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Seizure triggers identified postictally using a smart watch reporting system

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ABSTRACT

Persons with epilepsy (PWE) often report that seizure triggers can influence the occurrence and timing of seizures. Some previous studies of seizure triggers have relied on retrospective daily seizure diaries or surveys pertaining to all past seizures, recent and/or remote, in respondents. To assess the characteristics of seizure triggers at the granularity of individual seizures, we used a seizure-tracking app, called EpiWatch, on a smart watch system (Apple Watch and iPhone) in a national study of PWE. Participants tracked seizures during a 16-month study period using the EpiWatch app. Seizure tracking was initiated during a pre-ictal state or as the seizure was occurring and included collection of biosensor data, responsiveness testing, and completion of an immediate post-seizure survey. The survey evaluated seizure types, auras or warning symptoms, loss of awareness, use of rescue medication, and seizure triggers for each tracked seizure. Two hundred and thirty four participants tracked 2493 seizures. Ninety six participants reported triggers in 650 seizures: stress (65.8%), lack of sleep (30.5%), menstrual cycle (19.7%), and overexertion (18%) were the most common. Participants often reported having multiple combined triggers, frequent stress with lack of sleep, overexertion, or menses. Participants who reported triggers were more likely to be taking 3 or more anti-seizure medications compared to participants who did not report triggers. Participants were able to interact with the app and use mobile technology in this national study to record seizures and report common seizure triggers. These findings demonstrate the promise of longitudinal, self-reported data to improve our understanding of epilepsy and its related co morbidities.

1. Introduction

Many persons with epilepsy often report that various seizure triggers, such as stress and exhaustion or hormonal changes, can influence the occurrence and timing of their seizures [1,2]. Studies using prospective diaries have shown that a variety of triggers can be associated with an increase in the likelihood of some persons subsequently having seizures, though, these are somewhat limited in associating the precise timing of the risk factors and persons' seizures [3]. It also may be important to determine whether combinations of possible seizure triggers, e.g., stress and sleep deprivation, may be important in determining whether these factors increase risks of seizures in some persons. Persons with strong associations of single or combinations of seizure triggers may potentially be able to alleviate some of these factors if they could be identified.

We conducted a study using a wearable seizure tracking system (Apple Watch using the EpiWatch app) to determine whether participants report specific seizure triggers or combinations of triggers at the time of their seizures. This seizure tracking program also permits participants to report other seizure data after a period of cognitive recovery following the seizure. Using mobile devices in research can provide tools to help manage epilepsy and allow for medical research by enabling rapid collection of timestamped data in large clinical populations [4]. Similarly, our seizure tracking with surveys of participants immediately following seizures provides a method to survey a national cross-section of persons with epilepsy about seizure triggers. EpiWatch utilized a ResearchKit program

Abbreviations: PWE, persons with epilepsy; IHS, Initial Health Survey; ASM(s), anti-epilepsy medication(s); OR, odds ratio; CI, confidence interval; GED, General Education Development test.

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that permitted electronic consenting for participation in the study [5].

This study's objectives were to profile the demographics and clinical histories of persons who report and do not report seizure triggers, to identify common seizure triggers among participants, and to analyze whether various combinations of seizure triggers may occur versus single triggers.

2. Methods

2.1. Participant enrollment

This cross-sectional study enrolled a national population (United States) of voluntary participants with seizures who had Apple Watches, iPhones, and email addresses. Potential participants downloaded the app on their phone and Apple Watch and reviewed study procedures. Participants were recruited with self-selection from multiple sources: social media, general media coverage, support groups, or information from health professionals. Questionnaires screened participants for eligibility and comprehension of the study. Screened participants consented with electronic signatures and received copies of their consent form. Encrypted data were transmitted to a secure back-end server. Registration information was stored separately from study data. Participant data were de-identified and coded. Data were collected from 1/1/2016 until 4/17/2017.

Consented participants were those who downloaded the app, met the eligibility criteria, demonstrated understanding of study procedures, and completed the electronic consenting process. User status was determined on the date of data download (4/18/2017) depending on completion of registration, which consisted of verifying an email address and completing the Initial Health Survey (IHS). Active users completed these steps, while other users withdrew consent or did not complete registration. The primary analysis group included participants who tracked seizures and completed post-seizure logs. This group was divided into participants who reported at least one trigger and participants who did not report any triggers. Demographic, seizure, and trigger data were used for analysis.

Enrollment inclusion criteria were: 16 years or older (parental consent required for participants younger than 18 years); United States resident; history of epilepsy with minimum of one seizure in the past year; use of an Apple Watch and iPhone with a data plan. An exclusion was major learning or physical disabilities that impaired their ability to interact with the app (though caregivers were allowed to help participants carry out some study activities).

2.2. Ethics

The Johns Hopkins Medicine Institutional Review Board approved the use of human participants and the electronic consenting method for this protocol. Participant and guardian informed consent (if applicable) were obtained. This article does not use photographs, videos, or other information of recognizable persons.

