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Identification of risk factors and distinguishing psychogenic nonepileptic seizures from epilepsy: A retrospective case-control study

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ABSTRACT

Introduction: Patients with psychogenic non-epileptic seizures (PNES) experience significant morbidity and early mortality, secondary to delayed diagnosis. Better characterizing risk factors and exploring how PNES differentially affects sex and racial strata may facilitate earlier diagnosis.

Methods: From a Hawai'i neuroscience institution, 101 PNES patients were investigated in relation to sociodemographic and medical comorbidities. Cases were compared to 202 sex-, age-, and race-matched controls—representing patients with neurological disorders (general controls)—, as well as 404 unmatched epilepsy controls.

Results: Relative to general controls, PNES patients had increased odds ($p < 0.05$) of being: female, younger age, Native Hawaiian or other Pacific Islander (NHPI), suburban origin, from the lowest income quartile, Medicaid beneficiaries, homeless, current/former smoker, illicit drug users (marijuana, opioids/narcotics, polysubstance abuse), have anxiety, depression, post-traumatic stress disorder, bipolar disorder, traumatic history, World Health Organization obesity class 3, traumatic brain injury, epilepsy, and somatoform disorder. In relation to epilepsy controls, PNES patients exhibited increased odds of being: employed, having attention-deficit/hyperactivity disorder, asthma, migraines, and chronic pain. Relative to females, male PNES patients exhibited increased odds of military insurance, diabetes mellitus type 2, and hypertension. Relative to Whites, the NHPI and Asian PNES patients presented increased odds of asthma, migraines, chronic pain, gastroesophageal reflux disease, and thyroid disease. Per multivariable logistic regression, anxiety was the only consistent predictor of PNES across all sex and race strata.

Conclusion: Predictors of PNES's vary amongst the strata of race and sex. Lower socioeconomic status, along with several psychiatric and medical comorbidities, could increase a clinician's suspicion for earlier medical workup and diagnosis of PNES.

1. Introduction

Psychogenic nonepileptic seizures (PNES), also known as functional seizures, are a type of functional neurological disorder characterized by paroxysmal behavioral, experiential, or motor events without epileptiform cortical activity [1–3]. Given the clinical similarity with epilepsy, misdiagnosis is common: up to 30% of epilepsy surgery referrals are diagnosed with PNES [4–6]. Secondary to an average 8-year delay in diagnosis, PNES patients are usually treated with high-dose antiepileptic polytherapy regimens and undergo costly medical

Abbreviations: AIC, Akaike Information Criterion; AUDIT-C, Alcohol Use Disorders Identification Test-Consumption; BMI, Body Mass Index; EEG, Electroencephalogram; GERD, Gastroesophageal reflux disease; HPN, Hawaii Pacific Neuroscience; ICD-10, International Classification of Diseases 10th Edition; IQR, Interquartile Range; NAAN, Native American or Alaskan Native; NHPI, Native Hawaiian or Other Pacific Islander; PHQ-2, Patient Health Questionier-2; PNES, Psychogenic Non-Epileptic Seizures.

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Table 1
Crude odds of sociodemographic and medical comorbidities.

