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Psychological impact of the COVID-19 pandemic for patients with epilepsy: A systematic review and meta-analysis

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Abstract

Objective: To investigate psychological comorbidities in patients with epilepsy during the coronavirus disease 2019 (COVID-19) pandemic.

Method: A systematic review and meta-analysis approach was used to comprehensively search MEDLINE, CENTRAL, EMBASE, and ClinicalTrials.gov databases for relevant studies. Studies that reported psychological stress in patients with epilepsy during the COVID-19 pandemic were included. Psychological comorbidities were defined as anxiety, depression, and sleep disturbance. Pooled proportions of psychological comorbidities with 95% confidence intervals (CIs) were assessed using a random-effects model. The quality of assessment for each study, heterogeneity between the studies, and publication bias were also evaluated.

Results: A total of 28 studies with 7959 patients/caregivers were included in the meta-analysis. The pooled proportions of anxiety/worry, depression/bad mood, and sleep disturbance were 38.9% (95% CI: 31.3–46.7), I² = 97%; p < 0.01, 30.9% (95% CI: 23.3–38.9), I² = 97%; p < 0.01, and 36.5% (95% CI: 28.3–45.1), I² = 97%, p < 0.01, respectively.

Conclusion: Although the heterogeneity was high, our results showed a relatively high incidence of psychological comorbidities. Therefore, clinicians need to intervene early in the stress of patients with epilepsy to prevent worsening of stress, which can result in seizure worsening.

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1. Introduction

Epilepsy is a chronic neurological disorder that causes recurrent, unprovoked seizures. It is known that 20–30% of patients with epilepsy experience symptoms of depression [1]. Compared to healthy people, patients with epilepsy have a 40–50% higher suicide rate [2]. Coronavirus disease 2019 (COVID-19) initially occurred in Wuhan, China, in late 2019, before its global outbreak [3]. The COVID-19 pandemic has been stressful for people worldwide, and everyone has to adapt to the changes involved. We have discussed the importance of considering the psychological impact of this pandemic in patients with epilepsy [4,5]. It is known that increased psychological stress in patients with epilepsy not only increases the risk of developing psychiatric disorders such as depression but also that stress can trigger and exacerbate seizures. The effects of stress can even kill patients with epilepsy due to the rapid worsening of seizures or suicide caused by the onset of mental illness. Therefore, clinicians need to understand the impact of COVID-19 on the mental stress of patients with epilepsy to maintain appropriate treatment even during the COVID-19 pandemic.

Patients with epilepsy are reported to be more vulnerable to the psychological effects of the COVID-19 pandemic than those without epilepsy [6]. If we know the impact of the COVID-19 pandemic on the mental health of patients with epilepsy, clinicians can consider, prevent, or respond quickly to the psychological comorbidities of patients with epilepsy. [4] It would also allow us to put proper protective/proactive interventions in place for people with epilepsy during the pandemic and other times of crisis. However, the magnitude of its impact is uncertain and varies from study to study [4,6].
Therefore, this study aimed to clarify the impact of the COVID-19 pandemic on the mental health of patients with epilepsy. We investigated the incidence of psychological comorbidities in patients with epilepsy during the COVID-19 pandemic using a systematic review and meta-analysis.