2.3. EpiWatch Research app

The EpiWatch Research app V1.0 used the Apple Watch and iPhone to monitor seizures and treatment outcomes. After consenting, participants completed the IHS that profiled their seizure history. Sex was obtained through participants' HealthKit data profile. Participants or caregivers initiated seizure tracking based on auras/warning symptoms or observed seizures with collection of heart rate, movement, and intermittent memory tests (to measure cognitive recovery) on the Apple Watch. Seizures were tracked for up to 10 min, or until participants correctly answered a working memory test (ability to press a target on the Apple Watch and recall positions of 3 numbers in 4 boxes) that was repeated every minute until it was completed. A post-seizure survey was then delivered on the Apple Watch, asking participants about the seizure they just experienced, including: seizure type, if there was a warning, if there was a loss of consciousness, use of emergency medications, and if seizure triggers were present (Fig. 1). Participants selected none or any combination of seven triggers: menstrual cycle, stress, overexertion, diet, missed pills, lack of sleep, fever/infection. Participants could also log seizures and complete post-seizure surveys later on their phone's seizure journal. Participants were queried daily on seizure frequency and medication adherence for the previous 24 h.

2.4. Data analysis

Statistical analysis was performed using R v3.6.1 [6]. We tabulated IHS and registration data: demographic information (age, zip code, sex, income, employment status, relationship status, education, family history of seizures), and clinical factors (seizure onset, etiology, seizure types, treatments). Income quartiles were calculated (<$10,000; $10,001–30,000; $30,001–60,000; $60,001+). Developer user data were excluded. Participants could report multiple seizure types in the IHS, each with a corresponding age of onset and historical frequency. If multiple seizure types were reported, years since onset of seizures was calculated from the lowest age of onset for each participant. Seizure tracking and post-seizure survey results were tabulated. For each seizure type they reported, participants included an average monthly historical frequency (less than once per month, between 1 and 4 times per month, or more than 4 times per month). Proportions of participants reporting triggers and proportions of seizures associated with triggers were calculated. Historical frequency of seizure types for participants with and without triggers were compared using Fisher's Exact Test for Count Data with corresponding two-sided p-values. Demographics and seizure patterns were compared between participants who reported and those who did not report triggers using logistic regression models with odds ratio (OR), 95% confidence interval (CI), and two-tailed p-values. In instances where the same sample was used to evaluate multiple models, the Benjamini & Hochberg procedure was used to control for these multiple comparisons [7]. We present adjusted p-values to account for the false discovery rate. When comparing groups of those reporting triggers with those who did not report triggers, we evaluated five variables (relationship status, education level, disability, age, and number of anti-seizure medications). Medication adherence logs were used to identify the number of anti-seizure treatments. Individuals who completed medication logs but did not complete post-seizure surveys were not included in this comparison. When comparing seizures with triggers to seizures without triggers, we evaluated fourteen variables (presence of warning, use of rescue medication, loss of awareness, presumed focal seizures, presumed generalized seizures, unknown onset seizures, and the seizure types: absence, atonic, aura, complex partial, myoclonic, tonic-clonic, simple partial, tonic). Nomenclature for seizure types changed after research was conducted. Seizure types were collected with previously used terms: Absence = generalized absence, Atonic = generalized atonic, Aura = focal aware, Myoclonic = generalized myoclonic, Tonic-clonic = focal to bilateral tonic-clonic, Complex partial = focal impaired awareness, Simple partial = focal aware, Tonic = generalized tonic [8]. Regardless of subgroup, participants completed the same surveys. We also assessed patterns of combined triggers (e.g., both stress and diet).

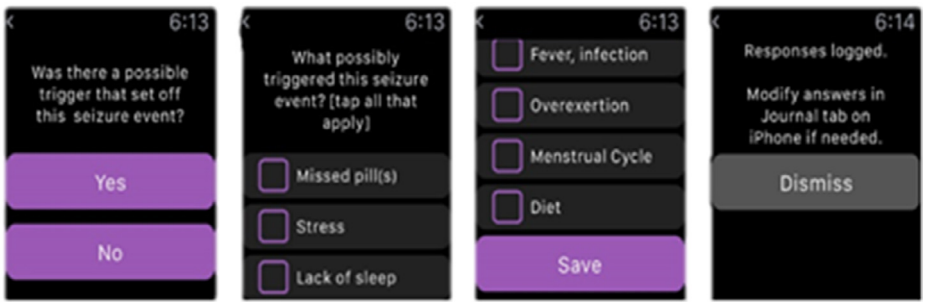

Fig. 1. Post-seizure survey example. Users were prompted to answer questions after their seizure event regarding seizure type, if there was a warning, if there was a loss of consciousness, use of emergency medications, and if seizure triggers were present.

Participants were included only if they reported their age; 18 subjects were excluded from analysis due to missing ages. A small proportion of participants did not permit access to HealthKit or did not complete all IHS questions; this information was not required for participation and resulted in exclusion of some missing survey values.

