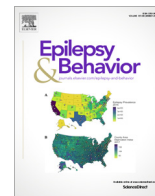




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Review

Prevalence of depression, anxiety, and psychological distress in patients with epilepsy during COVID-19: A systematic review



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ABSTRACT

Objective: COVID-19 pandemic disease has profound consequences for physical and mental health. In this regard, health care for chronic diseases, especially epilepsy is neglected. The purpose of this systematic review study was to investigate the epidemic effect of COVID-19 on increasing the prevalence of mental disorders such as depression, anxiety, and sleep disorders in people with epilepsy (PWE).

Methods: We systematically searched MEDLINE, Cochrane, Embase, Web of science, Scopus, and Psych info databases for studies that estimate the prevalence of mental disorders in PWE during the COVID-19 until December 2020. Inclusion criteria included samples of population, with a confirmed diagnosis of epilepsy.

Results: Irrespective of PWE or people without epilepsy (PWOE), all experienced stress and anxiety during COVID-19 pandemic. Most of the studies showed that PWE and even PWOE during the pandemic, suffer from depression. The highest rate of depression was attributed to female PWE with financial problems (66.7%) and the lowest rate of depression in PWE was reported in 8.6%. 7.1–71.2% and 28.2% of patients reported sleep disorders and insomnia, respectively. Less than 2% experienced a sleep improvement.

Limitations: Due to a large amount of heterogeneities across the results, we could not evaluate the exact rate of prevalence in spite of using effective measures.

Conclusions: People with epilepsy were considered as a susceptible group to the impact of the pandemic. Therefore, great attention should be paid to PWE and adequate psychological supports provided in this period to relieve or inhibit risks to mental health in PWE.

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1. Introduction

The advent of SARS-CoV-2 (COVID-19) pandemic in December 2019 has led to unprecedented changes in our lives, with profound consequences for physical and mental well-being [1]. The spread of COVID-19 quickly reached pandemic proportions and severely affected the health systems of several countries [2]. According to the WHO Situation Report published on March 3, 2021, there are >114,315,846 confirmed COVID-19 cases and >2,539,427 death tolls globally [3]. The pandemic has forced governments to crack

down on people, including forced house arrests, in order to curb the spread of the infection. The coronavirus crisis, quarantine, isolation leading to feelings of loneliness, boredom, anger, and anxiety threaten public mental health [4]. In this regard, extensive research on mental health has shown that emotional distress is present in affected populations everywhere – a finding that should be replicated in COVID-19 pandemic-affected populations [5].

Epilepsy is a chronic neurological disease that has affected more than 50 million people worldwide. In addition to the physical problems caused by epilepsy, this disease has also other significant neurological, cognitive, and psychosocial consequences [6]. In today's society, depressive disorders and anxiety are among the most mental disorders [7]. Meanwhile, insomnia, a common sleep complaint, may trigger epileptic seizures. Insomnia also affects the control of epileptic seizures; alongside, assessing insomnia is an important

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element in delivering comprehensive epilepsy care [8]. According to the reports, it is believed that 9.4% of people in the target population suffer from anxiety disorder; 8.2% of them show the symptoms of depressive disorder at every 12-month interval. In addition, population-based research on people with epilepsy (PWE) shows that concurrent depressive disorders and anxiety are more prevalent in PWE than in the general population [7]. Stress plays a major role in the recurrence of epileptic seizures. Also, it is a commonly reported factor for seizure recurrence [9]. Today, there is no doubt that stress associated with health concerns, limited access to health care, and lifestyle changes due to confinement at home and remote work can potentially contribute to seizures and the overall well-being of PWE [2]. Meanwhile, the prevalence of anxiety in PWE is 20.2% higher than that of patients with drug-resistant epilepsy [10].

Regarding PWE, COVID-19 pandemic has led to delays in outpatient visits, cancellation of epilepsy tests such as electroencephalogram (EEG) test and magnetic resonance imaging (MRI), and even problems in emergency attendance [4]. With respect to the mental health of PWE during COVID-19, there has been scant evidence so far that COVID-19 can directly affect seizures; however, there is evidence that the COVID-19 pandemic has led to increased psychological distress among PWE [11].

Research shows that PWE are at a higher risk of depression and anxiety than healthy controls and patients with other illnesses. Also, depression and anxiety have a significantly negative impact on the quality of life of PWE [12]. To this end and given the potential negative effect of COVID-19 on PWE, we set out the present systematic review to investigate the effect of COVID-19 pandemic on the prevalence of mental disorders, namely depression, anxiety, and sleep disorders among PWE.

2. Methods

2.1. Data sources and search strategy

The present systematic review was conducted according to the PRISMA guidelines, and registered with PROSPERO (International Prospective Register of Systematic Reviews) under No: CRD42021244383 [13]. We initially performed a systematic search in Cochrane, PubMed, Embase, Web of Science, Scopus, and Psych info. In the next step, we included all relevant studies published between December 29, 2019 and December 31, 2020. Also, we searched the reference lists of the selected studies. A detailed search strategy including keywords is presented in the [Supporting Information](#) section ([Supporting Appendix 1](#)). Also, we combined the search term 'COVID-19' with a term related to psychological indicators and epilepsy.

2.2. Eligibility criteria

In this study, we included only papers reported in English. Also, we included samples of children and adolescents with a confirmed diagnosis of epilepsy. In addition, both cross-sectional and observational studies aiming to assess the effects of COVID-19 on psychological indicators among PWE were considered eligible. With respect to exclusion criteria, we excluded letters to editors, review articles, conference abstracts, case reports, and animal studies. Meanwhile, studies that did not investigate the diagnosis of anxiety or depressive disorders or stress in PWE during the COVID19 pandemic were excluded. Also, we excluded studies whose population was not based on epilepsy, or their results have not been obtained during the pandemic. One of the authors (MT) of this study screened titles and abstracts of identified references; full texts of eligible studies were then independently retrieved and

reviewed by two authors (MT and ZB). The viewpoints of a third reviewer were also used in cases of disagreement.