2. Materials and methods

2.1. Searching strategy

We conducted a search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7]. This review protocol has not been registered previously. The following databases were searched systematically up to March 20, 2021, MEDLINE (accessed from PubMed), CENTRAL (accessed from the Cochrane Library), and EMBASE. In PubMed, the following key words were searched: "Epilepsy" [MeSH Terms] OR "Epilepsy" [Title/Abstract] OR "seizure disorder" [Title/Abstract] AND "COVID-19" [MeSH Terms] OR "SARS-CoV-2" [MeSH Terms] OR "COVID-19" [Title/Abstract] OR "2019 ncov infection" [Title/Abstract] OR "SARS-CoV-2" [Title/Abstract] OR "2019 novel coronavirus" [Title/Abstract]. The following keywords were searched in the Cochrane libraries: [MeSH Epilepsy] OR Epilepsy: [Title/Abstract] OR "seizure disorder" [Title/Abstract] AND [MeSH COVID-19] OR [MeSH SARS-CoV-2] OR COVID-19: [Title/Abstract] OR "2019 ncov infection": [Title/Abstract] OR SARS-CoV-2: [Title/Abstract] OR "2019 novel coronavirus": [Title/Abstract]. In the EMBASE database, the following key words were searched: 'Epilepsy'/exp OR Epilepsy: [Title/Abstract] OR "seizure disorder" [Title/Abstract] AND 'COVID-19'/exp OR 'SARS-CoV-2'/exp OR COVID-19: [Title/Abstract] OR "2019 ncov infection": [Title/Abstract] OR SARS-CoV-2: [Title/Abstract] OR "2019 novel coronavirus": [Title/Abstract]. We also used ClinicalTrials.gov to search for unpublished, ongoing, terminated, or completed studies to avoid publication bias. We screened the reference lists of all relevant articles for additional data.

2.2. Inclusion and exclusion criteria

Studies were included based on the following criteria: (1) studies that have reported data of at least one psychological comorbidity in patients with epilepsy or reported by their caregivers during the COVID-19 pandemic; (2) studies from which we can calculate the incidence proportion of patients/caregivers with psychological comorbidities during the COVID-19 pandemic. We excluded studies based on the following criteria: (1) studies that were not yet recruiting, currently recruiting, or were withdrawn according to ClinicalTrials.gov; (2) studies that reported patients diagnosed with psychogenic nonepileptic seizures; (3) case reports; and (4) studies written in languages other than English. In addition, we did not include studies focusing on patients with epilepsy during the pandemic, which reported only the number or proportion of patients with epilepsy who had preexisting psychiatric disorders as demographic data and did not examine anxiety, depression, or stress during the pandemic. This is because the existence of preexisting psychiatric disorders before the COVID-19 pandemic does not reflect the influence of COVID-19 on patients with epilepsy.

Psychological comorbidities were defined as anxiety, depression, or sleep disturbance. Anxiety included anxiety/worry in patients with epilepsy or their caregivers’ anxiety and worry. Depression included depression/bad mood in patients with epilepsy or their caregivers' depression/bad mood. Sleep disturbances included insomnia, nocturnal awakening, and sleep pattern changes in patients with epilepsy or their caregivers' sleep pattern changes. If studies categorized outcomes into four categories (i.e., less, mild, moderate, and severe) based on scales/scores, then we defined the incidence of psychological comorbidities in the studies as outcomes of moderate or severe. Any type of outcome was measured using a questionnaire, survey, or the presence of psychological consultation. However, we excluded studies that reported only the mean ± standard deviation of psychological scores because we could not calculate the incidence proportion.

To assess the quality of the included articles, we scored the level of risk of bias using the risk of bias instrument for cross-sectional surveys of attitudes and practices contributed by the CLARITY group at McMaster University [8] and Joanna Briggs Institute checklist for cohort studies [9]. Any disagreements or discrepancies between the reviewers regarding outcomes were resolved through discussion.

2.3. Data extraction and outcome measurements

Two reviewers (NK and TK) independently screened the titles and abstracts and evaluated the full texts of the selected articles. The risk of bias was independently assessed. Any disagreements were resolved through discussion between the reviewers (NK and TK). The following variables were extracted: author, publication year, study period, country in which the study was conducted, participants, study design, outcome measurement scales, the proportion of anxiety/worry, depression/bad mood, and sleep disturbance. We further extracted independent risk factors for anxiety, depression, and insomnia identified by multivariate analysis and their odds ratios (ORs).