3. Results

3.1. Study participants

The study enrolled 999 PWE who completed the electronic consenting process and study comprehension screening. A total of two hundred and thirty four participants (23.4% of all consented participants) tracked seizures and completed post-seizure surveys during the study period (Fig. 2). Participants were broadly distributed across the United States. Participants tracked 2493 seizures on the EpiWatch app (median two seizures each). The median age was 30 years (range 16–66). 65.4% of participants gave permission to access their HealthKit profile, which included the gender they reported therein: 58.2% were female. Participants reported a range of seizure types, frequent auras, simple partial seizures, and complex partial seizures. For participants who completed seizure frequency information in the IHS ($n = 211$), 93.3% reported historical seizure frequencies of one or more seizures per month for at least one seizure type. Most participants received treatment with one or two anti-seizure medications (ASMs). Participants had a broad range of employment status and incomes (Table 1).

A large group of persons enrolled in the study ($n = 765$) did not track seizures during the study and did not provide information on possible seizure triggers. Their profiles were generally similar to participants tracking seizures: median age 30 years, range 16–73; 48% were females; they listed similar seizure types. Subjects not tracking seizures had a mean duration of epilepsy of 12.3 years, range 0–39; compared to a mean of 11.2 for participants tracking seizures. They appeared to have been less involved in study participation: only 20% permitted access to their HealthKit profile, compared to 65.4% of those tracking seizures. Proportions of incomes, employment status, education, and relationship status were similar among the two groups.

3.2. Seizure triggers

A total of ninety six participants (41.0% of participants who tracked seizures) reported having seizures with one or more sei-

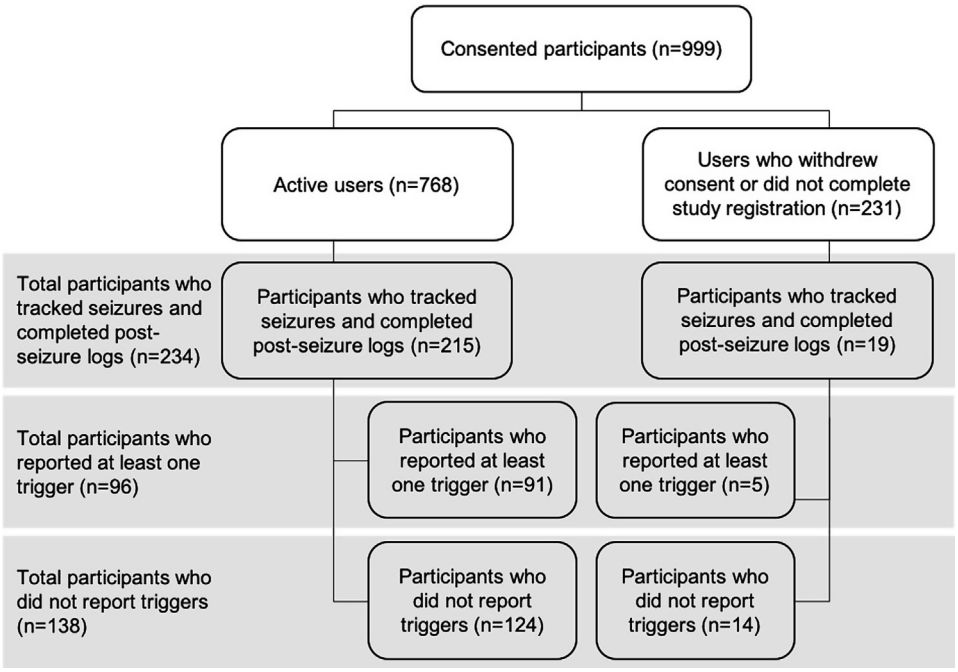

Fig. 2. Study participant profile. Active users completed the e-consenting and activation process (verification of email address). Nineteen participants withdrew consent or did not complete the study activation process. A total of two hundred and thirty four participants tracked seizures and completed post-seizure logs.

Table 1
Demographic information for participants who tracked seizures and completed post-seizure logs ($n = 234$).

Median age (range), years	30 (16–66)
Years since onset of seizures [a]	Mean 11.2 (median 8; range 0–39)
Number of anti-seizure medications ($n = 213$, range 0–5) [b]	% of participants who reported
0	6.5%
1	36.9%
2	34.6%
3 or more	22.0%
Income ($n = 194$) [b]	
<$10,000	25.8%
$10,001–30,000	20.6%
$30,001–60,000	33.0%
$60,001+	20.6%
Employment status ($n = 215$) [b]	
Full time	48.4%
Part time	16.3%
Unemployed	20.9%
Disabled	14.4%
Relationship status ($n = 217$) [b,c]	
In a relationship/not single	70.1%
Single/not in a relationship	30.0%
Education ($n = 217$) [b,d]	
Less than 4-year college degree	58.1%
4-year college degree or advanced degree	41.9%
Family history of seizures ($n = 216$) [b]	
Yes	21.8%
No	78.2%
Seizure type (original report from IHS) ($n = 209$) [e]	
Absence	98
Atonic	37
Aura	124
Myoclonic	55
Tonic-clonic	130
Tonic	38
Complex partial	130
Simple partial	88

