestation is that this evokes disequilibrium in the hypothalamic thermoregulatory system or dilates the gut splanchnic vasculature, thereby inducing vomiting, which may be reversed through hot water bathing or excessive exercise.[3–5] However, our study suggests that this proposed pathophysiological mechanism and behavioral activity is not isolated to cannabinoid hyperemesis syndrome, but can be seen across all FNVDs and is aggravated by cannabis use. In essence, hot water bathing activity in CVS should not be interpreted as a pathognomonic sign of cannabinoid hyperemesis syndrome despite the emerging number of case reports/series highlighting this interesting association.[3,4] In fact, an Internet survey of CVS subjects also supports its lack of specificity, having noted that those who do not take marijuana also have reported hot water bathing to relieve their symptoms.[11]

The strength of our study was that it sampled the prevalence of FNVDs, using the recently published Rome IV criteria and the same methodologic process, across a large sample of adults from 3 English-speaking countries. Moreover, we have provided an overarching perspective on multiple characteristics seen in Rome IV FNVDs, and their subtypes, while using a non-FNVD

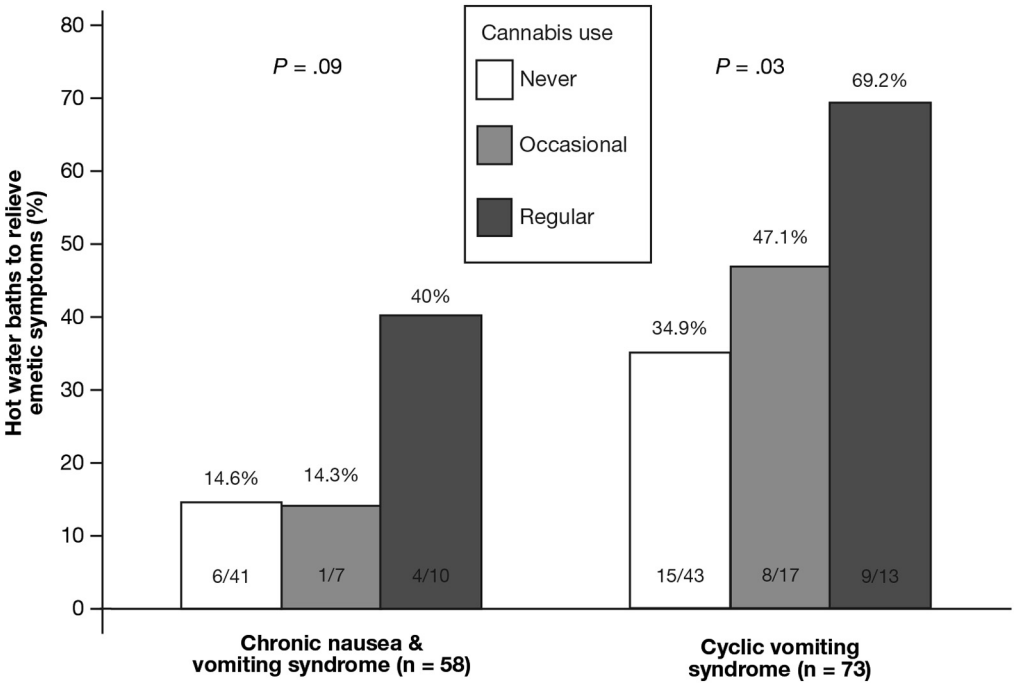

Figure 2. The association between functional vomiting subtypes, cannabis use, and the need for hot water baths to alleviate emetic symptoms. *P* values denote chi-square test results for trend.

control group. Our findings are supported by the literature, although these studies have used previous Rome definitions and generally have not been as comprehensive.[9–11] For example, a secondary-care outpatient gastroenterology clinic compared CVS with its other gastrointestinal referrals,[9] a retrospective tertiary-care study compared functional vomiting against CVS,[10] and an Internet study involving patients from a tertiary-care CVS clinic (and those who were members of its affiliated website) compared CVS against cannabinoid hyperemesis syndrome.[11] Moreover, 1 of these studies did not routinely ask about marijuana use,[9] and the other 2 studies showed wide variations in marijuana use ranging from 30% in the clinic setting, up to 80% in the CVS association website.[10,11] This may be explained by a reluctance to disclose marijuana use in the clinic setting because of legal reasons as compared with anonymous Internet surveys in which the quality of data is enhanced when assessing sensitive health behaviors such as illicit drug use.[30,31] However, the aforementioned Internet study may have been open to selection bias by tempting only those with ongoing symptoms to become members of the CVS association and complete the survey.[11] In contrast, although our study also was Internet-based, it was disseminated to the general adult population and described as a general