2.3. Data extraction

Data extraction was conducted and documented independently by two reviewers (MT and ZB). We used a data extraction form to collect data on the setting, population, sample size, data source, study design, gender, depression assessment, anxiety assessment, psychological distress assessment, epilepsy diagnosis, number of disorders, and findings.

2.4. Quality assessment

The Joanna Briggs Institute (JBI) Prevalence Critical Appraisal tool was used to assess the methodological quality of the included studies [14]. Two authors of the present study (ZB and MT) independently conducted the assessment of the risk of bias. Disagreements were solved first by discussion, and then by consulting a third reviewer, if disagreements persisted. Finally, the entire body of studies was summarized descriptively. Also, we performed a qualitative synthesis of results.

3. Results

3.1. Included studies

After a meticulous search across databases, we were able to initially find 347 studies. In the next step, we removed duplicated articles, and then came up with 154 studies. Based on the exclusion/inclusion criteria, we evaluated the titles and abstracts of these 154 studies, and were able to select 33 papers. In the next step, we reviewed these 33 articles and excluded 17 studies; details with regard to why these 17 studies have been excluded are given in PRISMA flow diagram (see [Fig. 1](#)). Finally, we came to the conclusion that only 16 studies met the inclusion/exclusion criteria, and thus were selected as the final included studies in this systematic review. The outcomes of search processes and the selection of the various sources are also presented in [Fig. 1](#).

3.2. Data extraction

16 studies examined the effect of the COVID-19 on anxiety, depression, stress, and sleep disorder based on questionnaires developed for PWE and/or their caregivers. The data extracted from these studies are summarized in [Table 1](#). These 16 studies were conducted in nine countries/regions, namely Italy: 5, China: 2, United Kingdom: 1, Belgium:1, Iran:1, Spain:2, Saudi Arabia:1, United States:2, and Lithuania:1. In all of the 16 studies, both genders participated; however, the female participants were more than those of male [6,15]; therefore, the results of this study cannot be generalized to the whole community.

3.3. Risk of bias within studies

Due to the fact that all qualified studies used surveys, we decided to use the Joanna Briggs Institute Critical Appraisal tool for studies that reported the prevalence and incidence of data [16,17]. In 43% of the studies, the sample was representative of the target population. Considering the fact that most of the participants were women, this result cannot be generalized to the general population. Also, 75% of the studies reported a suitable sample size. In addition, only 37.5% of the study subjects and the settings were described in detail. 68.75% of the data analysis were also conducted with sufficient coverage of the identified sample.