Data are from participants' Initial Health Survey and medication adherence logs.
[a] Data based on information from $n = 207$ participants.
[b] Responses were not required for participation. Sample size for each variable has been adjusted for missing responses.
[c] "In a relationship/not single" is defined as married, in a civil union, cohabitating, dating, long-distance relationship; "Single/not in a relationship" is defined as single, divorced (or going through divorce), separated, widowed.
[d] "Lower than 4-year college degree" includes: 2-year college degree, Some college, Nursery school to high school (no diploma), Trade/Technical/Vocational training, High school graduate or equivalent (e.g., GED), No schooling. "4-year college degree or advanced degree" includes: 4-year college degree, Master's degree, Professional degree, Doctorate degree.
[e] Nomenclature for seizure types changed after research was conducted. Data were collected with seizure types listed in Table 1, the reporting nomenclature was updated: Absence = generalized absence, Atonic = generalized atonic, Aura = focal aware, Myoclonic = generalized myoclonic, Tonic-clonic = focal to bilateral tonic-clonic, Complex partial = focal impaired awareness, Simple partial = focal aware, Tonic = generalized tonic [8]. Participants were able to select multiple seizure types.

zure triggers. They tracked a total of 650 seizures and reported 1121 triggers during these events (up to 7 triggers each). Single triggers were reported in 15% ($n = 375$) of all tracked seizures, 2 triggers in 6.1% ($n = 153$), and 3 or more triggers in 4.9% ($n = 122$) (Fig. 3). One hundred and thirty eight participants tracked 1843 seizures (74%) that were not associated with triggers.

The most common triggers in the post-seizure surveys were stress (65.8% of seizures with triggers, $n = 428$ seizures), lack of sleep (30.5%, $n = 198$), and menstrual cycle factors (19.7%, $n = 128$) (Fig. 4A). Many seizures were reported by participants to be associated with various combinations of triggers. These were predominantly stress combined with one or more other seizure triggers ($n = 232$ seizures) (Fig. 4B). Stress as a trigger was commonly linked to reports of lack of sleep (22.2%, $n = 144$ seizures), menses (11.4%, $n = 74$), and overexertion (11.4%, $n = 74$). Although stress was by far most commonly as a trigger associated with other triggers, "menstrual cycle" triggers and lack of sleep also often occurred together (8.8% of seizures with triggers, $n = 57$).

Participants who reported having seizure triggers were generally similar in demographics and their clinical backgrounds to those who did not report triggers (Table 2A). Based on IHS data, similar proportions of participants with and without triggers reported having at least one seizure type more than 4 times per month (56.18% and 50.82%, respectively). Participants with triggers and without triggers reported experiencing similar frequencies of various seizure types (Table 2B). Approximately 65% of each group reported their gender in the ResearchKit study. 66.7% of those with seizure triggers were female, while 52.2% of those without triggers were female. The groups reporting and not reporting triggers were similar in relationship status, education level, and age (Table 3). Participants who reported triggers were taking a slightly higher number of ASMs compared to participants not reporting triggers (mean 2 ASMs versus 1.6 ASMs) and they were more likely to be treated with 3 or more ASMs: 30.8% compared to participants who did not report triggers 15.6% (OR: 2.41, 95% CI 1.25–4.73, p-value = 0.009, adjusted p-value = 0.046). There was a slightly higher proportion of individuals who indicated they were disabled in participants reporting triggers: 21.1% to 9.6% of participants without triggers (OR: 2.52, 95% CI 1.17–5.63, p-value = 0.0204, adjusted p-value = 0.051).

Participants reported many seizure types in post-seizure surveys ($n = 2493$): absence 8.8% ($n = 220$), atonic 1.6% ($n = 40$), aura 16% ($n = 398$), complex partial 24.5% ($n = 610$), myoclonic 6.3% ($n = 156$), simple partial 32.9% ($n = 820$), tonic-clonic 9.2% ($n = 230$), tonic 0.8% ($n = 19$). Table 4 shows associations between various seizure types and reported triggers. Simple partial seizures accounted for 15.85% of seizures with triggers and 38.88% of seizures without triggers. The most commonly reported trigger with each seizure type was stress, followed by lack of sleep (except in simple partial seizures where menstrual cycle was the second most common trigger after stress). Many of the seizures associated with stress were complex partial seizures: 38.3% ($n = 164$) compared to 21.6% ($n = 446$) of seizures not associated with stress triggers.

In addition to reports of seizure triggers, participants' post-seizure surveys evaluated whether seizures were associated with loss of awareness, whether they received rescue medications, and whether they had seizure warnings. A slightly larger proportion of seizures associated with triggers were treated with acute rescue medications (13.4%) compared to seizures not reported with triggers (5.8%) (OR: 2.51, 95% CI 1.86–3.38, p-value = 1.6e-9, adjusted p-value = 4.3e-9). A slightly lower proportion of seizures linked to triggers were preceded by warning symptoms (36.9%) compared to seizures not reported as being associated with triggers (50.7%) (OR: 0.57, 95% CI 0.47–0.68, p-value = 1.9e-9, adjusted p-value = 5.3e-9). A slightly lower proportion of seizures associated with triggers were associated with loss of awareness (59.7%) compared to 76.5% of seizures without triggers (OR: 0.45, 95% CI 0.38–0.55, p-value = 4.6e-16, adjusted p-value = 3.2e-15). There was a slightly higher proportion of seizures with triggers (21.1%) that had a generalized onset compared to seizures without triggers (16.8%) (OR: 1.33, CI 1.06–1.66, p-value = 0.014, adjusted p-value = 0.028). All variables tested in seizures with and without triggers are displayed in Table 4.