2.4. Statistical analysis

In this systematic review and meta-analysis, we used a single-arm analysis. Percentages, means, and standard deviations were calculated for the categorical variables. We used random-effects models with the DerSimonian-Laird estimator to consider the variance between and among the studies. We calculated the pooled proportions using the variance-stabilized Freeman Tukey’s double arcsine transformation. Confidence intervals (CIs) for individual studies were computed using the Wilson score CI method, adjusting for continuity. The I² statistic and Cochran’s Q test were used to indicate heterogeneity between the studies. For the I² statistic, 0% < I² < 25%, 25% ≤ I² < 50%, 50% ≤ I² < 75%, and ≥75% were considered very low, low, moderate, and high heterogeneity, respectively [10]. For Cochran’s Q test, P < 0.10 was considered to indicate severe heterogeneity [11,12]. Publication bias was assessed using a funnel plot and Egger’s test, which is a quantitative analysis of asymmetry in the funnel plot. For Egger’s test, P < 0.10 was considered significant publication bias [12,13]. We did not assess publication bias for outcomes reported in fewer than ten studies. All statistical analyses were conducted using R software (version 3.6.2; R Development Core Team 2019), with meta version 4.15-0 and metaphor version 2.4-0.

2.5. Subgroup analysis

Subgroup analyses were conducted to investigate potential explanatory variables of heterogeneity using the following methods: (1) analysis limited to studies reporting only patients with epilepsy, excluding studies that included caregivers of patients with epilepsy; (2) analysis limited to studies that measured outcomes using valid and established measurement scales; (3) analysis based on each valid and established measurement scale; (4) analysis divided into each continent (Asia/Oceania, Africa, Europe, North America, and, South America – Turkey was included in both Asia/Oceania and Europe); (5) analysis was divided into low/middle-income and high-income countries based on the Develop
3. Results

3.1. Summary of reviewed articles

The selection process is illustrated in Fig. 1. A total of 802 studies were retrieved (217 papers from MEDLINE, 0 papers from CENTRAL, 583 papers from EMBASE, and two studies from ClinicalTrials.gov) up to March 20, 2021. After removing duplicates and screening the titles and abstracts, 88 studies were identified. The full-text screening of these studies led to the exclusion of 60 studies that did not meet the inclusion criteria. Thus, a total of 28 studies with 7,959 patients/caregivers fulfilled the eligibility criteria for inclusion in the meta-analysis [14–41]. Table 1 summarizes the findings of the included studies. The mean scores for the quality of 23 cross-sectional studies and five cohort studies were 2.7 out of 5 and 5.0 out of 11, respectively (Table 1 and Supplementary Table 1).

The outcomes of our meta-analysis are summarized in Table 2. The pooled proportions of anxiety/worry, depression/bad mood, and sleep disturbance were 38.9% (95% CI: 31.3–46.7); I² = 97%; P < 0.01, 30.9% (95% CI: 23.3–38.9); I² = 97%; P < 0.01, and 36.5% (95% CI: 28.3–47.1); I² = 97%; P < 0.01, respectively (Fig. 2).

We looked for publication bias for anxiety/worry, depression/bad mood, and sleep disturbance using a funnel plot and Egger’s test (Table 2). There was no significant publication bias for each outcome (P = 0.48, P = 0.87, and P = 0.42, respectively) (Table 2).

We have summarized the reported independent risk factors and their ORs for anxiety, depression, or insomnia in Table 3.