	PNES vs. General Population		PNES vs. Epilepsy	
	Median (25% Quartile, 75% Quartile)		Median (25% Quartile, 75% Quartile)	
Patient Age				
PNES	43.00 (30.00, 54.00)	$p < 0.0001$	43.00 (30.00, 54.00)	$p = 0.0004$
Controls	60.00 (42.75, 74.00)		51.00 (33.00, 66.00)	
Median Household Income				
PNES	77,188 (59,284, 100,311)	$p = 0.005$	77,188 (59,284, 100,311)	$p = 0.02$
Controls	91,646 (72,349, 100,311)		82,742 (70,110, 100,311)	
Overall Poverty Level in Municipality				
PNES	0.10 (0.060, 0.12)	$p = 0.17$	0.10 (0.06, 0.12)	$p = 0.10$
Controls	0.060 (0.050, 0.12)		0.07 (0.05, 0.12)	
Poverty Level for Ages 18–64				
PNES	0.098 (0.054, 0.12)	$p = 0.19$	0.10 (0.05, 0.12)	$p = 0.08$
Controls	0.060 (0.050, 0.12)		0.07 (0.05, 0.12)	
Poverty Level for Ages 65 and Older				
PNES	0.060 (0.040, 0.090)	$p = 0.39$	0.06 (0.04, 0.09)	$p = 0.93$
Controls	0.050 (0.040, 0.080)		0.05 (0.04, 0.08)	
Geographic Origin Population Size				
PNES	43,488 (14,856, 51,601)	$p = 0.06$	43,488 (14,856, 51,601)	$p = 0.031$
Controls	51,511 (25,261, 51,601)		51,511 (25,446, 51,601)	
	Odds Ratio		**Odds Ratio**	
Insurance Type				
Medicare	1.28 (0.59, 2.66)	$p = 0.65$		
Medicaid	1.75 (1.04, 2.94)	$p = 0.04$		
Private	0.52 (0.32, 0.84)	$p = 0.01$		
Military	1.44 (0.50, 3.91)	$p = 0.66$		
Income Quartiles				
Quartile 1	1.68 (1.01, 2.80)	$p = 0.046$	1.56 (0.99, 2.50)	$p = 0.06$
Quartile 2	0.92 (0.28, 2.69)	$p = 1.00$	0.26 (0.086, 0.64)	$p = 0.0027$
Quartile 3	0.52 (0.30, 0.89)	$p = 0.02$	0.098 (0.054, 0.18)	$p < 0.0001$
Quartile 4	2.57 (0.54, 13.25)	$p = 0.17$	1.00 (0.26, 3.32)	$p = 1.00$
Geographic Origin				
Urban	0.56 (0.33, 0.93)	$p = 0.03$	0.56 (0.35, 0.89)	$p = 0.01$
Suburban	1.71 (1.03, 2.86)	$p = 0.04$	1.75 (1.10, 2.79)	$p = 0.02$
Rural	1.51 (0.22, 9.13)	$p = 0.69$	1.21 (0.21, 4.80)	$p = 0.73$
Race				
White	0.99 (0.61, 1.58)	$p = 1.00$	0.92 (0.57, 1.47)	$p = 0.80$
Black	0.89 (0.092, 4.38)	$p = 1.00$	0.80 (0.084, 3.82)	$p = 1.00$
Asian	0.41 (0.21, 0.76)	$p = 0.004$	0.61 (0.31, 1.13)	$p = 0.13$
Native Hawaiian or Other Pacific Islander	2.13 (1.30, 3.48)	$p = 0.002$	1.44 (0.89, 2.33)	$p = 0.14$
Hispanic	0.60 (0.15, 1.79)	$p = 0.48$	1.24 (0.29, 4.13)	$p = 0.76$
Native American or Alaskan Native	4.08 (0.54, 30.91)	$p = 0.10$	1.51 (0.25, 6.45)	$p = 0.47$
Employment Status				
Employed	0.82 (0.49, 1.36)	$p = 0.49$	1.67 (1.03, 2.70)	$p = 0.034$
Unemployed	1.50 (0.90, 2.50)	$p = 0.13$	1.07 (0.67, 1.70)	$p = 0.84$
Retired	0.83 (0.22, 2.61)	$p = 0.93$	0.19 (0.06, 0.47)	$p < 0.0001$
Student	0.49 (0.16, 1.30)	$p = 0.19$	2.79 (0.80, 9.04)	$p = 0.10$
Marital Status				
Divorced	0.87 (0.38, 1.89)	$p = 0.86$	1.19 (0.55, 2.43)	$p = 0.74$
Married	0.74 (0.44, 1.23)	$p = 0.27$	1.26 (0.78, 2.01)	$p = 0.37$
Single	1.44 (0.86, 2.42)	$p = 0.17$	0.91 (0.58, 1.45)	$p = 0.77$
Widowed	1.00 (0.09, 7.11)	$p = 1.00$	0.27 (0.03, 1.11)	$p = 0.06$
Packs per Day				
Never Smoker	0.57 (0.33, 0.96)	$p = 0.03$		
Less than Half-Pack	2.07 (0.60, 7.13)	$p = 0.29$		
Half-Pack	2.10 (0.73, 6.00)	$p = 0.18$		
Single Pack	2.14 (0.87, 5.25)	$p = 0.10$		
Former Smoker	0.92 (0.42, 1.94)	$p = 0.95$		
Illicit Drug Type Utilized				
Marijuana	2.51 (1.15, 5.56)	$p = 0.02$		
Methamphetamine	2.02 (0.14, 28.18)	$p = 0.60$		
Opioids/Narcotics	12.32 (1.48, 568.58)	$p = 0.01$		
Polysubstance Abuse	6.27 (1.10, 64.76)	$p = 0.02$		
No Drug Use	0.27 (0.14, 0.54)	$p < 0.0001$		
	Median (25% Quartile, 75% Quartile)		**Median (25% Quartile, 75% Quartile)**	
Body Mass Index (kg/m^2)				
PNES	28.66 (23.20, 34.33)	$p = 0.39$	28.66 (23.20, 34.33)	$p = 0.051$
Matched Controls	27.26 (23.60, 31.73)		26.39 (23.14, 31.29)	
	Odds Ratio		**Odds Ratio**	
Weight Class				
Underweight	0.80 (0.07, 4.97)	$p = 1.00$	0.89 (0.092, 4.38)	$p = 1.00$
Normal	1.20 (0.70, 2.05)	$p = 0.57$	0.95 (0.58, 1.53)	$p = 0.91$
Overweight	0.72 (0.38, 1.31)	$p = 0.32$	0.61 (0.34, 1.06)	$p = 0.09$
Obesity Class 1	0.77 (0.41, 1.43)	$p = 0.47$	1.05 (0.57, 1.86)	$p = 0.98$
Obesity Class 2	0.72 (0.25, 1.86)	$p = 0.61$	0.84 (0.30, 2.00)	$p = 0.84$
Obesity Class 3	2.73 (1.17, 6.46)	$p = 0.02$	3.80 (1.75, 8.17)	$p = 0.0002$

workup for prolonged periods of time [6–8]. Moreover, when considering PNES patients have a 2.5 times greater rate of dying than the general population, there becomes increased impetus to further characterize PNES risk factors for facilitating prompt diagnosis and treatment [9].

To efficiently recognize PNES, a comprehensive understanding of how the disorder affects populations differentially should be developed. In particular, an awareness of sociodemographic risk factors—in addition to the biological—will not only identify disparities within the population, but also provide better direction for etiology elucidation and earlier diagnosis [10–12].

Hawai'i status as a minority-majority state provides an ideal backdrop for identifying unique risk factors for PNES, especially amongst historically underserved patients (i.e., Asians, Native Hawaiians and Other Pacific Islanders [NHPI], etc.) [13]. Hence, utilizing a large Hawai'i neuroscience center, we conducted a case-control study to characterize PNES risk factors across racial and sex strata, in comparison to the general patient population and those with only epilepsy.

2. Methods

Prior to investigation, institutional review board exemption was attained from the University of Hawai'i at Mānoa, Office of Research Compliance (protocol number: 2020–01010). To conduct this retrospective case-control study, the electronic medical records at Hawai'i Pacific Neuroscience (HPN) were queried between January 1, 2014 to October 9th, 2020, for patients with PNES, via the International Classification of Diseases 10th edition (ICD-10) codes for *unspecified convulsions* (R56.9) and *conversion disorder with seizures or convulsions* (F44.5). Subsequently, patients were included if adults (18 years or older), there was at least one video electroencephalogram available, and an official diagnosis of PNES was made by an epileptologist (E.C., K.K.L.) utilizing a video-EEG recording.

For all patients, sociodemographic, psychiatric, and general medical comorbidity data was collected from the most recent patient visit, utilizing similar methods described in a prior investigation [14,15].

2.1. Predictor and outcome variables

For each PNES case, data collected included sex, age of diagnosis, semiology, employment status, marital status, homeless status, self-identified race (White, Black, Hispanic, Asian, Native Hawaiian or other Pacific Islander [NHPI]) [16].

To assess socioeconomic status, data on patient's insurance type and the Zone Improvement Plan (zip) code of the residence were collected [14]. Zip code served as a proxy for median household income, extent of poverty in the patient's municipality, population density of patient residence, and patient's geographic origin (rural, suburban, urban) [14]. Median household income, population proportion below the poverty level, population size, and geographic stratification data were attained from the United States Census Bureau, American Community Survey Estimates (http://www.census.gov). Insurance type was stratified as Medicare, Medicaid, Private Insurance, or Military Insurance [17,18].