4. Discussion

We demonstrated that mobile devices could be used in a diverse, national population of PWE to track seizures and complete postictal surveys to identify seizure triggers. 41% of participants who tracked seizures reported seizure triggers; 26% of all seizures

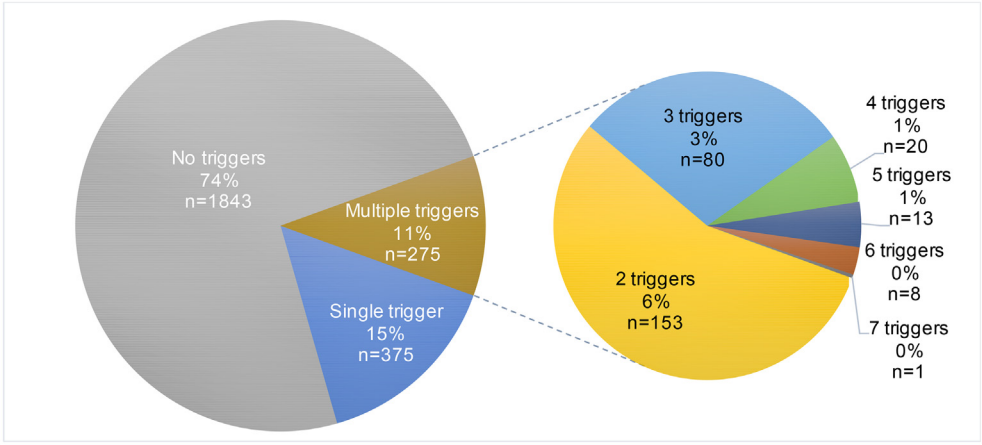

Fig. 3. Distribution of the number of triggers. Participants could report up to seven triggers during each seizure event (stress, lack of sleep, menstrual cycle, overexertion, diet, missed medication, and/or fever/infection).

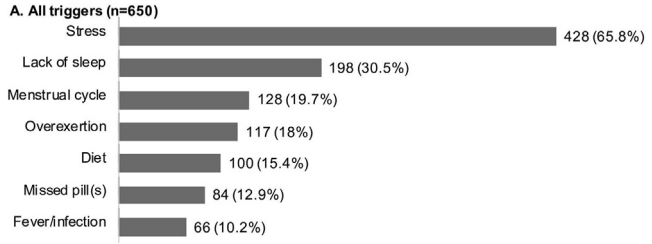

Fig. 4A. Distribution of triggers during seizure events. Participants reported a total of 650 seizures with triggers, in which they could choose no or any combination of seven triggers (stress, lack of sleep, menstrual cycle, overexertion, diet, missed medications, and fever/infection) after tracking a seizure. Percentages may not add to 100 because participants could report multiple triggers.

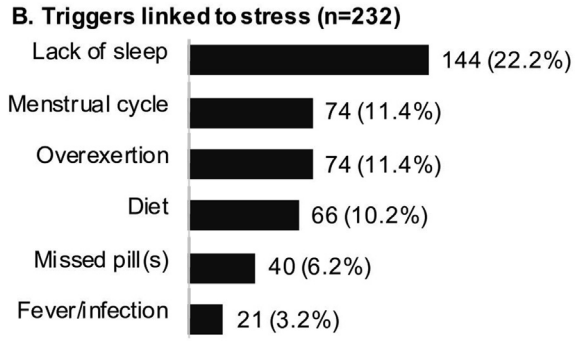

Fig. 4B. Distribution of triggers reported with stress for seizures associated with multiple triggers. Participants reported a total of 232 seizures linked with stress. Participants could choose any combination of 7 triggers.

were associated with various triggers. PWE in this study reported stress overwhelmingly as their most common seizure trigger, followed by lack of sleep and menstrual cycle associations. Many participants with seizure triggers, however, reported multiple factors combined to act as seizure triggers, most commonly stress and other factors such as exhaustion or sleep deprivation. This suggests that these factors together may alter seizure thresholds and influence the timing and risks of seizures.

Previous studies have reported that triggers can increase the severity of seizures or impact the timing of seizures, but have reported incidences varying from 62% to 97% of study participants reporting at least one trigger. These studies, however, did not query participants at the time of their seizures or only asked participants generally about their seizures [9,10]. Correlating seizures with stress has been difficult due to variable participant reporting; however, several reports have documented stress as the most commonly self-identified seizure trigger [11]. Another study did not find that stress and mood were associated with the occurrence of seizures. This study used twice daily surveys, instead of querying participants immediately after seizures, and evaluated seizure counts for 24 h after surveying mood [12]. The strong link we found between stress and exhaustion warrants further research. The use of mobile devices in our study allowed for acute evaluation of seizures in a broadly distributed population of participants with a large range of seizure frequencies. Our findings indicate stress was commonly linked to participants' seizures, in both cases of single and multiple triggers.