3.2. Results of subgroup analysis

Subgroup analysis for each outcome with the removal of studies that included caregivers of patients with epilepsy slightly reduced but still had high heterogeneity (anxiety: I² = 95%, P < 0.01; depression: I² = 95%, P < 0.01; sleep disturbance: I² = 96%, P < 0.01; Table 2 and Supplementary Fig. 1), with a pooled response proportion of 34.7% (95% CI: 26.5–43.3; Supplementary Fig. 1) for anxiety, 28.1% (95% CI: 20.5–36.3; Supplementary Fig. 1) for depression,
| Authors, year                      | Study period               | Country     | Participants | Study design to assess the mental stress | Score of Quality | Anxiety | Depression | Insomnia (sleep disturbance) | Outcome measurement scales | Cut-off value |
|-----------------------------------|---------------------------|-------------|--------------|------------------------------------------|------------------|---------|------------|----------------------------|-------------------------------|---------------|
| Abokalawa, et al. 2021 [14]      | January 8–October 8, 2020 | Kuwait      | 151 PwE      | CSS                                      | 3/5              | 76/151  | 80/151     | 84/151                      | DASS-21, PSQI                   | ≥6 for PSQI  |
| Aledo-Serrano, et al. 2020 [15]  | April 7–April 11, 2020    | Spain       | 277 caregivers of individuals with genetic, developmental, and epileptic encephalopathies | CSS              | 3/5    | 190/277   | 193/277             | Reported new-onset symptoms of anxiety or depression | ≥20 for BDI-II, ≥10 for GAD-7, ≥6 for PSQI |               |
| Alkotani, et al. 2020 [16]       | April, 2020               | Saudi Arabia| 156 PwE      | CSS                                      | 2/5              | –       | –          | 111/156                     | Perceived stress during the pandemic, sleep changes |               |
| Assenza, et al. 2020 [17]        | April 11–April 16, 2020   | Italy       | 456 PwE      | CSS                                      | 4/5              | 209/456 | 90/456     | 214/456                     | BDI-II, GAD-7, PSQI             |               |
| Conde Blanco, et al. 2021 [18]   | N.D.                      | Spain       | 312 PwE      | CSS                                      | 1/5              | –       | –          | 135/312                     | Reported anxiety, depressed than usual, and difficulty with sleep during the lockdown |               |
| Fonseca, et al. 2020 [19]        | March 16–April 17, 2020   | Spain       | 255 PwE      | CSS                                      | 3/5    | 68/255   | 22/255     | 72/255                      | Reported anxiety, depression, and sleep disturbance |               |
| Grande, et al. 2021 [20]         | April–May, 2020           | Italy       | 30 PwE who underwent VNS surgery | CSS              | 4/5    | 7/13      | 3/13       | 5/13                       | BDI-II, GAD-7, PSQI             | ≥14 for BDI-II, ≥5 for GAD-7, ≥6 for PSQI |               |
| Huang, et al. 2020 [21]          | February 23–March 5, 2020 | China       | 362 PwE      | CSS                                      | 4/5    | 34/362   | 47/362     | 71/362                      | PHQ-9, GAD-7, ISI               | ≥8 for GAD-7, ≥10 for PHQ-9, ≥8 for HADS |               |
| Koh, et al. 2021 [22]            | June 7–July 5, 2020       | Malaysia    | 461 PwE      | CSS                                      | 3/5    | 47 (+80) / 461 | 32 (+55) / 461 | –                        | HADS                         | ≥8 for HADS |               |
| Miller, et al. 2020 [23]         | March 27–March 30, 2020   | USA         | 94 participants (78 PwE and 16 caregivers) | CSS          | 3/5    | –         | –          | 64/94                      | PROMIS anxiety scale            |               |
| Millevert, et al. 2021 [24]      | July 26–December 3, 2020  | International (Belgium) | 407 participants (337 PwE and 70 caregivers) | CSS          | 3/5    | 295/407   | 159/407   | –                         | HADS                         | ≥8 for HADS |               |
| Mostacci, et al. 2020 [25]       | May 7–July 31, 2020       | Italy       | 157 PwE and 65 caregivers in HI, USA | CSS          | 2/5    | –         | –          | 53/222                     | Reported sleep changes New or worsening depression, anxiety, sleep problem (Yes/No) |               |
| Nakamoto, et al. 2020 [26]       | April 22–May 18, 2020     | Lithuania   | 67 PwE       | CSS                                      | 3/5    | 23/67    | 17/67      | 23/67                      | Reported disturbed sleep      |               |
| Puteikis, et al. 2020 [27]       | March 16–June 16, 2020    | India       | 143 PwE      | CSS                                      | 3/5    | –         | –          | 47/143                     | More worried about epilepsy control during COVID-19 pandemic |               |
| Rathore, et al. 2021 [28]        | September 26–October 6, 2020 | India    | 325 PwE      | CSS                                      | 3/5    | 107/325   | –          | –                         | Reported mood, sleep           |               |
| Reilly, et al. 2021 [29]         | May–June, 2020            | UK          | 71 young PwE and 130 caregivers (young: 59, caregiver:105) | CSS          | 1/5    | –         | 38/59 & 64/105 | 43/59 & 59/105           | Worsened sleep BAI-II, sleep problem Problems sleeping, depressed, feel sad, worry most of the time (Yes/No) Likert questions about their perceived well-being (depressed) |               |