Table 4. Multivariate Analysis Evaluating Factors Independently Associated With Rome IV FNVDs and Subtypes in Comparison With Non-FNVD Controls

	FNVDs		CNVS		CVS	
	AOR (95% CI)	*P* value	AOR (95% CI)	*P* value	AOR (95% CI)	*P* value
Decreasing age	1.03 (1.02–1.05)	<.0001	1.04 (1.02–1.06)	.001	1.03 (1.01–1.05)	.01
Female sex	1.22 (0.79–1.88)	.37	1.55 (0.84–2.88)	.16	1.03 (0.58–1.81)	.93
White race	1.22 (0.78–1.92)	.38	0.91 (0.5–1.66)	.76	1.67 (0.89–3.1)	.11
Single	1.17 (0.75–1.83)	.49	1.23 (0.66–2.29)	.52	1.1 (0.61–2)	.76
Location						
United States	1	-	1	-	1	-
Canada	0.71 (0.44–1.13)	.15	1.32 (0.68–2.56)	.41	0.45 (0.23–0.86)	.02
United Kingdom	0.67 (0.41–1.09)	.10	0.83 (0.40–1.7)	.61	0.62 (0.34–1.15)	.13
Irritable bowel syndrome	2.09 (1.30–3.37)	.002	2.14 (1.09–4.19)	.03	2.07 (1.12–3.81)	.02
Functional dyspepsia	4.4 (2.82–6.76)	<.0001	3.4 (1.8–6.5)	<.0001	5.33 (2.96–9.6)	<.0001
Worsening Short Form 8-PCS	1.04 (1.02–1.06)	<.0001	1.07 (1.04–1.10)	<.0001	1.02 (0.99–1.05)	.13
Worsening Short Form 8-MCS	1.03 (1.01–1.05)	<.0001	1.04 (1.02–1.07)	<.0001	1.02 (0.99–1.04)	.10
PHQ-12 somatic symptom severity	1.14 (1.08–1.2)	<.0001	1.03 (0.96–1.11)	.44	1.2 (1.13–1.28)	<.0001

AOR, adjusted odds ratio; CNVS, chronic nausea and vomiting syndrome; CVS, cyclic vomiting syndrome; FNVD, functional nausea and vomiting disorder; MCS, mental component score; PCS, physical component score; PHQ, patient health questionnaire.

health survey, and not gastrointestinal-related. Finally, other pros and cons of conducting population-based surveys have been discussed extensively elsewhere for our data set.[15]

The main limitation of our study was that the diagnosis of FNVDs was based on fulfilling symptom-based criteria and not subsequently confirmed by investigations to exclude the possibility of organic pathology that may otherwise explain the symptoms. However, a recent study from a secondary-care gastroenterology clinic has shown that almost 90% of adults presenting with symptoms consistent with CVS do not have organic pathology after appropriate investigations, which thereby would support our assumption.[9] Arguably, the likelihood of organic pathology may be even lower in the general population setting, although no such studies have been performed. Furthermore, our data set was limited to 3 English-speaking countries and did not cover the epidemiology of FNVDs globally, although the Rome IV diagnostic questionnaire now will be disseminated worldwide after appropriate translation and validation. Another issue was regarding the diagnosis of cannabinoid hyperemesis syndrome, which can be challenging and open to debate. In our study, only a subset of CVS subjects who took marijuana subsequently were diagnosed with cannabinoid hyperemesis syndrome based on self-reporting clinical improvement after occasions when they stopped marijuana for several weeks. Those reporting no improvement, or who had not previously tried to stop cannabis, were not given a diagnosis of cannabinoid hyperemesis syndrome. However, in clinical practice a physician posed with this dilemma still may believe the diagnosis to be cannabinoid hyperemesis syndrome. Hence, it could be argued that the Rome IV diagnostic questionnaire may be underestimating the prevalence of cannabinoid hyperemesis syndrome. Moreover, it also was unclear how we should consider those patients with CNVS who disclose marijuana use and report that symptoms improve after its cessation; interestingly, this was seen to a similar extent as in CVS. In addition, because of the questionnaire design, this study did not determine the use of cannabis in the healthy population but only in those with FNVDs. Moreover, the reason for taking cannabis in FNVDs was not delineated, so its cause or effect association is debatable, with a previous study having shown that in CVS approximately 55% take cannabis for health reasons (ie, as an antiemetic), and the rest for recreational reasons.[11]

In conclusion, approximately 2% of the adult population in the United States, Canada, and the United Kingdom fulfill symptom-based criteria for Rome IV FNVDs. They incur considerable health impairment compared with non-FNVD controls. The need for compulsive hot water bathing is not isolated to cannabinoid hyperemesis syndrome, but also has been reported in subjects with CNVS and pure CVS, although the use of cannabis augments this behavioral tendency.

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Conflicts of interest
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