There were several differences in our study between participants who reported and did not report seizure triggers. Participants reporting triggers were more likely to be taking three or more ASMs. A slightly larger proportion of participants reporting triggers reported being disabled compared to those without triggers. Our study also found differences between seizures associated and not associated with triggers. Seizures associated with triggers were more likely to be accompanied by loss of consciousness and the use of rescue medications compared to seizures not linked to triggers. Conversely, seizures associated with triggers were less likely to be preceded by a warning. These differences may indicate participants' sensitivity to stress, exhaustion, and similar triggers as part of having more severe, "brittle" and drug-resistant epilepsy. Seizure triggers may also reflect some participants' responses to seizures and may be associated with increased perceptions of an external locus of control on their health. External health locus of control has been related to higher scores on the Hospital Anxiety and Depression scale in a group of individuals with epilepsy [13].

Previous studies using daily diaries, which tracked seizure frequency, hours of sleep, and self-reported stress and anxiety levels, showed lack of sleep and stress/anxiety both increased the risk of seizures the next day [3]. A similar retrospective study using one-time interviews found associations between seizure triggers, especially stress, fatigue, and sleep deprivation [9]. Our study surveyed participants immediately after their seizures and confirmed and extended these findings, showing that combined trigger factors – usually stress with exhaustion, sleep deprivation, or menses – are common with seizures. Nearly half of the seizure triggers reported by participants occurred in combination. There may be a physiological basis for the association between combined triggers

Table 2A
Demographic information of participants reporting and not reporting seizure triggers.

	Participants reporting seizure triggers (n = 96)	Participants not reporting seizure triggers (n = 138)
Median age (range), years	29.5 (16–52)	30 (16–66)
Years since onset of seizures	Mean 11.2 (median 7.5; range 0–35; n = 86)	Mean 11.2 (median 8; range 0–39; n = 122)
Number of ASMs	n = 91	n = 122
0	3.3%	9.0%
1	35.2%	37.7%
2	30.8%	37.7%
3 or more	30.8%	15.6%
Employment status	n = 90	n = 125
Full time	48.9%	48.0%
Part time	12.2%	19.2%
Unemployed	17.8%	23.2%
Disabled	21.1%	9.6%
Relationship status [f]	n = 91	n = 126
In a relationship/ not single	71.4%	69.1%
Single/not in a relationship	28.6%	31%
Education [g]	n = 90	n = 127
Less than 4-year college degree	53.3%	61.4%
4-year college degree or advanced degree	46.7%	38.6%
Family history of seizures	n = 90	n = 126
Yes	23.3%	20.6%
No	76.7%	79.4%
Seizure type (original report from IHS)[e]	n = 89	n = 122
ABS	48.31% (n = 43)	45.08% (n = 55)
ATO	22.47% (n = 20)	13.93% (n = 17)
AUR	59.55% (n = 53)	58.2% (n = 71)
CPS	65.17% (n = 58)	59.02% (n = 72)
MYO	31.46% (n = 28)	22.13% (n = 27)
SPS	42.7% (n = 38)	40.98% (n = 50)
TC	59.55% (n = 53)	63.11% (n = 77)
TON	17.98% (n = 16)	18.03% (n = 220)

Data are from participants' Initial Health Survey. Participants were able to select multiple seizure types and responses were only required for current age, all other responses were optional; percentages may not add to 100 due to rounding.

[f] "In a relationship/not single" is defined as married, civil union/domestic partnership, cohabitating, dating, long-distance relationship; "Single/not in a relationship" is defined as single, divorced (or going through divorce), separated, widowed.

[g] "Lower than 4-year college degree" includes: 2-year college degree, Some college, Nursery school to high school (no diploma), Trade/Technical/Vocational training, High school graduate or equivalent (e.g., GED), No schooling. "4-year college degree or advanced degree" includes: 4-year college degree, Master's degree, Professional degree, Doctorate degree.

Table 2B
Seizure frequency per month and seizure type information of participants reporting and not reporting seizure triggers.

More than 4 seizures per month	Triggers	No Triggers	P-value
ABS	48.84% (n = 21)	34.55% (n = 19)	0.21
ATO	20% (n = 4)	11.76% (n = 2)	0.67
AUR	45.28% (n = 24)	40.85% (n = 29)	0.71
CPS	43.1% (n = 25)	44.44% (n = 32)	1
MYO	46.43% (n = 13)	40.74% (n = 11)	0.79
SPS	65.79% (n = 25)	46% (n = 23)	0.085
TC	22.64% (n = 12)	11.69% (n = 9)	0.14
TON	18.75% (n = 3)	22.73% (n = 5)	1
Between 1 and 4 seizures per month			
ABS	34.49% (n = 15)	38.18% (n = 21)	0.83
ATO	35% (n = 7)	52.94% (n = 9)	0.33
AUR	35.85% (n = 19)	43.66% (n = 31)	0.46
CPS	44.83% (n = 26)	38.89% (n = 28)	0.59
MYO	35.71% (n = 10)	37.04% (n = 10)	1
SPS	23.68% (n = 9)	46% (n = 23)	0.044
TC	39.62% (n = 21)	38.96% (n = 30)	1
TON	50% (n = 8)	36.36% (n = 8)	0.51
Less than 1 seizure per month			
ABS	16.28% (n = 7)	27.27% (n = 15)	0.23
ATO	45% (n = 9)	35.29% (n = 6)	0.74
AUR	18.87% (n = 10)	15.49% (n = 11)	0.64
CPS	12.07% (n = 7)	16.67% (n = 12)	0.62
MYO	17.86% (n = 5)	22.22% (n = 6)	0.75
SPS	10.53% (n = 4)	8% (n = 4)	0.72
TC	37.74% (n = 20)	49.35% (n = 38)	0.21
TON	31.25% (n = 5)	40.91% (n = 9)	0.74