| Rosengard, et al. 2020 [30]      | March 1–May 31, 2020      | NY, USA     | 177 PwE      | CSS                                      | 3/5    | –         | –          | 76/177                     | Worsened sleep BAI-II, sleep problem Problems sleeping, depressed, feel sad, worry most of the time (Yes/No) Likert questions about their perceived well-being (depressed) |               |
| Salari, et al. 2020 [31]         | N.D.                      | Iran        | 141 PwE      | CSS                                      | 2/5    | 41/141   | –          | 29/141                     | Problems sleeping, depressed, feel sad, worry most of the time (Yes/No) Likert questions about their perceived well-being (depressed) |               |
| Sureka K, et al. 2021 [32]       | N.D.                      | India       | 134 PwE      | CSS                                      | 4/5    | 29/134   | 23/134     | 26/134                     | Problems sleeping, depressed, feel sad, worry most of the time (Yes/No) Likert questions about their perceived well-being (depressed) |               |
| Tedrus, et al. 2020 [33]         | August 1–September 10, 2020 | Brazil   | 114 PwE      | CSS                                      | 3/5    | –         | 41/114     | –                         | Problems sleeping, depressed, feel sad, worry most of the time (Yes/No) Likert questions about their perceived well-being (depressed) |               |
| Authors, year           | Study period       | Country                                      | Participants                                                                 | Study design to assess the mental stress | Score of Quality | Anxiety (21/399) | Depression (HADS) and 187/399 (PHQ) | Insomnia (sleep disturbance) | Outcome measurement scales                 | Cut-off value |
|------------------------|--------------------|----------------------------------------------|------------------------------------------------------------------------------|------------------------------------------|-----------------|-----------------|-------------------------------------|-------------------------------------|-------------------------------------------|---------------|
| Thorpe, et al. 2021    | April–September, 2020 | UK                                           | 463 responses (316 PwE and 147 caregivers) 3321 participants (3209 caregivers and 112 PwE) | CSS                                      | 3/5             | 161/463         | 161/464                             | 121/463                             | Disrupted sleep patterns, anxiety, depression | ≥7 for HADS, ≥9 for PHQ-9 |
| Trivisano, et al. 2020 | May 8–May 31, 2020 | Italy                                        |                                                                              | CSS                                      | 1/5             | 870/2283        | 425/2283                             | 398/2340                             | Changes in sleep disturbances and psychological consultations | ≥19 for BDI |
| Van Hees, et al. 2020  | April 10–May 18, 2020 | Belgium, Brazil, Netherlands, USA, and other 14 countries | 399 PwE                                                                      | CSS                                      | 2/5             | 201/399         | 159/399 (HADS) and 187/399 (PHQ)   | –                                   | HADS, PHQ-9                                  | ≥7 for HADS, ≥9 for PHQ-9 |
| Gul, 2021              | June–July, 2020    | Turkey                                       | 116 PwE                                                                      | CHS                                      | 8/11            | 42/131           | –                                   | –                                   | BDI                                        | ≥19 for BDI |
| Modi, et al. 2021      | April–September, 2020 | USA                                          | 131 family members of pediatric PwE                                          | CHS                                      | 3/11            | 27/116           | –                                   | –                                   | Likert scale for emotional health (e.g., worries and mood) | ≥19 for BDI |
| Sanchez-Larsen, et al. 2020 | May 17–June 7, 2020 | Spain                                        | 100 PwE                                                                      | CHS                                      | 6/11            | 42/100           | 35/100                              | 20/100                              | Reported anxiety, depression, and sleep disturbance (more than normal) | ≥8 for GAD-7 |
| Tailby, et al. 2020    | N.D.               | Australia                                    | 29 participants (first unprovoked seizure: n = 17, new diagnosis epilepsy: n = 6, refractory epilepsy: n = 6) | CHS                                      | 5/11            | 8/29 (EASI) or 11/29 (GAD7)        | 10/29                              | –                                   | NDDIE, EASI, GAD-7                          | ≥8 for GAD-7 |
| Lima, et al. 2020      | N.D.               | Brazil                                       | Seven patients with pharmacoresistant epilepsy underwent ketogenic diet treatment | CAS                                      | 3/11            | –                | –                                   | –                                   | Reported anxiety, stress, fear               | ≥8 for GAD-7 |

BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; CAS: case series; CHS: cohort study; CSS: cross-sectional study; DASS-21: depression, anxiety, stress scale 21; EASI, epilepsy anxiety survey instrument; GAD-7, Generalized Anxiety Disorder-7; HADS, Hospital Anxiety and Depression Scale; N.D., not described; NDDIE, Neurological Disorders Depression Inventory for Epilepsy; PHQ-9, Patient Health Questionnaire-9; PROMIS, Patient-Reported Outcomes Measurement Information System; PSQI, Pittsburgh Sleep Quality Index; PwE, people/patients with epilepsy.
and 38.3% (95% CI: 29.5–47.6; Supplementary Fig. 1) for sleep disturbance.

Subgroup analysis with only studies that measured outcomes using valid and established measurement scales also slightly reduced, but still had high heterogeneity (anxiety: $I^2 = 98\%$, $P < 0.01$; depression: $I^2 = 96\%$, $P < 0.01$; sleep disturbance: $I^2 = 97\%$, $P < 0.01$; Table 2 and Supplementary Fig. 2), with a pooled response proportion of 40.7% (95% CI: 28.4–52.6; Supplementary Fig. 2) for anxiety, 28.6% (95% CI: 19.8–38.3; Supplementary Fig. 2) for depression, and 40.9% (95% CI: 24.9–57.8; Supplementary Fig. 2) for sleep disturbance.

Regarding subgroup analysis with each valid and established measurement scale, the analysis was done based on Beck Depression Inventory (BDI/BDI-II), Generalized Anxiety Disorder-7 (GAD-7), Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire-9 (PHQ-9), and Pittsburgh Sleep Quality Index (PSQI). Analysis with BDI/BDI-II showed low heterogeneity ($I^2 = 98\%$, $P < 0.01$), with a pooled response proportion of 32.1% (95% CI: 19.5–45.7; Supplementary Fig. 3). Analysis with the PHQ-9 showed high heterogeneity ($I^2 = 98\%$, $P < 0.01$), with a pooled response proportion of 28.4% (95% CI: 3.3–65.1; Supplementary Fig. 3). Analysis with PSQI showed low heterogeneity ($I^2 = 49\%$, $P = 0.14$), with a pooled response proportion of 49.7% (95% CI: 42.3–57.2; Supplementary Fig. 3).

Subgroup analysis dividing studies into each continent still had high heterogeneity (anxiety in Asia and Oceania: $I^2 = 95\%$, $P < 0.01$; anxiety in Europe: $I^2 = 95\%$, $P < 0.01$; anxiety in North America: $I^2 = 97\%$, $P = 0.02$; depression in Asia/Oceania: $I^2 = 95\%$, $P < 0.01$; depression in Europe: $I^2 = 96\%$, $P < 0.01$; sleep disturbance in Asia/Oceania: $I^2 = 98\%$, $P < 0.01$; sleep disturbance in Europe: $I^2 = 97\%$, $P < 0.01$; sleep disturbance in North America: $I^2 = 91\%$, $P < 0.01$; Table 2 and Supplementary Fig. 4). The pooled response proportions for anxiety were 28.6% (95% CI: 18.6–39.7; Supplementary Fig. 4) in Asia/Oceania, 43.2% (95% CI: 34.1–52.5; Supplementary Fig. 4) in Europe, and 32.8% (95% CI: 26.4–39.6; Supplementary Fig. 4) in North America. The pooled response proportions for depression were 25.2% (95% CI: 14.9–37.1; Supplementary Fig. 4) in Asia/Oceania and 32.9% (95% CI: 19.4–48.0; Supplementary Fig. 4) in Europe. Pooled response proportions for sleep disturbance were 36.2% (95% CI: 16.8–58.4; Supplementary Fig. 4).
Fig. 4) in Asia/Oceania, 33.1% (95% CI: 23.5–43.4; Supplementary Fig. 4) in Europe, and 48.6% (95% CI: 30.3–67.1; Supplementary Fig. 4) in North America. Subgroup analyses for anxiety, depression, and sleep disturbance reported in studies in South America, and depression reported in studies in North America were not performed because these subgroups had only one or zero studies.