Data on medical comorbidities was also collected, at the time of PNES diagnosis. Such variables included body mass index (BMI; kg/m^2), weight class, presence of hypertension, hyperlipidemia, diabetes mellitus type II, congestive heart failure, coronary artery disease, peripheral vascular disease, prosthetic valve replacement, history of cardiac arrythmia, stroke, autoimmune disease, thyroid disease, glaucoma, fibromyalgia, traumatic brain injury, asthma, GERD, migraine, and epilepsy. Smoking status was classified as never (less than 100 cigarettes over lifetime) or current/former (100 or more cigarettes over lifetime) smoker, based on terms derived from the United States Centers for Disease Control and Prevention (CDC), National Health Interview Survey, Adult Tobacco Use (https://www.cdc.gov/nchs/surveys.htm) [14,16].

Neuropsychiatric data was also collected, including presence of: anxiety, depression or dysthymic disorder, post-traumatic stress disorder, attention deficit hyperactivity disorder, bipolar disorder, schizophrenia, somatoform disorder, stiff-person syndrome, chronic pain, family history of psychiatric disorders, alcohol use, and illicit drug use. Depression was quantified on the day of PNES diagnosis utilizing the Patient Health Questionier-9 (PHQ-9) [19]. Harmful alcohol drinking habits were determined via the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) [20–24]. Diagnoses of comorbid psychiatric disorders was based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders* 4^{th} *or* 5^{th} *Edition (DSM)* [16].

2.2. Controls

Three sets of controls were randomly collected. The first set of controls, collected at a 2:1 ratio, represented the general population of HPN patients with neurological disorders (*general controls*), and were matched to cases, by age, sex, and race. The second control group, collected at a 4:1 ratio, was unmatched, enabling investigation of age, sex, and race of PNES relative to the general clinic population ($n = 29{,}049$). The third control set, also unmatched, was collected at a 4:1 ratio and represented the epilepsy patient population (*epilepsy controls*).

2.3. Statistical analysis

Continuous variables were assessed by the independent Wilcoxon rank sum test, while categorical variables by either the Pearson's chi-squared test or the Fisher's exact test of independence, with Haldane-Anscombe correction [25–29]. Univariate and multivariable logistic regression, with Firth's correction, were performed to identify variables independently associated with PNES [30]. After regression diagnostics, multivariable logistic analysis was conducted. All tests were two-tailed and used an alpha level of 0.05 for deeming statistical significance.

3. Results

3.1. Population characteristics

From a clinic population of 29,049 patients, 348 were identified with ICD-10 codes, from which only 101 met inclusion criteria as PNES; 303 matched general (non-epilepsy) neurological disorder controls were collected and 404 epilepsy controls. Semiology breakdown included the following: 36.63% mixed, 28.71% aura, 11.88% complex, 9.90% dialeptic, 9.90% hypermotor, and 2.97% rhythmic. Upon examining comorbidities by semiology, no unique statistically significant associations were identified.

Median age of PNES patients was 43.00 years old (interquartile range [IQR]: 30.00, 54.00), 16 years (95% CI: 11.00, 20.00; $p < 0.0001$) younger than the neurological disorder controls and 7.00 years (95% CI: 3.00, 11.00; $p = 0.0004$) younger than epilepsy controls (Table 1).

Compared to neurological disorder controls, PNES cases had 1.84 (95% CI:1.13, 3.06; $p = 0.01$) fold greater odds of being female, while compared to epilepsy controls a 2.34 (95% CI: 1.44, 3.88; $p = 0.0005$) fold greater odds. By race, female odds remained statistically greater for NHPI and Asian patients only, when comparing PNES against epilepsy.

Relative to neurological disorder controls, PNES patients had a 2.13 (95% CI: 1.30, 3.48; $p = 0.002$) fold greater odds of being NHPI, while a reduced odds of being Asian (0.41, 95% CI: 0.21, 0.76, $p = 0.004$).

3.2. Socioeconomic Variables

Of the socioeconomic variables examined, the bivariate analysis identified trends amongst geographic origin, income, insurance, employment, and housing status; however, after multivariate analysis only income, insurance, and marital status remained significant

Table 2
Multivariable Logistic Regression for PNES Compared to Non-Epilepsy Neurological Disorder Population and Epilepsy Patients.

	PNES vs. Non-Epilepsy Neurologic Disorders Best Fit Model: Adjusted Odds Ratios	PNES vs. Epilepsy Best Fit Model: Adjusted Odds Ratios
Age		0.98 (0.96, 1.00), p = 0.12
Sex		
Male		Referent
Female		2.01 (1.11, 3.63), p = 0.02
Overall Poverty Level	26.08 (0.095, 7163.55), p = 0.26	
Employment Status		
Employed		Referent
Unemployed		0.75 (0.42, 1.35), p = 0.34
Retired		0.55 (0.16, 1.83), p = 0.33
Student		3.43 (0.94, 12.50), p = 0.06
Marital Status		
Married		Referent
Divorced		0.44 (0.17, 1.14), p = 0.09
Single		0.43 (0.22, 0.83), p = 0.01
Widowed		0.47 (0.090, 2.41), p = 0.36
Homeless Status		
Housed		Referent
Homeless		14.97 (0.92, 242.64), p = 0.06
Alcohol Consumption within Past Year		
No Consumption	Referent	
Alcohol Consumption	0.46 (0.22, 0.95), p = 0.04	
Illicit Drug Use		
No Drug Use	Referent	Referent
Drug Use	2.64 (1.10, 6.31), p = 0.03	2.76 (1.39, 5.49), p = 0.004
Anxiety		
No Anxiety	Referent	Referent
Anxiety	4.89 (2.45, 9.78), p < 0.0001	3.53 (2.03, 6.14), p < 0.0001
Post-Traumatic Stress Disorder (PTSD)		
No PTSD		Referent
PTSD		2.48 (1.08, 5.68), p = 0.03
Bipolar Disorder		
No Bipolar Disorder	Referent	Referent
Bipolar	3.74 (0.94, 14.80), p = 0.06	3.13 (1.04, 9.46), p = 0.04
Schizophrenia		
No Schizophrenia	Referent	
Schizophrenia	0.33 (0.026, 4.22), p = 0.98	0.69 (0.18, 2.54), p = 0.99
Suicide Attempt		
No Suicide Attempt	Referent	
Suicide Attempt	6.60 (0.88, 49.62), p = 0.07	
Traumatic History		
No Traumatic History	Referent	
Traumatic History	31.70 (6.64, 151.34), p < 0.0001	
BMI		1.05 (1.02, 1.09), p = 0.003
Type 2 Diabetes Mellitus		
No Diabetes Mellitus	Referent	
Diabetes Mellitus	1.92 (0.78, 4.70), p = 0.15	
Stroke		
No Stroke		Referent
Stroke		0.46 (0.17, 1.27), p = 0.13
Fibromyalgia		
No Fibromyalgia		Referent
Fibromyalgia		3.66 (1.10, 12.25), p = 0.04
Migraine		
No Migraine		Referent
Migraine		2.13 (1.17, 3.87), p = 0.01
Epilepsy		
No Epilepsy	Referent	
Epilepsy	7.52 (3.14, 18.02), p < 0.0001	
Somatoform Disorder		
No Somatoform Disorder	Referent	
Somatoform Disorder	47.13 (5.06, 439.31), p = 0.001	