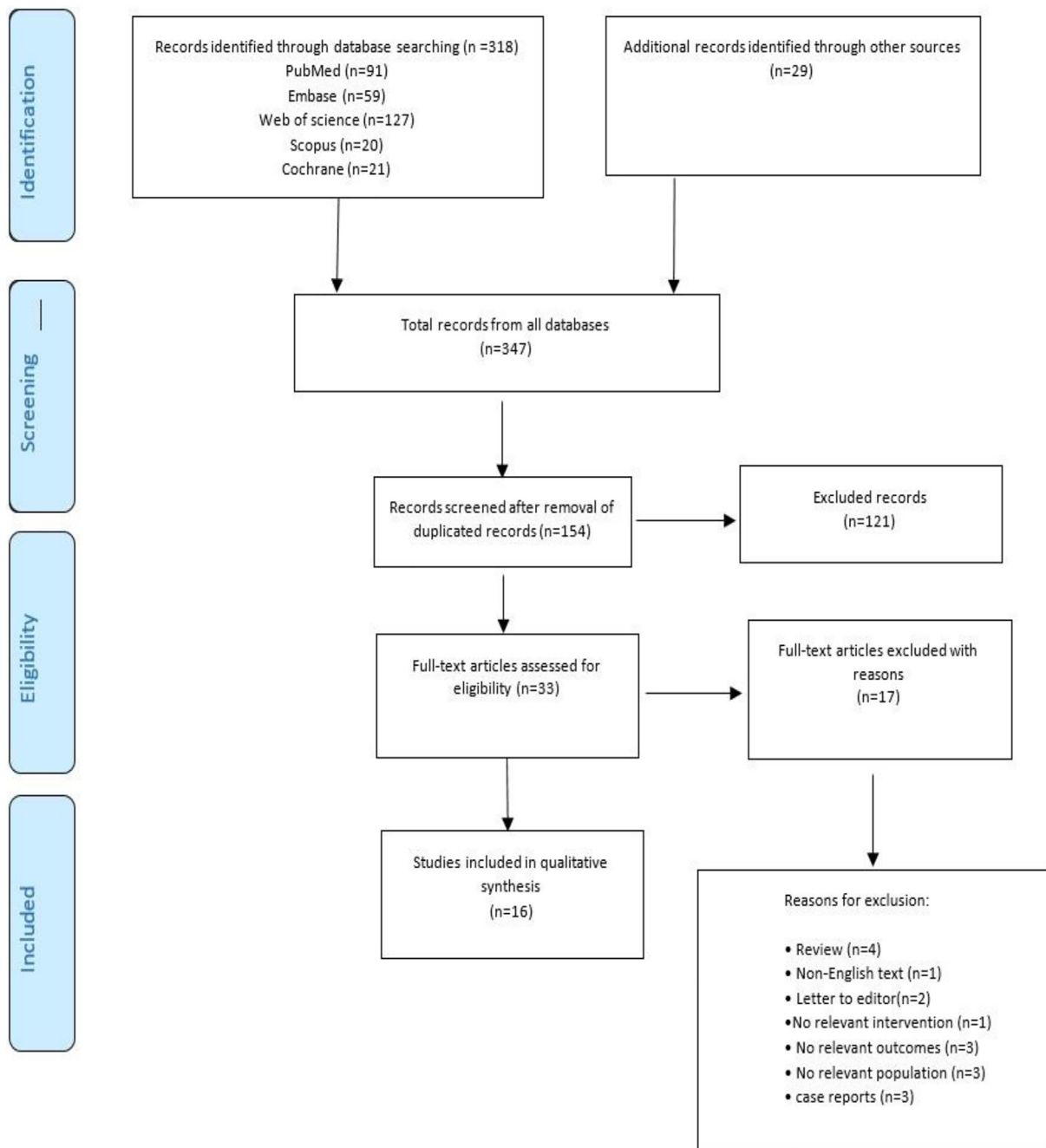


Fig. 1. PRISMA flow diagram for study selection. Population: patients with epilepsy; Intervention: COVID-19 pandemic; Comparison: Period before COVID-19; Outcomes: Stress, depression, anxiety, and insomnia.

Meanwhile, 68.75% of studies had appropriate statistical analysis, and 25% of them were objective, for which standard criteria were used for the measurement of the condition (Table 2).

3.4. Psychiatric assessment

Anxiety, depression, stress, and sleep disorder were considered and measured using various methods.

3.5. The effect of COVID-19 pandemic on the depression of people with epilepsy

In seven studies, depression was measured via polarization score [18], such as Beck depression inventory scale II (BDI-II)

[19], 9-item Patient Health Questionnaire (PHQ-9) [6,15], Hospital Anxiety and Depression Scale (HADS) [6,20], a 19-item questionnaire [4], and a survey [21]. We used the PHQ-9 scale to measure the symptoms of depression. Also, we applied a threshold level of 10 points to diagnose depression severity. The adequate sensitivity and specificity PHQ-9 scale are 88.0% and 88.0%, respectively [22].

Results of one of the reviewed articles in this study showed that PWE (19%) and people without epilepsy (PWOE) (17%) have psychiatric disorders such as depression. Both groups (8%) received anti-depressant drugs at the moment of the survey. Also, results revealed that PWE showed more severe depressive symptoms (3.8%) (higher BDI-II scores) than PWOE [19].

Table 1
Features of the online questionnaires.

First author (publish year)/country	Sample size/ number of disorder/gender	Data source	Study design	Assessment of depression/ anxiety/psychological distress/sleep disorder	Epilepsy diagnosis/ prevalence	Significant predictors in multivariate analysis	Findings
Amal Alkhotani (2020)/Saudi Arabia	156/156/Female n = 97(62%) Male n = 59 (38%)	An electronic self-administered questionnaire was distributed to PWE via their treating neurologist.	Cross-sectional	Self-report/an electronic self-administered questionnaire (self-reported stress/self-reported stress/disturbed sleep	Self-report/NR	59.4% of PWE self-reported a significant increase in stress, 71.2% of PWE experienced a significant change in their sleep. Anxiety (15.4%) increased, depression (7.1%) increased significantly.	Patients with uncontrolled epilepsy, sleep disorders, and self-reported stress who were also unable to take medication were more likely to have seizures during the epidemic.
Jacopo Lanzone (2020)/Italy	879/427/Female n = 327 77% Male n = 100 23%	The survey was spread by the efforts of LICE [Lega Italiana Contro l'Epilessia, the Italian chapter of the International League Against Epilepsy (ILAE)] Foundation and included clinical data and psychometric scales.	Case control	Polarization score/Survey NLP methods/NR/	Self-report/NR	Distribution between group (significant) increased frequency in the occurrence of words with positive "Affin" score in the PWE group compared to the PWOE (X ² = 5.3953, df = 1, p = 0.045, PWE = 10.2%, 29/282; PWOE = 5.2%, 17/323). Mean polarization value of - 1.28 in PWE and - 1.39 in PWOE (not significant)	During the lockdown, PWOE increased reactive stress responses to the restrictions, PWE, instead, appeared to internalize more the damage of lockdown. Interestingly, PWE also reported positive feelings about the restrictions more frequently than PWOE.
Giovanni Assenza (2020)/Italy	928/456/Female n = 344 (78%) Male n = 112 (22%)	An online survey was created using the free open-access Google TM Forms (https://www.google.com/forms/about/) application.	Case control	BDI-II/GAD-7/NR/PSQI for sleep	Survey/NR	Anxiety: 39.5% had normal, 28.9% had mild, 21.3% had moderate, and 10.3% had severe (not significant). PSQI scale scores did not differ between PWE and PWOE depressive: (65.1%) had normal, 15.1% had mild, 11.6% had moderate, 8.1% had severe depressive (not significant).	During the pandemic, many patients had increased number of seizures and had difficulty following-up, especially patients with chronic ASM and poor sleep quality.
Stijn Van Hees (2020)/Belgium	399/399/Female n = 320 80.2% Male n = 79 19.8%	Online questionnaire surveys were developed in Belgium, English, Dutch, French, and Portuguese.	Cross-sectional	PHQ-9 and HADS/PHQ-9 and HADS/NR/NR	Follow-up consultation with the treating physician or visit via telephone or online consult./YES	50.4% of cases showed positive anxiety according to the HADS; also, 39.8% and 46.9% PWE showed positive symptoms for depression via the HADS and PHQ-9 scale, respectively. Female and thus PWE with financial problems experience depression and anxiety.	Patients were faced with problems accessing ASM during the pandemic. 50% of the patients had been measured positive for depression. They showed less positive symptoms of anxiety. Also, almost 50% of the respondents cancelled their follow-up consultation with the physicians.
Corrado Cabona (2020)/Italy	189/189/Female N = 103 (55%) Male N = 86 (45%)	Three Italian Epilepsy Centers set up telephone consultations using a semi-structured interview, allowing collection of data on seizure course during the pandemic.	Cohort	NR/numeric rating scale/NR	Follow-up visit via telephone/NR	Median score for COVID-19 concern was 6 (IQR: 3-8) (not significant).	Telephone counseling was set up using a semi-structured interview with the aim of managing seizures and treating AED.