Subgroup analysis of studies from high-income countries and studies from low/middle-income countries still had high heterogeneity (anxiety in high-income countries: $I^2 = 97\%$, $P < 0.01$; anxiety in low/middle-income countries: $I^2 = 97\%$, $P < 0.01$; depression in high-income countries: $I^2 = 96\%$, $P < 0.01$; depression in low/middle-income countries: $I^2 = 86\%$, $P < 0.01$; sleep disturbance in high-income countries: $I^2 = 98\%$, $P < 0.01$; sleep disturbance in low/middle-income countries: $I^2 = 0\%$, $P = 0.96$; Table 2 and Supplementary Fig. 5). The pooled response proportions for anxiety were 41.7% (95% CI: 34.8–48.7; Supplementary Fig. 5) in high-income countries and 24.9% (95% CI: 15.4–35.6; Supplementary Fig. 5) in low/middle-income countries. The pooled response proportions for depression were 28.0% (95% CI: 19.0–38.0; Supplementary Fig. 5) in high-income countries and 20.7% (95% CI: 12.6–30.8; Supplementary Fig. 5) in low/middle-income countries.
14.6–27.7; Supplementary Fig. 5) in low/middle-income countries. The pooled response proportions for sleep disturbance were 39.1% (95% CI: 29.1–49.5; Supplementary Fig. 5) in high-income countries and 19.8% (95% CI: 16.7–23.0; Supplementary Fig. 5) in low/middle-income countries.

Subgroup analysis dividing studies into the early and late pandemic phases still had high heterogeneity (anxiety in early phase: $I^2 = 97\%$, $P < 0.01$; anxiety in late phase: $I^2 = 99\%$, $P < 0.01$; depression in early phase: $I^2 = 94\%$, $P < 0.01$; sleep disturbance in early phase: $I^2 = 98\%$, $P < 0.01$; Table 2 and Supplementary Fig. 6). The pooled response proportions for anxiety were 34.7% (95% CI: 23.7–46.7; Supplementary Fig. 6) in the early phase and 44.2% (95% CI: 17.7–72.7; Supplementary Fig. 6) in the late phase. The pooled response proportions for depression in the early phase were 29.2% (95% CI: 19.9–39.4; Supplementary Fig. 6) and 48% (95% CI: 37.4–58.6; Supplementary Fig. 6) for the late phase. Subgroup analysis for sleep disturbance in the late phase was not performed, as no studies were included.

4. Discussion

4.1. Summary

This systematic review and meta-analysis of 28 studies showed that the incidence rates of anxiety, depression, and sleep disturbance were 38.9%, 30.9%, and 36.5%, respectively. However, the heterogeneity in the meta-analysis was very high for every outcome (anxiety: $I^2 = 97\%$; depression: $I^2 = 97\%$; sleep disturbance: $I^2 = 97\%$). We performed subgroup analyses to consider potential heterogeneity due to participants (patients or caregivers), the validity of outcome measurements, and differences among outcome measurement scales, continents, study period, and wealth of countries. However, even after subgroup analysis to consider participants, continents, study period, and wealth of countries, heterogeneity hardly improved. Subgroup analysis of the same outcome measurement scale showed a relatively improved heterogeneity.

These results indicate that the incidence of psychological complications may vary greatly depending on the scale used to measure them. Meanwhile, there was some heterogeneity in the incidence of psychological complications, even among studies using the same measurement scale, within the same continent, similar period, or similar wealth of country.