predictors of PNES (Tables 1–5).

PNES patients had a median household income of $77,188 (IQR: $59,284, $100,311), significantly less than both neurological disorder (p = 0.005) and epilepsy (p = 0.02) controls. While there were an increased odds of PNES amongst patients from the first (lowest) income quartile, upon conducting the multivariate analysis, only relative to White patients from the neurological disorder controls were the odds of PNES were significantly increased with lower income (second quartile: 10.36, 95% CI: 1.55, 69.19; p = 0.016; Table 4).

Insurance type also remained significant after adjusting for covariance. In the stratified analysis examining for unique predictors of PNES in White and male patients only—relative to neurological disorders—, PNES odds were increased in both strata for those with Medicaid (White: p = 0.020; male: p = 0.0044) and military (White: p = 0.033; male: p = 0.0033) insurances (Tables 3, 4). In addition, for male PNES patients only—relative to neurological disorder controls—, Medicare (p = 0.01) insurance also predicted an increased odds of PNES (Table 4).

Another socioeconomic predictor of PNES was marital status.

Table 3
Multivariable Analysis Stratified by Patient Sex.

	PNES vs. Non-Epilepsy Neurologic Disorders		PNES vs. Epilepsy	
	Females Best Fit Model: Adjusted Odds Ratios	Males Best Fit Model: Adjusted Odds Ratios	Females Best Fit Model: Adjusted Odds Ratios	Males Best Fit Model: Adjusted Odds Ratios
Age				0.96 (0.93, 1.00), p = 0.04
Insurance				
Private		Referent		
Medicaid		80.66 (3.94, 1650.84), p = 0.004		
Medicare		180.01 (4.22, 7679.39), p = 0.01		
Military		18,818.41 (26.68, 1.33 x10^7), p = 0.003		
Employment Status				
Employed			Referent	
Unemployed			0.99 (0.50, 1.96), p = 0.99	
Retired			0.26 (0.055, 1.26), p = 0.09	
Student			4.84 (0.74, 31.43), p = 0.10	
Marital Status				
Married		Referent		
Divorced		0.20 (0.013, 3.06), p = 0.25		
Single		4.41 (0.43, 45.31), p = 0.21		
Widowed		NA		
Homeless Status				
Housed		Referent		Referent
Homeless		0.086 (0.0015, 4.85), p = 0.23		10.94 (0.51, 234.61), p = 0.13
Smoking Status				
Never Smoker		Referent		
Current/Former Smoker		0.13 (0.010, 1.71), p = 0.12		
Alcohol Consumption within Past Year				
No Consumption	Referent			
Alcohol Consumption	0.32 (0.13, 0.79), p = 0.01			
Illicit Drug Use				
No Drug Use		Referent	Referent	Referent
Drug Use		35.84 (2.35, 546.92), p = 0.01	3.14 (1.31, 7.54), p = 0.01	2.31 (0.74, 7.15), p = 0.15
Anxiety				
No Anxiety	Referent	Referent	Referent	Referent
Anxiety	6.07 (2.72, 13.53), p < 0.0001	2.83 (0.38, 21.18), p = 0.31	3.85 (1.98, 7.49), p = 0.0001	3.16 (1.06, 9.44), p = 0.04
Post-Traumatic Stress Disorder (PTSD)				
No PTSD				Referent
PTSD				3.36 (0.68, 16.48), p = 0.14
Bipolar Disorder				
No Bipolar Disorder		Referent		Referent
Bipolar		227.14 (3.87, 13,340.25), p = 0.01		6.02 (1.24, 29.24), p = 0.03
Schizophrenia				
No Schizophrenia				Referent
Schizophrenia				0.43 (0.050, 3.68), p = 0.99
Suicide Attempt				
No Suicide Attempt	Referent			
Suicide Attempt	6.38 (0.77, 52.60), p = 0.09			
Traumatic History				
No Traumatic History	Referent	Referent		
Traumatic History	97.68 (11.61, 821.56), p < 0.0001	146.64 (1.57, 13,673.53), p = 0.03		
BMI				1.06 (1.00, 1.11), p = 0.05
Type 2 Diabetes Mellitus				
No Diabetes Mellitus		Referent		Referent
Diabetes Mellitus		35.71 (1.21, 1057.82), p = 0.04		2.34 (0.61, 8.88), p = 0.21
Hypertension				
No Hypertension		Referent		
Hypertension		64.84 (2.81, 1494.75), p = 0.01		
Stroke				
No Stroke			Referent	
Stroke			0.093 (0.017, 0.50), p = 0.01	
Traumatic Brain Injury (TBI)				
No TBI			Referent	
TBI			2.18 (0.85, 5.55), p = 0.10	
Migraine				
No Migraine		Referent	Referent	
Migraine		0.29 (0.039, 2.21), p = 0.23	2.26 (1.14, 4.49), p = 0.02	
Epilepsy				
No Epilepsy	Referent	Referent		
Epilepsy	5.62 (2.18, 14.45), p = 0.0003	183.33 (3.25, 10,326.21), p = 0.01		
Somatoform Disorder				
No Somatoform Disorder		Referent		

(*continued on next page*)

Table 3 (*continued*)

	PNES vs. Non-Epilepsy Neurologic Disorders		PNES vs. Epilepsy	
	Females Best Fit Model: Adjusted Odds Ratios	Males Best Fit Model: Adjusted Odds Ratios	Females Best Fit Model: Adjusted Odds Ratios	Males Best Fit Model: Adjusted Odds Ratios
Somatoform Disorder		412.52 (3.27, 52,037.73), p = 0.02		
Chronic Pain				
No Chronic Pain			Referent	
Chronic Pain			2.96 (1.20, 7.34), p = 0.02	

Independent of the other covariates, where being single predicted a reduced odds (0.43, 95% CI: 0.22, 0.83; p = 0.012) of PNES, relative to epilepsy controls (Table 2).