Table 1 (continued)

First author (publish year)/country	Sample size/ number of disorder/gender	Data source	Study design	Assessment of depression/ anxiety/psychological distress/sleep disorder	Epilepsy diagnosis/ prevalence	Significant predictors in multivariate analysis	Findings
Mehri Salari (2020)/Iran	900/141/Female n = 78 (55.40%) Male n = 63 (44.6%)	The online questionnaire with two referrals at Shahid Beheshti and Isfahan Universities of Medical Sciences.	Cross-sectional and case-control survey	NR/(BAI-II)/NR/NR	Participants before entering the survey by telephone call/NR	The mean BAI-II total score between patient (11.82 ± 9.71) and control (10.28 ± 8.98) (no significant). 13.5% of patients and 6.9% of controls have experienced severe level of anxiety (significant).	The total level of anxiety in PWE did not increase compared with the general population. Anxiety in men of younger ages was significantly higher in the control group. There was no correlation between anxiety, age, and gender in the patient group.
Elena Fonseca (2020)/Spain	255/255/Female N = 121 (47.5%) Male N = 134 (52.5%)	The Vall d' Hebron Research Institute Clinical Research Ethics Committee and a neurologist administered a 19-item questionnaire to all participants.	Cross-sectional	Routine clinical telephone visits with a neurologist and a 19-item questionnaire were systematically completed/routine clinical telephone visits with a neurologist and 19-item questionnaire were systematically completed/No/ questionnaire	Medical records/NR	Sixty-eight (26.7%) patients reported confinement-related anxiety, 22 (8.6%) depression, 31 (12.2%) both, and 72 (28.2%) insomnia. (significant).	A significant number of patients experienced an increase in the frequency of seizures, and many of them reported anxiety, depressive symptoms, and insomnia. It was found that insomnia and decreased economic status are risk factors for increasing the frequency of tumor-related seizures and drug-resistant epilepsy.
Alfonso Giordano (2020)/Italy	40/40/Female N = 32 (80%) Male N = 8 (80%)	Outpatient epilepsy clinic of the First Division of Neurology at the University of Campania "Luigi Vanvitelli" (Naples, Italy).	Cohort	Hospital Anxiety and Depression Scale (HADS)/Hospital Anxiety and Depression Scale (HADS)/Scale-Revised (IES-R)/sleep disturbances were measured by Insomnia Severity Scale (ISI)	Outpatient clinic during the pre-lockdown period medical records/NR	Anxiety sub-score (8.7%) increased. Depression sub-score (4.7%) increased. Insomnia Severity Index (7.0%) increased (significant).	A stressful event such as the outbreak of COVID-19 could adversely affect the course of epilepsy.
Xiaoting Hao (2020)/China	504/252/Female N = 132 (52.3%) Male N = 120 (47.6%)	Electronic clinical records in Epilepsy Center in West China Hospital.	Cross-sectional and case-control	NR/NR/K-6 scale/NR	Diagnosed with epilepsy at least 1 year before, and they had to be followed up monthly by an epilepsy specialist and they self-reported seizures within 48 hours before completing the questionnaires/NR	Severe psychological distress (defined as K-6 score > 12; both P ≤ 0.001). 1.6% of the control group and 13.1% of PWE reported severe psychological distress (p < 0.001) (significant).	During an outbreak, public health, physicians, and caregivers should focus not only on seizure control but also on the mental health of patients with epilepsy, especially drug-resistant patients with epilepsy.

(continued on next page)

Table 1 (continued)

First author (publish year)/country	Sample size/ number of disorder/gender	Data source	Study design	Assessment of depression/ anxiety/psychological distress/sleep disorder	Epilepsy diagnosis/ prevalence	Significant predictors in multivariate analysis	Findings
Colin Reilly (2021)/UK	201/Female PWE: 61 (86%) caregiver: 64 Male PWE: 10 (14%) caregiver: 66	An anonymous online survey hosted on Survey Monkey.	Cross-sectional	NR/online survey/online survey/online survey	Self-reports/NR	The majority of young people had poor sleep (72 %) and bad mood (64 %).	The pandemic and associated restrictions have had a negative effect on young PWE. Increases in seizures and reluctance to go to hospital is likely to affect epilepsy handling.
Barbara Mostacci (2020)/Italy	222/222 Female N = 128 (57.64%) Male: N = 94 (42.23%)	Epilepsy Center clinicians and telephone survey.	Cross-sectional	NR/NR/NR/questionnaire for sleep disorder	Self-reported/YES	23.9% of PWE reported sleep changes. 8.5% reported various degrees of disturbed sleep, 11.3% a change of sleep pattern, and 1.8% of them an improvement in sleep.	Most PWE did not report a significant alteration in their clinical conditions during the COVID-19. However, the severity of epilepsy, attendant disability, comorbid psychiatric conditions, sleep disorders, and limited availability to healthcare may impact their health condition.
Shanshan Huang/ (2020)/China	362/362/ Female N = 166 (45.86%) Male N = 196 (54.14%)	Via online questionnaires in Wuhan, and its surrounding cities.	Cross-sectional	PHQ-9 scale/GAD-7 scale/ Patient health questionnaire to identify insomnia and sleep disorders: Insomnia Severity Index (ISI)	Questionnaire/NR	Depression among PWE and PWOE increased; number of seizures was 22.58% versus 12.08%, respectively (significant). Anxiety among patients with or without an increased number of seizures was 19.35% versus 8.46% (not significant). Among patients with or without an increased number of seizures 25.81% versus 19.03% (not significant).	A small proportion of PWE experienced seizure exacerbations during the COVID-19 outbreaks. Stress is an independent factor in causing seizures.
Wendy R. Miller/ (2020)/USA	94/74/Female N = 47 (50%) Male N = 47 (50%)	A questionnaire including 65 questions, shared via social media like Facebook pages & Twitter, and also via the link embedded in the online advertisement. (hashtags: #COVID-19, #epilepsy, #pandemic, and #research).	Cross-sectional and descriptive study	NR/PROMIS anxiety scale/NR	Medical records/NR	Through using the PROMIS anxiety scale, it was asked to rate how they were coping with the current pandemic on a scale of 0–10, with 0 being not at all and 10 being very well, the mean score was 7.08 (SD: 1.89; range: 0–10) (significant).	During the pandemic, patients' medical needs were not met; in some cases, it also increased.
Kristijonas Puteikis/ (2020)/ Lithuania	143/143/ Female N = 84 (58.7%) Male N = 59 (41.3%)	A questionnaire in Lithuanian was designed to gather information about the clinical characteristics of PWE, their health changes and altered the use of healthcare services during a national lockdown.	Cross-sectional	NR/GAD-7/survey/survey	Questionnaire/NR	The majority of young people and caregivers expressed that the young person's mood (PWE: 64%; caregiver: 61%) and sleep (PWE: 72%; caregiver: 56%) had worsened since COVID-19 lockdown (significant).	Quarantine during the pandemic may lead to worsening seizure control and health status in some PWE.