The reason for the heterogeneity among studies that used the same measurement scale was the difference in cutoff values in each study. Indeed, several studies have reported that different cutoff values are optimal [42–49], depending on the profile of patients and translated language. Another explanation for this heterogeneity is that the mental health effects of COVID-19 may vary greatly depending on the condition of the disease, such as the severity of epilepsy or the presence of complications. Indeed, some measurement scales, such as the HADS, were evaluated as near cutoff values; nevertheless, the heterogeneity was still high.

4.2. Comparison with stress in the general population during the COVID-19 pandemic

Some studies have compared stress between patients with epilepsy and the general population [17,31]. A study from Italy reported that patients with epilepsy experienced more severe depressive and anxiety symptoms than those in the control group [17]. As for insomnia, it was reported that there were no differences between patients with epilepsy and the control group. Another study from Iran also reported that the proportion of people with severe anxiety was higher in patients with epilepsy than in the control group [31]. On the other hand, it was also reported that the proportion of people with insomnia was higher in the control group than in the epilepsy group.

4.3. Comparison with stress in patients with other diseases during the COVID-19 pandemic

The impact of COVID-19 on mental health has been reported in several studies. A study reported that 16% of patients with diabetes mellitus experienced mental stress, and 24% experienced sleep change [50]. Meta-analysis of mental stress due to the COVID-19 pandemic on healthcare staff reported various incidence proportions of anxiety, depression, and sleep disturbance depending on each study, as well as in our study [51].

Multiple sclerosis, similar to epilepsy, is a chronic neurological disease. A study reported mental stress in patients with multiple sclerosis [52]. According to this study, 22% of the patients reported moderate or severe anxiety/depression.

Our results showed a relatively high incidence of psychological comorbidities compared to studies on patients with diabetes mellitus and multiple sclerosis. People with epilepsy are known to have more psychiatric complications than people without epilepsy,
4.4. Comparison with stress in patients with epilepsy under other situations

Although COVID-19 is a pandemic like no other in history, it is important to characterize the stress caused by COVID-19 in patients with epilepsy, compared to the stress caused by other major social events, such as disasters and accidents. These data may be important in predicting the impact of the next major social event on patients with epilepsy.

In terms of the impact of major social events (disasters, accidents, etc.) on patients with epilepsy, some studies have been reported in the past. A study reported the impact of the 9/11/2001 terror attacks in the US on patients with epilepsy [53]. According to this study, 15/66 (22.7%) patients experienced moderate or severe stress. Another study reported that 70% of evacuees from an extremely high water level in 1995 in the Netherlands had any type of mental stress [54].

Our study, as well as other studies [53–54], showed that patients with epilepsy are vulnerable to disasters. People with epilepsy are considered to be exposed to psychological stress in many ways. In the event of a disaster, these may include concerns, such as whether they will be able to secure antiepileptic drugs or stress related to the disease, such as when seizures occur. These findings will be important for epileptologists, neurologists, and other physicians, nurses, and healthcare providers to prepare for other disasters, including pandemics, and to protect patients with epilepsy from psychological stress. Specifically, some included studies reported the importance of maintaining access to healthcare providers or obtaining anti-seizure medications for patients/people with epilepsy [24,36]. To keep it, telemedicine is one of the good options during the COVID-19 pandemic.

In addition, the COVID-19 pandemic is unique compared to other disasters in that it is prolonged, global, and has a direct impact on infection risk as well as restrictions on social and work life. During the prolonged COVID-19 pandemic, clinicians need to intervene early in the stress of patients with epilepsy to prevent worsening stress, which can result in seizure worsening. Specifically, a study suggests the effectiveness of early physical consultation with stringent precautionary measures during the COVID-19 pandemic [55].

5. Conclusion

We investigated the psychological impact of patients with epilepsy during the COVID-19 pandemic by performing a systematic review and meta-analysis of the incidence of anxiety, depression, and sleep disturbances. Although the heterogeneity was high, our results showed a relatively high incidence of psychological comorbidities. Therefore, clinicians need to intervene early in the stress of patients with epilepsy to prevent worsening stress, which can result in seizure worsening.

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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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2021.108340.

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