3.3. Substance use

After adjusting the odds, illicit drug use and alcohol consumption also remained statistically significant predictors of PNES (Table 2). Compared to neurological disorder (2.64, 95% CI: 1.10, 6.31; p = 0.03) and epilepsy (2.76, 95%: 1.39, 5.49; p = 0.004) controls, illicit drug use independently increased odds of PNES. When examining the strata of male and NHPI patients with PNES—relative to neurological disorder controls—, as well as female PNES patients—relative to epilepsy controls—, illicit drug use continued to remain a significant covariate increasing odds of PNES (Tables 3, 4). In contrast, alcohol consumption was found to reduce odds of PNES (0.46, 95% CI: 0.22, 0.95; p = 0.036) relative to neurological disorder controls, with the trend persisting amongst the female (p = 0.014) and White (p = 0.0010) PNES strata (Tables 3, 4).

3.4. Psychiatric comorbidities

Several psychiatric comorbidities were also found to independently predict PNES, including: anxiety, post-traumatic stress disorder (PTSD), bipolar disorder, traumatic history, and somatoform disorder (Tables 2–5). Relative to both neurological disorder and epilepsy controls, odds of anxiety were increased in PNES patients by a factor of 4.89 (95% CI: 2.45, 9.78; p < 0.0001) and 3.53 (95% CI: 2.03, 6.14; p < 0.0001), respectively. The association with anxiety remained pronounced within the PNES female, White, and NPHI strata—relative to general neurological disorder control—, as well as PNES male and Asian strata—relative epilepsy controls. For PTSD, odds were greater amongst PNES patients relative to epilepsy (2.48, 95% CI: 1.08, 5.68; p = 0.03) controls, with stratification exhibiting the trend persisting for NHPI patients. There was likewise a 3.13 (95% CI: 1.04, 9.46; p = 0.04) fold increased odds of bipolar disorder amongst PNES patients, relative to epilepsy controls; with the trend present in the male (relative to both control sets) and White (relative to epilepsy controls) strata. Regarding traumatic history, odds were 31.70 (95% CI: 6.64, 151.34; p < 0.0001) fold greater amongst PNES patients relative to neurological disorder controls; specifically, the male and female strata exhibited increased odds. Finally, compared to neurological disorder controls, for somatoform disorder, odds were increased amongst PNES patients by 22.09 (95% CI: 2.79, 175.06; p = 0.03) fold, with association persisting in the male PNES strata.

3.5. Medical/biological comorbidities

Of the biological variables examined, twelve exhibited associations with PNES in univariate analysis, yet ten remained independently significant in the multivariable analysis (Tables 2–5). Concomitant diagnosis of epilepsy was present in 27.7% of the PNES cohort. Relative to neurological disorder controls, PNES patients exhibited increased odds of epilepsy (7.52, 95% CI: 3.14, 18.02; p < 0.0001), with the trend persistent amongst the female, male, and NHPI strata.

Relative to epilepsy controls, a higher BMI was more predictive of PNES (p = 0.003)—with the trend observed amongst the male and NHPI strata. Amongst male PNES patients exclusively, hypertension (64.84, 95% CI: 2.81, 1494.75; p = 0.01) and diabetes mellitus type 2 (35.71, 95% CI: 1.21, 1057.82; p = 0.04) both independently increased odds of PNES, relative to neurological disorder controls (Table 3). Meanwhile, only among Asian PNES patients, thyroid disease was found to independently be associated with increased odds (74.87, 95% CI: 1.63, 3440.54; p = 0.03) of PNES, relative to epilepsy controls (Table 5). Amongst White and NHPI PNES patients, traumatic brain injury (3.06, 95%: 1.09, 8.57; p = 0.03) independently increased odds of PNES, relative to epilepsy controls (Table 5). For female PNES patients, chronic pain (2.96, 95% CI: 1.20, 7.34; p = 0.02) was associated with increased odds of PNES, relative to epilepsy controls (Table 3). Finally, fibromyalgia (3.66, 95% CI: 1.10, 12.25; p = 0.04) and migraines (2.13, 95% CI: 1.17, 3.87; p = 0.01) were also associated with increased odds of PNES—relative to epilepsy; on stratification, only female and Asian PNES strata exhibited the association with migraines.

Unlike the other comorbidities, there was reduced odds of stroke history (0.093, 95% CI: 0.017, 0.50; p = 0.01) amongst PNES patients, relative to epilepsy controls.

4. Discussion

By examining PNES stratified by sex and race, several unique trends and associations were identified, indicating the etiology of PNES may be reliant on a patient's sociodemographic background. Our investigation also validated prior recognized associations with PNES, but further identified some of these associations were linked only to specific demographic strata.

The younger age of PNES patients was consistent with prior findings of PNES being prevalent in the 20–30 s, indicating age of convulsion onset may aid in differentiating PNES from epilepsy—however, after race stratification, only amongst Whites was a younger age associated with PNES [31–33]. Meanwhile, despite the association between female sex and PNES being reaffirmed in our investigation's overall cohort, the trend only persisted amongst NHPIs and Asians [34–37]. Such an association may arise secondary to NHPI and Asian females experiencing greater psychosocial stressors than their White counterparts [38]. For race, that odds of PNES amongst NHPIs were increased, while reduced for Asians [15]. Increased odds amongst NHPI may arise secondary to NHPI experiencing greater social alienation and discrimination, as well as experiencing lower social status relative to other racial groups, therefore predisposing the population to greater psycho-socioeconomic stressors [39–41].