Table 1 (continued)

First author (publish year)/country	Sample size/ number of disorder/gender	Data source	Study design	Assessment of depression/ anxiety/psychological distress/sleep disorder	Epilepsy diagnosis/ prevalence	Significant predictors in multivariate analysis	Findings
Jillian L. Rosengard/ (2020)/USA	177/177 Female N = 120 (67.8%) Male N = 57 (32.2%)	The questionnaire was created by neurologists in the Montefiore Health System.	Cross-sectional and cohort	NR/survey	Medical records/YES	Subjects with poorer seizure control were more likely to express increased or worsened stress (80.6% versus 50.0%, $P = 0.002$) (significant). Worse sleep increased in those PWE who reported no change or improved seizure control and those who reported worsened seizure control were 41.8% and 48.4% respectively (no significant).	The poor access to care and difficulty in receiving anticonvulsant medication are important factors in inducing stress. Many patients reported stress as the main factor in recurrent seizures.
Alvaro Sanchez-Larsen/(2020)/ Spain	100/100/Female N = 52 (52%) Male N = 48 (48%)	In an epilepsy outpatient clinic of a tertiary center in Albacete University General Hospital in the province of Albacete (Castilla-La Mancha, Spain).	Observational and retrospective study based on prospective data collection	Survey/survey/survey/survey	Patients who attended an epilepsy outpatient clinic either face-to-face or via phone during the months of the COVID-19 outbreak and national state of emergency/NR	Exacerbation of stress/anxiety (21 [77.8%] vs 21 [28.8%], OR: 8.67, 95% CI: 3.07–24.50; $p < 0.001$), sadness/depression (15 [55.6%] vs 20 [27.4%], OR: 3.31, 95% CI: 1.32–8.29; $p = 0.01$), sleep deprivation (16 [59.3%] vs 15 [20.5%], OR: 5.62, 95% CI: 2.16–14.61; $p < 0.001$) (significant).	Anxiety and stress due to the confinement were reported as the most important factors in changing the frequency of seizures. Also, seizure control of the patients worsened during the pandemic.

Note: PHQ-9: 9-item of Patient Health Questionnaire (PHQ-9); NLP methods: Natural Language Processing methods; HADS: Hospital Anxiety and Depression Scale; BAI-II: Beck Anxiety Inventory II-Persian; GAD7: General Anxiety Disorder-7; IES-R: Impact of Event Scale-Revised; ISI: Insomnia Severity Index; BDI- II: Beck Depression Inventory scale II; PSQI: Pittsburg Sleep Quality Index; K-6 scale: 6-item Kessler Psychological Distress scale; PWE: People With Epilepsy; PWOE: People Without Epilepsy; NR: Not Reported.

Table 2
Risk of bias assessment (Joanna Briggs Institute Critical Appraisal tool) for prevalence studies.

First author/year	1	2	3	4	5	6	7	8	9	10
Amal Alkhotani/2020	Y	Y	Y	N	Y	Y	NA	Y	N	Y
Giovanni Assenza/2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Corrado Cabona/2020	Y	Y	Y	N	N	Y	NA	N	NA	Y
Elena Fonseca/2020	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Alfonso Giordano/2020	N	Y	N	N	N	Y	Y	N	N	Y
Xiaoting Hao/2020	Y	Y	Y	Y	N	Y	Y	N	NA	Y
Shanshan Huang/2020	N	Y	Y	N	Y	Y	Y	Y	Y	Y
Wendy R. Miller/2020	N	Y	Y	N	N	Y	Y	N	UC	Y
Kristijonas Puteikis/2020	N	Y	Y	N	Y	Y	Y	Y	UC	Y
Jillian L. Rosengard/2020	N	Y	N	N	Y	Y	Y	UC	UC	Y
Alvaro Larsen/2020	N	Y	N	N	Y	Y	Y	Y	UC	Y
Shanshan Huang/2020	N	Y	Y	N	Y	Y	N	Y	N	Y
Barbara Mostacci/2020	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Mehri Salari/2020	N	Y	N	Y	N	Y	Y	Y	Y	Y
Stijn Van Hees/2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Jacopo Lanzone/2020	N	Y	Y	N	Y	Y	N	Y	N	Y
The percentage of "yes" scores	43.75%	100%	75%	37.5%	68.75%	100%	75 %	68.75%	25%	100%

- 1: Was the sample representative of the target population?
 - 2: Were study participants recruited in an appropriate way?
 - 3: Was the sample size adequate?
 - 4: Were the study subjects and the setting described in detail?
 - 5: Was the data analysis conducted with sufficient coverage of the identified sample?
 - 6: Were objective and standard criteria used for the measurement of the condition?
 - 7: Was the condition measured reliably?
 - 8: Was there appropriate statistical analysis?
 - 9: Are all important confounding factors/sub-groups/differences identified and accounted for?
 - 10: Were sub-populations identified using objective criteria?
- Y: yes, N: NO, UC: unclear, NA: Not applicable.