Seizure types and associated retrospective frequencies were obtained from the IHS for participants who reported and did not report triggers. Participants were able to select any combinations (or all) of these seizure types. This was an optional field and proportions are calculated based on the total number of participants in each seizure type sample with triggers vs no triggers from Table 2A.

and increased occurrence of seizures. Effects of single triggers in altering brain excitability are likely to be increased when stress and other triggers are combined. Specific triggers may have combined effects on neuro-excitatory and neuro-endocrine systems.

Stress was by far the most common seizure trigger in our participants. Both acute and chronic stress have been well-reported as triggers and studied as pathways to increase seizure frequency, duration, or severity [14,15]. The influence of stress on the nervous system and in increasing cortical excitability has been well documented previously. In one study, the frequency of EEG spikes often increased in PWE when exposed to acute stress [16]. Several possible effects of stress on seizures that involve endocrine, autonomic, and direct brainstem-cortical arousal mechanisms have been explored [17–19]. Elevated cortisol levels during acute stress are associated with an increase in seizure frequencies in PWE [20]. Autonomic activation may alter amygdala neuronal firing through adrenergic influences on alpha and beta adrenergic receptors, influencing seizures [21]. Using chronic isolation in rats, a study proposed the relationship between chronic stress and decreased concentrations of some neurosteroids (allopregnanolone, pregnenolone, and progesterone), increased corticosterone levels, and reduction in GABA(A) receptor function. GABA is a prominent inhibitory neurotransmitter and changes in its receptors may lead to reduced seizure threshold. Chronic stress also exacerbated the effects of acute stress and increased the concentration of neuroactive steroids in the brain by a larger magnitude compared to rats experiencing acute stress only [22]. Several studies have documented the increase in seizures during stressful life events, which could also impact sleep and medication compliance, thus further augmenting changes in seizures [23,24]. Catamenial triggers also appear linked changes in hormones, specifically to drops in progesterone in the luteal phase of the menstrual cycle [25–27].

4.1. Limitations

The study has several limitations in identifying and characterizing seizure triggers. Recall bias or amnesia caused by seizures

Table 3
Comparing participants who reported triggers with participants who did not report triggers.

	OR	95% CI	*P*-value	Adjusted *P*-value
Age	1.00	[0.98–1.03]	0.77	0.77
ASM use	2.41	[1.25–4.73]	0.0092	0.046
Relationship	1.12	[0.62–2.04]	0.71	0.77
Disability	2.51	[1.67–5.64]	0.020	0.051
Education	1.39	[0.81–2.41]	0.24	0.39

Participants who reported triggers were compared with those not reporting triggers based on age, ASM use, relationship status, disability, and education level. "Age" tested whether groups differed based on age. "ASM use" assessed differences based on taking three or more ASMs. "Relationship" evaluated the number of participants in each group who were in a relationship/not single compared to not in a relationship/single. "Disability" measured the difference in reporting disability in work status. "Education" compared the groups based on having a 4-year degree or higher versus less than a 4-year degree. Odds ratio greater than one equals an increased association between seizures with triggers and the variable. P-values were adjusted using the Benjamini-Hochberg procedure.

Table 4
Comparing seizures associated and not associated with seizure triggers.

	Trigger present (n = 650)	No trigger present (n = 1843)	OR	95% CI	*P*-value	Adjusted *P*-value
Absence	10.13%	8.3%	1.27	[0.93–1.71]	0.12	0.17
Atonic	2.31%	1.36%	1.72	[0.88–3.24]	0.10	0.16
Aura	24.15%	13.07%	2.12	[1.69–2.65]	6.4e-11	3.0e-10
Complex-partial	29.54%	22.67%	1.43	[1.17–1.75]	4.9e-4	1.1e-3
Myoclonic	6.62%	6.13%	1.08	[0.75–1.55]	0.66	0.66
Tonic	1.08%	0.65%	1.66	[0.62–4.15]	0.34	0.40
Tonic-clonic	10.15%	8.95%	1.16	[0.85–1.56]	0.29	0.37
Simple-partial	15.85%	38.88%	0.30	[0.23–0.37]	3.6e-25	5.1e-24
Lost awareness	59.69%	76.51%	0.45	[0.38–0.55]	4.6e-16	3.2e-15
Rescue medicine	13.38%	5.81%	2.51	[1.86–3.38]	1.6e-9	5.3e-9
Warning	36.92%	50.73%	0.57	[0.29–0.36]	1.9e-9	5.3e-9
Presumed focal onset	77.38%	81.23%	0.79	[0.64–0.99]	0.035	0.061
Presumed generalized onset	21.08%	16.77%	1.33	[1.06–1.66]	0.014	0.028
Unknown onset	1.54%	2.0%	0.76	[0.36–1.48]	0.45	0.49