4.1. Socioeconomic variables

Through analyzing a collection of socioeconomic variables, PNES was found to associate with poverty, confirming prior observations in the literature [42,43]. For women and NHPI in particular, PNES patients

Table 4
Race stratified univariate and multivariable logistic regression for PNES compared to general neurological disorder population comorbidities. No variables were found statistically significant in the multivariable analysis for Asian patients.

	PNES vs. Non-Epilepsy Neurologic Disorders	
	White	NHPI
	Best Fit Model: Adjusted Odds Ratios	Best Fit Model: Adjusted Odds Ratios
Overall Poverty Level		7.27 (0.00, 3.94 x10^7), p = 0.07
Income Quartiles		
Third Quartile (Middle Class)	Referent	Referent
First Quartile	1.89 (0.57, 6.19), p = 0.30	1.15 (0.19, 6.89), p = 0.40
Second Quartile	10.36 (1.55, 69.19), p = 0.02	0.87 (0.046, 16.47), p = 0.13
Fourth Quartile	0.72 (0.031, 16.68), p = 0.99	5.67 (0.00, 2.59 x10^6), p = 1.00
Insurance		
Private	Referent	
Medicaid	4.34 (1.26, 14.92), p = 0.02	
Medicare	2.57 (0.40, 16.73), p = 0.32	
Military	6.54 (1.16, 36.90), p = 0.03	
Employment Status		
Employed	Referent	Referent
Unemployed	0.41 (0.12, 1.42), p = 0.16	0.77 (0.26, 2.23), p = 0.53
Retired	0.56 (0.073, 4.30), p = 0.58	1.48 (0.031, 71.39), p = 0.61
Student	0.22 (0.032, 1.55), p = 0.13	0.47 (0.055, 4.11), p = 0.08
Marital Status		
Married		Referent
Divorced		1.09 (0.24, 4.97), p = 1.00
Single		1.46 (0.44, 4.86), p = 0.07
Widowed		1.45 (0.077, 27.26), p = 0.12
Alcohol Consumption within Past Year		
No Consumption	Referent	
Alcohol Consumption	0.11 (0.030, 0.41), p = 0.001	
Illicit Drug Use		
No Drug Use		Referent
Drug Use		3.62 (0.39, 33.81), p = 0.04
Anxiety		
No Anxiety	Referent	Referent
Anxiety	10.21 (3.05, 34.17), p = 0.0002	2.85 (0.66, 12.30), p = 0.03
Depression or Dysthymic Disorder		
No Depression/Dysthymic Disorder		Referent
Depression/Dysthymic Disorder		0.61 (0.16, 2.31), p = 0.46
Post-Traumatic Stress Disorder (PTSD)		
No PTSD		Referent
PTSD		16.53 (0.015, 18,808.37), p = 0.07
Bipolar Disorder		
No Bipolar Disorder	Referent	
Bipolar	5.86 (0.68, 50.73), p = 0.11	
Suicide Attempt		
No Suicide Attempt		Referent
Suicide Attempt		1.51 (0.068, 33.81), p = 0.08
Traumatic History		
No Traumatic History		Referent
Traumatic History		17.88 (0.0082, 39,180.15), p = 0.34
Family History of Psychiatric History		
No Family History		Referent
Family History		1.94 (0.032, 118.50), p = 0.18
BMI		1.02 (0.96, 1.08), p = 0.24
Fibromyalgia		
No Fibromyalgia	Referent	
Fibromyalgia	7.68 (0.39, 151.23), p = 0.18	
Traumatic Brain Injury (TBI)		
No TBI	Referent	Referent
TBI	2.58 (0.52, 12.70), p = 0.24	1.15 (0.21, 6.34), p = 0.13
GERD		
No GERD		Referent
GERD		2.64 (0.047, 149.79), p = 0.60
Epilepsy		
No Epilepsy		Referent
Epilepsy		1.90 (0.29, 12.39), p = 0.02
Somatoform Disorder		
No Somatoform Disorder		Referent
Somatoform Disorder		2.71 (0.041, 179.52), p = 0.08

were from lower income households (i.e., first income quartile) and more likely to come from suburban regions (areas with the greatest number of poor Americans) [44]. The markers of poverty associated with male PNES patients differed, in that homelessness and being a Medicaid beneficiary were associated instead. Overall, these findings allude to the possibility that socioeconomic stresses could contribute to the development of PNES, whereby the traumas and comorbidities associated with poverty serve as the etiology.

Table 5
Race stratified univariate and multivariable logistic regression for PNES compared to epilepsy patients.

	PNES vs. Epilepsy		
	White Best Fit Model: Adjusted Odds Ratios	NHPI Best Fit Model: Adjusted Odds Ratios	Asian Best Fit Model: Adjusted Odds Ratios
Age	0.98 (0.95, 1.01), p = 0.21		
Sex			
Male		Referent	Referent
Female		3.25 (1.03, 10.22), p = 0.04	2.54 (0.34, 18.96), p = 0.36
Geographic Origin			
Urban			Referent
Suburban			14.32 (0.63, 324.32), p = 0.09
Rural			1.19 (0.0083, 171.), p = 1.00
Income Quartiles			
Third Quartile (Middle Class)			Referent
First Quartile			0.040 (0.0016, 1.00), p = 0.05
Second Quartile			0.0079 (0.000050, 1.25), p = 0.06
Fourth Quartile			0.091 (0.0013, 6.15), p = 0.26
Employment Status			
Employed	Referent		
Unemployed	0.45 (0.19, 1.11), p = 0.08		
Retired	0.55 (0.11, 2.85), p = 0.48		
Student	4.28 (0.37, 49.56), p = 0.24		
Marital Status			
Married			Referent
Divorced			0.098 (0.0044, 2.21), p = 0.14
Single			0.88 (0.13, 5.97), p = 0.90
Widowed			0.57 (0.073, 4.38), p = 0.99
Illicit Drug Use			
No Drug Use		Referent	
Drug Use		2.84 (0.94, 8.58), p = 0.07	
Anxiety			
No Anxiety	Referent	Referent	Referent
Anxiety	4.25 (1.77, 10.20), p = 0.001	4.62 (1.68, 12.66), p = 0.003	8.43 (1.19, 59.66), p = 0.03
Post-Traumatic Stress Disorder (PTSD)			
No PTSD		Referent	
PTSD		5.17 (1.59, 16.81), p = 0.006	
Bipolar Disorder			
No Bipolar Disorder	Referent		
Bipolar	5.96 (1.38, 25.76), p = 0.02		
BMI		1.09 (1.03, 1.15), p = 0.002	
Hypertension			
No Hypertension	Referent		
Hypertension	0.55 (0.19, 1.56), p = 0.26		
Coronary Artery Disease or Myocardial Infarction (CAD/MI)			
No CAD/MI			Referent
CAD/MI			33.56 (0.95, 1185.28), p = 0.05
Stroke			
No Stroke	Referent		
Stroke	0.21 (0.024, 1.85), p = 0.16		
Thyroid Disease			
No Thyroid Disease			Referent
Thyroid Disease			74.87 (1.63, 3440.54), p = 0.03
Traumatic Brain Injury (TBI)			
No TBI	Referent	Referent	
TBI	3.06 (1.09, 8.57), p = 0.03	6.22 (1.34, 28.94), p = 0.02	
Migraine			
No Migraine		Referent	Referent
Migraine		2.59 (0.90, 7.45), p = 0.08	31.93 (3.24, 315.00), p = 0.003
Chronic Pain			
No Chronic Pain		Referent	
Chronic Pain		2.94 (0.82, 10.61), p = 0.10	