Van Hees et al.'s study indicated that out of the 399 PWE, 159 (39.8%) and 187 (46.9%) PWE showed symptoms of depression measured by the HADS and PHQ-9 scales, respectively. They also claimed that women are more sensitive than men, so are more prone to psychiatric disorders. Meanwhile, their results showed that out of the 66 female PWE with financial problems, 44 cases (66.7%) suffered from depression [6]. In Huang et al.'s study (2020), depression was measured using PHQ-9. Results revealed that the worsening of depression among PWE and PWOE was associated with increasing the number of seizures (22.58% vs 12.08%, respectively) [15]. In addition, Sanchez-Larsenet al.'s study showed that depression in 8.6% of subjects appeared with lockdown-related symptoms [4]. In this regard, Sanchez-Larsen et al. claimed that depression was exacerbated in PWE [21].

3.6. The effect of COVID-19 pandemic on the stress of people with epilepsy

Seven studies evaluated stress through administering Impact of Event Scale-Revised (IES-R) [20], K6 scores [23], questionnaires [11,15,24], self-report [9], and Likert scale [25]. IES-R is one of the commonly used self-report tools within the trauma literature [26]. It has three subscales, namely (1) tapping intrusion like repeated thoughts about the occurrence, (2) avoidance like effortful attempts not to think about the occurrence, and (3) hyper arousal like anger, irritability, hypervigilance, and difficulty in concentrating measures related to the traumatic event [26]. According to the results of Giordano et al.'s study, higher scores on the IES-R intrusion subscale can be attributed to age, gender, and higher scores on the HADS. Meanwhile, higher scores on HADS could be related to higher scores on IES-R Hyperarousal subscales. Also, results revealed that higher scores on the IES-R Avoidance scale were associated with the higher age and higher scores on the HADS subscale. This result further suggests that there is a direct correlation between anxiety and stress levels [20].

Hao et al. measured psychological distress based on K-6 scores. They claimed that K-6 scores >12 indicated severe psy-

chological distress. Results of their study revealed a significantly higher level of psychological distress among PWE compared to that of the control group. Also, results showed that 13.1% of PWE and 1.6% of the control group reported severe psychological distress ($p < 0.001$). Confinement-related anxiety and depression symptoms were reported by 68 (26.7%) and 31 patients (12.2%). The PWE, who submitted their answers online, experienced a higher level of stress and anxiety ($p < 0.0001$) accompanied by worse mental health condition during the COVID-19 lockdown ($p = 0.015$). Also, PWE who had changes in the use of AED one month before or during the lockdown expressed greater stress and GAD7scores [23].

Nearly 20% of subjects who reported worsened seizure control during the peak of COVID-19 showed more severe epilepsy and seizures accelerated by stress. The increased stress, associated with the pandemic, was directly correlated with the increased seizures in some PWE. 19.61% of patients reported moderate-to-critical concerns about the adverse effect of the pandemic on issues related to epilepsy. Also, 24.03% of patients expressed moderate-to-critical concerns about sudden seizures during the pandemic; alongside, 41.16% and 48.62% of patients worried about the loss of professional counselors and drug supply, respectively [15].

Rosengard et al. indicated that stress is the most important typical seizure trigger. They reported that patients with worsening seizure control showed more stress than patients with no change or improved seizure control (54.8% versus 26.0%, $P = 002$) [24]. Rosengard et al.'s study reported that stress level due to the COVID-19 pandemic was increased/worsened to 50% in those PWE who have no change or improved seizure control, and to 80.6% in those PWE who have worsened seizure control [24]. Therefore, based on the results of Rosengard et al., seizure control in patients during the COVID-19 pandemic can be effective in reducing the stress caused by COVID-19 [24]. Alongside, results of the Alkhotani et al.'s study indicated that a total of 59.4% of PWE reported a rise in self-reported stress during the COVID-19 lockdown [9].

3.7. The effect of COVID-19 pandemic on the anxiety of people with epilepsy

14 studies in this systematic review measured the level of anxiety in patients with epilepsy through collecting information from questionnaires [4,9,11,19,21,24], behavioral scores such as promise anxiety scale [27], PHQ9 [6], GAD7 [15,19,25], HASD [6,20], and BAI-II [10]. The GAD-7 scale was applied to determine clinically important anxiety symptoms [22]. Results of the studies show that the level of anxiety increased in both PWE and PWOE; however, the rate of increase in anxiety is much more evident in PWE. In Assenza et al.'s study, 92 cases (28.9%) of PWE experienced mild anxiety symptoms, 162 (21.3%) reported moderate symptoms, and 47 (10.3%) had severe anxiety symptoms. With respect to PWOE, 128 cases (32.4%) reported mild anxiety symptoms, 142 (12.9%) and 34 (7.2%) reported moderate anxiety and severe anxiety symptoms, respectively [19]. Also, results revealed that PWE had higher anxiety symptoms than PWOE (higher GAD-7 scores; 8 ± 5.3 and 6.8 ± 4.9 , respectively; $p < 0.001$). In addition, 44 PWE and 32 PWOE reported that they received new psychotropic drugs such as anxiolytics for depression and anxiety since the beginning of COVID-19 lockdown. However, no significant difference was observed with respect to GAD-7 values among responders from Italian region [19], GAD-7 scale was also used in Huang et al.'s study whose results showed that anxiety was observed among patients with or without an increased number of seizures, 19.35% and 8.46%, respectively. They observed no meaningful difference with respect to psychological reactions shown between the groups with and without seizure exacerbation [15].