Seizures with triggers were compared with seizures without triggers based on seizure types (Absence, Atonic, Aura, Complex-partial, Myoclonic, Tonic, Tonic-clonic, Simple-partial), loss of awareness, use of rescue medicine, presence of warning, presumed focal onset of seizures, presumed generalized onset of seizure, and unknown onset of seizures. "Lost awareness" tested whether groups differed based on concurrent reporting of loss of awareness in the post-seizure log. "Rescue medicine" assessed differences based on taking a rescue medicine following the seizure. "Warning" compared the number of seizures in each group that were preceded by a warning. Presumed focal onset include Aura, Complex-partial, Simple-partial seizures, and Tonic-clonic seizures (if participants have a history of focal seizures). Presumed generalized onset include Absence, Atonic, Myoclonic, Tonic seizures, and Tonic-clonic seizures (if participants do not have a history of focal seizures). Unknown onset includes tonic-clonic seizures for participants who did not report seizure type history or only reported tonic-clonic in the IHS. Odds ratio greater than one equals an increased association between seizures with triggers and the variable. P-values were adjusted using the Benjamini-Hochberg procedure.

could limit reporting. However, we surveyed participants immediately following their seizures and used a repeated two-stage cognitive test to determine recovery from seizures prior to obtaining surveys (ability to press a target on the Apple Watch followed by a working memory task). This minimized the effect of recall bias and may have improved screening for triggers compared to using standard seizure diaries. Some persons with tonic-clonic seizures experience prolonged recovery times, which may prevent them from completing the post-seizure logs 10 min after their seizures. Nevertheless, many participants with tonic-clonic seizures still completed post-seizure surveys after recovery. Participants were also prompted daily to complete surveys about the occurrence of their seizures, providing them additional opportunity to log seizures.

Although 40% of participants who tracked seizures and completed post-seizure logs reported triggers, it is possible that a larger proportion of participants had seizure triggers and did not report these due to lack of awareness or amnesia following seizures. The proportion of PWE reporting triggers, however, is comparable to prior studies [28,29]. Seizure triggers could also be potentially over-reported by participants looking for factors to explain the timing or occurrence of their seizures. Many triggers, however, were specific events, such as menses and episodes of sleep deprivation, and accounted for a large proportion of the reported triggers. When the data were collected, the app did not specify chronic versus acute stress and participants may list stress as their trigger if they experienced either type. However, in a previous study, participants were likely to endorse either chronic or acute stress as a trigger for seizures [14]. The study is limited in reporting results for participants due to self-selection bias and inclusion criteria (such as the possession of an iPhone and Apple Watch); the generalizability of these findings to populations outside participant eligibility criteria is undetermined. There was a slightly larger proportion of participants living in urban coastal areas than other regions. Participants, however, represented a national cross-sectional sample of PWE with broad geographical, demographic, and clinical backgrounds.

Despite these limitations, this is a first step in assessing seizure triggers in a national population of PWE using a mobile research device. Some previously reported seizure triggers, such as alcohol use, were not evaluated, partially to limit sensitive data exposure. Additional research using monitoring devices and apps may more comprehensively assess the presence and severity of triggers by assessing factors such as stress and sleep patterns during periods with and without seizures. Due to the remote, self-reported survey responses, it is difficult to validate some participant data. We were unable, for example in the national study using mobile devices, to differentiate between epileptic seizures and psychogenic nonepileptic seizures or to validate seizure types. However, self-reporting methods, especially using long-term assessments, may be helpful for PWE to identify trends related to their seizures. Self-reporting allows for data collection from a large and diverse

population of participants. Self-reports are also complementary to other health data, such as medication history, and can help provide a more complete picture of the condition of participants [30]. Monitoring seizure information such as triggers may help individuals initiate conversations with their healthcare provider or with counselors regarding stress management [31]. We identified stable trends across the broad range of participants' demographic profile.

4.2. Conclusion

Screening for seizure triggers in PWE may help individuals identify and minimize these and potentially reduce seizures. Recognizing the relationship among combined triggers and seizures suggests the potential of targeting stress and related triggers in order to reduce seizures. Especially for persons reporting stress and related triggers, relaxation methods, including yoga, may be useful in reducing seizure frequency and duration, and to improve quality of life and other comorbidities [32–34]. Practicing some yoga positions decreases levels of cortisol, reversing the effect of stress triggers [35]. Improving general health hygiene with sleep and diet practices may mitigate other triggers. Progressive relaxation therapy, a practice of consciously contracting and relaxing muscles, has shown promise to reduce seizure frequency [36]. These types of behavioral changes are non-invasive and affordable interventions to help PWE potentially reduce triggered seizures. As mobile health continues to increase in popularity, further review of data will be useful in dissemination of educational materials and improvement of the current study.

5. Data availability

The data analyzed during the study are available upon request to the corresponding author.

6. Code availability

The code used for statistical analysis is available upon request to the corresponding author.

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