4.2. Substance use

As recognized in the literature, drug use among PNES patients was higher, including for marijuana, opioids/narcotics, and polysubstance abuse; while unrecognized prior, tobacco smoking was associated with PNES within our cohort [45]. PNES has been described as a learned pattern of avoidant behavior for dealing with stressors, therefore substance use may reflect another avenue for coping with the comorbid stressors triggering PNES [46]. On the contrary, alcohol use was found at reduced odds in our PNES patients; such may be secondary to the recognition of alcohol reducing the seizure threshold, and therefore PNES patients—who are often comorbid with epilepsy—being actively discouraged to consume alcohol [47].

4.3. Psychiatric comorbidities

The recognition of the large burden of psychiatric comorbidities in PNES patients was consistent with our study, in that 74.3% of PNES

Table 6
Summary of Variables Associated with PNES Compared to the Patients with General Neurological Disorders and Epilepsy. Data presents all associations with PNES from univariate analyses, including variables that potentially covary.

PNES Odds Increased	Relative to Neurological Disorders	Relative to Epilepsy	Female Neurological Disorders	Female Epilepsy	Male Neurological Disorders	Male Epilepsy	White Neurological Disorders	White Epilepsy	NHPI Neurological Disorders	NHPI Epilepsy	Asian Neurological Disorders	Asian Epilepsy
Younger Age	✓	✓		✓		✓		✓				
Female	✓	✓								✓		✓
Native Hawaiian or Other Pacific Islander	✓											
Lower Population Density		✓		✓								
Suburban	✓	✓	✓	✓					✓	✓		
Lower Household Income	✓	✓	✓	✓			✓		✓			
First Income Quartile	✓	✓	✓	✓					✓			
Medicaid Insurance	✓				✓		✓					
Military Insurance					✓							
Employed		✓										
Homeless	✓	✓				✓						
Current/Former Smoker	✓								✓			
Illicit Drug Use	✓	✓	✓	✓	✓	✓			✓	✓		
Marijuana	✓											
Opioids/Narcotics	✓											
Polysubstance Abuse	✓											
Anxiety	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Depression or Dysthymic Disorder	✓	✓	✓	✓		✓	✓	✓	✓	✓		
Post-Traumatic Stress Disorder	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
ADHD		✓				✓		✓				
Bipolar Disorder	✓	✓			✓	✓	✓	✓				
Traumatic History	✓		✓						✓			
Great BMI		✓		✓		✓			✓	✓		
Obesity Class 3	✓	✓										
Traumatic Brain Injury	✓	✓		✓			✓	✓				
Epilepsy	✓		✓		✓		✓					
Somatoform Disorder	✓											
Asthma		✓								✓		✓
Migraine		✓		✓						✓		✓
Chronic Pain		✓		✓						✓		
Type 2 Diabetes Mellitus					✓							
Hypertension					✓							
GERD				✓					✓			
Thyroid Disease												✓

PNES Odds Reduced	Relative to Neurological Disorders	Relative to Epilepsy	Female Neurological Disorders	Female Epilepsy	Male Neurological Disorders	Male Epilepsy	White Neurological Disorders	White Epilepsy	NHPI Neurological Disorders	NHPI Epilepsy	Asian Neurological Disorders	Asian Epilepsy
Asian	✓											
Urban	✓	✓										

(*continued on next page*)

Table 6 (*continued*)

Unemployed							✓		
Retired		✓		✓			✓		✓
Second Income Quartile		✓							
Third Income Quartile (Middle Class)	✓	✓							
Private Insurance	✓								
Never Smoker	✓								
Alcohol Consumption	✓		✓			✓			
Schizophrenia		✓		✓	✓				
Stroke		✓		✓					
Migraines						✓			
Thyroid Disorder								✓	

cases had at least one psychiatric comorbidity: odds of anxiety, depression, bipolar disorder, and PTSD were all greater than neurological disorder or epilepsy controls [31,48]. Similarly, odds of traumatic abuse were greater in PNES, yet relative to prior investigations where trauma was present in up to 70% of cases, our prevalence was 28% [31]. The disparity in findings may indicate for certain populations, traumatic history may not be the driving etiology behind PNES; on the other hand, the lower prevalence we observed may represent the cultural barriers present in speaking about traumatic abuse in minority populations (i.e., NHPI and Asians) [31,49]. Regarding ADHD, while elevated proportions of ADHD have been noted in PNES and epilepsy populations, our results indicate ADHD had significantly greater odds in the PNES population—potentially insinuating a common pathway between ADHD and PNES development [50,51]. Meanwhile, other psychiatric variables, such as schizophrenia, were not found to predict PNES, thus emphasizing presence of any psychiatric disorders simply does not increase odds of PNES.

Odds of somatoform disorder itself were greater in PNES, which could indicate PNES patients are predisposed to other non-convulsive functional neurological disorders. However, when considering literature indicating PNES patients have lower rates of other somatoform disorders, along with the finding of fibromyalgia not being statistically associated in our study, the increased odds of somatoform disorders we observed may instead be secondary to clinicians utilizing the diagnosis of somatoform disorder rather than PNES (i.e., when a patient is diagnosed with PNES, a diagnosis of somatoform disorder is also documented) [31].