Meanwhile, Fonseca et al.'s study found that confinement-related anxiety was reported by 68 patients (26.7%); alongside, 31 patients (12.2%) showed symptoms of both depression and anxiety from the onset of quarantine [4]. Using the PROMIS anxiety scale in their study, Miller et al. reported that respondents showed a statistically significant higher level of post-pandemic anxiety compared to that of pre-pandemic [27]. Similar to the results of the Miller et al.'s study, Puteikis et al. found that PWE had a higher level of stress and anxiety ($p < 0.0001$), and reported worse mental health conditions ($p = 0.015$) during the quarantine [25]. In Reilly et al.'s study, caregivers reported that the level of stress (55%) and anxiety (52%) increased among young PWE during the COVID-19 lockdown [11]. According to the results of the HADS scale, out of the 399 PWE, 201 (50.4%) were screened positive with respect to anxiety [6].

Based on the total BAI-II score in Salari et al.'s study, a meaningful difference was observed between the control and patient groups on severe levels of anxiety (13.5% of patients versus 6.9% of controls). However, at a lower level of anxiety (45.4% versus 48.7%), no difference was observed. Results of Salari et al.'s study showed that men of younger ages experienced significantly higher levels of anxiety in the control group; however, no correlation was found among anxiety, age, and gender in the patient group. Also, no correlation was observed among anxiety level, epilepsy duration, and epilepsy type [10].

Results of Lanzone et al.'s study revealed that during the COVID-19 pandemic, the PWOE have been continually over reporting several terms showing anxiety (words such as *prison*, *distance*, *loneliness*, *anguish*, *stress*, and *change*) as a reactive response to the stress they experienced under lockdown. Also, Lanzone et al. argue that one of the main reasons for PWOE' anxiety is being worried about practical issues and restrictions of lockdown. Meanwhile, words such as *fear*, *boredom*, *sadness*, and *apathy* have been reported frequently. Results of Lanzone et al.'s study showed that PWE feel restricted and anxious during the lockdown. Also, they were worried about their disease that would subsequently lead to developing depressive symptoms [18].

Sanchez-Larsen et al. conducted their study with 100 patients (52% women with an average age of 42.4). An increase of more than 50% in the frequency of seizures was observed in 27% of the patients. Increased stress/anxiety (odds ratios (OR): 5.78; $p = 0.008$) and a higher seizure frequency (OR: 12.4; $p = 0.001$) were associated with worsening of the seizures. Also, seizure control was improved in 9% of patients. Reducing stress/anxiety (OR: 0.05; $p = 0.03$) and using recent adjustment of antiepileptic drugs as protecting agents (OR: 0.07; $p = 0.01$) was effective. The risk factors (increases in depression, sleep disorder, less physical activity, and history of epilepsy operation) were statistically accompanying an important deterioration in seizure control: exacerbation of stress/anxiety (77.8% vs 28.8%, OR: 8.67, 95% CI: 3.07–24.50; $p < 0.001$), sadness/depression (55.6% vs 27.4%, OR: 3.31, 95% CI: 1.32–8.29; $p = 0.01$) [21].

3.8. The effect of COVID-19 pandemic on the sleep disorders of people with epilepsy

Ten studies that reviewed sleep disorders, [2,4,9,11,15,19,20,24,25], have shown that PWE experienced sleep disorders during the COVID-19. Out of these 10 studies, six studies were cross-sectional in which sleep disorders and insomnia were reported 7.1–71.2% [4,9] and 28.2%, respectively [4]. Giordano et al. measured sleep disturbances through Insomnia Severity Scale (ISI). Their study reported a figure of 7% for sleep disorders [20]; however, Assenza et al.'s study showed that there was no meaningful difference in the sleep quality between PWE and healthy individuals (PWOE). Also, PWE's and PWOE's scores in PSQI scale were reported 6.8 ± 3.7 (46.9%) and 6.6 ± 3.8 (42.4%), respectively ($p = 0.3117$) [19]. Also, results of Reilly et al.'s study showed that insomnia measured through ISI among patients with or without an increased number of seizures was 25.81% versus 19.03%. Reilly et al. observed no significant difference with respect to sleep responses between the groups with and without a seizure [11]. Meanwhile, Rosengard et al.'s study found that sleep quality decreased due to the COVID-19 pandemic among those PWE who reported no change or improved seizure control (41.8%) as well as those PWE who reported worsened seizure control (48.4%) [24]. However, no significant difference was observed in the rates of worsened sleep across groups during this three-month period [24].

The majority of young people and caregivers expressed that their mood (PWE: 64%; caregiver: 61%) and sleep (PWE: 72%; caregiver: 56%) have worsened during the COVID-19 lockdown. Additionally, the majority of caregivers reported increased anxiety, stress, and sleep disorder as a result of the pandemic [25]. Also, results of Masaccio et al.'s study indicated that 1.8% of patients have experienced a kind of improvement in sleep; however, 23.9% of the cases reported fluctuations in sleep, 8.5% of them reported disturbed sleep, and 11.3% mentioned changes in their sleep patterns [2].