Overall, considering all psychiatric variables, multivariable logistic analysis found depression did not independently predict PNES, while anxiety, PTSD, bipolar disorder, and traumatic history all did. Anxiety was the only variable to remain a significant predictor across all sex and racial substrata, thus lending support to the hypotheses that anxiety arising from traumatic history or stressors may play a central role in PNES pathogenesis [52,53].

4.4. Medical/biological comorbidities

In addition to the psychiatric variables, our investigation identified roughly eleven physical illness/biological variables associated with PNES, including modifiable risk factors (i.e., BMI, hypertension). Our study corroborated data supporting an association between PNES with traumatic brain injury, epilepsy, asthma, chronic pain, and migraines [31,53–59]. Yet, we also identified several novel variables increasing odds of PNES, including: greater BMI (specifically obesity class 3), diabetes mellitus type 2, hypertension, and thyroid disease. Thyroid disease was only an independent predictor of PNES amongst Asian patients, a population disproportionately affected by hyperthyroidism (i.e., Grave's disease), which itself is associated with greater risk for anxiety and depression [60,61]. Similarly, migraines independently predicted an increased odds of PNES amongst Asians, as well as females. Overall, physical illness and disability may contribute to PNES, by increasing vulnerability to health anxiety [62].

4.5. Race: Whites, Native Hawaiians and Other Pacific Islanders, and Asians

With a diverse cohort (38.61% White, 37.62% NHPI, 14.85% Asian), our study identified racial differences between Whites, NHPI, and Asians (Tables 4, 5). Specifically, physical illnesses (higher BMI, migraines, and thyroid disorders) were independent predictors of PNES in NHPI and Asian patients, but not Whites. Such differences potentially arise secondary to differing sociocultural stressors and determinants of health between these three groups [63].

Table 7
Summary of variables associated with PNES compared to the patients with general neurological disorders and epilepsy from multivariable analysis. Data also stratified by sex and race.

PNES Odds Increased	Relative to Neurological Disorders	Relative to Epilepsy	Female Neurological Disorders	Female Epilepsy	Male Neurological Disorders	Male Epilepsy	White Neurological Disorders	White Epilepsy	NHPI Neurological Disorders	NHPI Epilepsy	Asian Neurological Disorders	Asian Epilepsy
Younger Age						✓						
Female		✓								✓		
Second Income Quartile							✓					
Medicare					✓							
Medicaid					✓		✓					
Military Insurance					✓		✓					
Illicit Drug Use	✓	✓		✓	✓				✓			
Anxiety	✓	✓	✓	✓		✓	✓	✓	✓	✓		✓
Post-Traumatic Stress Disorder		✓								✓		
Bipolar Disorder		✓			✓	✓		✓				
Traumatic History	✓		✓		✓							
Great BMI		✓				✓				✓		
Traumatic Brain Injury								✓		✓		
Epilepsy	✓		✓		✓				✓			
Somatoform Disorder	✓				✓							
Fibromyalgia		✓										
Migraine		✓		✓								✓
Chronic Pain				✓								
Type 2 Diabetes Mellitus					✓							
Hypertension					✓							
Thyroid Disease												✓

PNES Odds Reduced	Relative to Neurological Disorders	Relative to Epilepsy	Female Neurological Disorders	Female Epilepsy	Male Neurological Disorders	Male Epilepsy	White Neurological Disorders	White Epilepsy	NHPI Neurological Disorders	NHPI Epilepsy	Asian Neurological Disorders	Asian Epilepsy
Single		✓										
Alcohol Consumption	✓		✓				✓					
Stroke				✓								

4.6. Sex: female and males

Differences in patient sex were likewise observed in our PNES cohort (Table 3). Uniquely, females presented increased odds of variables indicative of lower socioeconomic status (i.e., lower household income, being in the lowest income quartile, suburban origin), while men exhibited increased odds of military insurance and bipolar disorder. These findings are likely a reflection of the males and females experiencing different rates of environmental stressors due to sociological differences in society [64].

4.7. Limitations

Overall, the results should be considered in the context of several limitations. First, with data from a single epilepsy monitoring unit, the outcomes may be sensitive to the referral patterns and not be representative of PNES or epilepsy population within Hawai'i. Second, due to the retrospective nature, further patient psychiatric history beyond the medical records could not be explored. Lastly, given the ethnocultural background assessment was limited to a single self-identified race, we were unable to explicitly investigate the sociocultural roles of multiracial heritage on PNES.

5. Conclusion

Our findings demonstrated associations with PNES can be dependent on sex and race (Tables 6 and 7). In particular, female patients were more likely to experience lower socioeconomic status, while men were more likely exposed to military service and have bipolar disorder. Amongst race, relative to Whites, NHPI and Asians were more likely to have PNES associated with physical illness. Overall, these findings may provide better direction in etiology elucidation and addressing health disparities within PNES—which is particularly important, given that PNES disproportionally impacts historically vulnerable and underresourced populations [15,32].

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CRediT authorship contribution statement

Rachel Gorenflo: Data curation, Investigation, Methodology, Software, Validation, Writing – original draft. **Richard Ho:** Data curation, Investigation, Methodology, Software, Validation, Writing – original draft. **Enrique Carrazana:** Conceptualization, Methodology, Software, Validation, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing. **Catherine Mitchell:** Conceptualization, Methodology, Software, Validation, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing. **Kore Liow:** Conceptualization, Methodology, Software, Validation, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing. **Jason Viereck:** Conceptualization, Methodology, Software, Validation, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing. **Arash Ghaffari-Rafi:** Conceptualization, Methodology, Software, Validation, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing.

Code Availability (software application or custom code)

Not applicable.

Authors' contributions

Development: AGR, RH, RG, EC, JV, KKL; Data Collection: RH, RG; Analysis and Interpretation of Data: AGR, RH, RG; Writing of Manuscript: AGR, RG.

Ethics approval

Institutional review board exemption; University of Hawai'i at Mānoa, Office of Research Compliance (protocol number: 2020–01010).

Consent to participate

Not applicable.

Consent for publication

All authors approved the submitted manuscript version.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.clineuro.2022.107221.

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