4. Discussion

In the present systematic review, we investigated the prevalence of psychological effects of COVID-19 pandemic, namely depression, stress, anxiety, and sleep disorders among PWE; we also assessed the relationship among these psychological symptoms during the pandemic. Findings of our systematic review revealed that PWE experienced a dramatic increase in the severity of mental problems. It is believed that COVID-19 pandemic has led to increased mental health problems as a result of death tolls, high level of infection, and rapid distribution among populations. Meanwhile, it has been reported that stress is more prevalent during the

pandemic [28]. Alongside, recent studies have demonstrated that following the pandemic, anxiety and depression widely increased that is ultimately accompanied by sleep disorders in the general population [28]. In this respect, patients with epilepsy are at considerable risk to the psychosocial impact of the pandemic [29].

Diverse factors may involve in the high prevalence of psychological distress in PWE during the COVID-19 pandemic such as social separation and aloneness [30]. Putting restrictions in order to control the pandemic has a number of behavioral and social consequences that would in turn trigger epileptic seizures, and lower the threshold level of epileptic seizures in PWE [19]. Also, stress has been found to exacerbate epilepsy control. In fact, there is a direct correlation between stress and the frequency of epileptic seizures among PWE [31]. Results of studies on the effects of the COVID-19 pandemic on stress levels among PWE showed a higher stress and anxiety level in PWE; in addition, they also experienced a worse mental health condition during the COVID-19 restrictions [23]. Meanwhile, about 20% of subjects, who reported worsened seizure control during the pandemic, showed more severe epilepsy and seizures accelerated by stress. The increased stress, associated with the pandemic, has been shown to have a direct correlation with worsening seizures among some PWE [15].

Also, it has been estimated that one in every three patients with epilepsy experienced mental issues. In the meantime, psychological distress frequently occurred in their everyday life [32]; therefore, it is expected that in stressful situations such as COVID-19 restrictions, the incidence of depression and anxiety would likely increase. Among psychological distress, anxiety and depression are the most common epilepsy-related problems frequently observed among PWE during the COVID-19 period. Results of studies on COVID-19 in Italy showed that PWE (19%) and PWOE (17%) reported psychiatric disorders such as depression. However, PWE had more severe depressive symptoms than PWOE [19]. Additionally, Van Hees et al. believe that there are remarkably gender differences among PWE, as it was reported that females are at a higher risk of increased depression problems during the COVID-19 pandemic [6]. Excessive exposure to stressors not only exacerbates seizures in PWE but also triggers acute seizures even in people who have no history of epilepsy [33]. In this regard, Huang et al.'s study reported that depression among PWE and PWOE increased the number of seizures (22.58% vs 12.08%, respectively) [15]. Moreover, several studies conducted during the COVID-19 pandemic have indicated that there were gender and age differences in relation to the prevalence of stress and anxiety symptoms among PWE. In this respect, female and older individuals had higher scores on the HADS which showed an anxiety subscale [20]. Other studies also showed that both PWE and PWOE experienced anxiety symptoms during the pandemic; however, significantly higher prevalence of anxiety was observed in PWE [19].

On the other hand, it seems that imposed restrictions during COVID-19 pandemic could affect negatively the sleep quality in general population due to the increasing rate of psychological disorder prevalence, reducing exercise activity, staying home, and insufficient access to sunlight [34]. In this respect, results showed that 7.1–71.2% of PWE experienced sleep problems [4,9], and the prevalence of insomnia was also 28.2% in patients with epilepsy [4]. However, one study reported that there was no significant difference in the sleep quality between PWE and healthy individuals [15]. Sleep disturbance in PWE is a significant activator that can lead to an increase in motor excitability which develops the frequency of epileptic seizures in these patients [35]. Generally, deficiency of the sleep-wake cycle during the COVID-19 restriction may influence both PWE and PWOE; however, sleep disturbance may lead to an increase in EEG epileptiform abnormalities resulting in exacerbation of seizure in PWE [36].

5. Conclusion

The present systematic review evaluated the prevalence of mental health disorders in PWE during the COVID-19 pandemic. Collectively, results of this study indicated that the prevalence of psychological disorders, namely stress, depression, anxiety, and sleep disruption in PWE was higher than that of PWOE. Based on the results of the present study, we argue that gender and age play a significant role in the level of psychological disorders, especially stress, in PWE. Some of the included papers in this study have shown that PWE above 60 years old, especially women, and young people with the age range of 12–25 have a higher risk of psychological stress compared to other groups in PWE. We think that the reason for the increase in prevalence of stress in these patients are as follows: (1) home confinement, social isolation, and other social restrictions imposed during the COVID-19 pandemic, (2) changes in sleep quality and lifestyle due to COVID-19 restrictions, (3) lack of adequate physical activity, and (4) following up the news and information about COVID-19 [6,9,10,15,20].

We thus believe that PWE, especially the above-mentioned groups within the PWE, are at considerable risk during the pandemic. Therefore, adequate psychological supports should be given to these patients in order to relieve the mental health risks among them. In doing so, we recommend that PWE alongside their families learn working with psychometric assessment tools in order to better grasp PWE's emotional states. In addition, receiving meditation and relaxation training by experts can help cope with the worsening stress and anxiety. Meanwhile, we think that online follow-up sessions, known as telemedicine, alongside phone chats, and video calls offered by specialists in the field can be effective in reducing the risk of psychological disorders in PWE during the pandemic and post-pandemic era.

6. Limitations

Although the present study provided some significant lines of evidence demonstrating a high level of prevalence of psychological distress in PWE, this systematic review still has some limitations. First, due to a large amount of heterogeneities observed in the results, we could not evaluate the exact rate of prevalence in spite of using effective measures. Meanwhile, meta-analysis and robust conclusions cannot be drawn because of the significant heterogeneity of the invalidated tools used. Second, most studies were conducted with a limited number of European population or in English-speaking countries; thus, we could not examine the prevalence of mental health problems in African and Asian populations. Third, due to lack of evidence from low-income countries that presumably have a higher level of stress during COVID-19 pandemic, we thus cannot generalize the results of this study to such countries.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Consent for publication

All authors consented for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.yebeh.2021.108410>.

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