

## Central Lancashire Online Knowledge (CLOK)

Title	The prevalence of comorbidity in rheumatoid arthritis: a systematic review and meta-analysis
Type	Article
URL	<a href="https://clock.uclan.ac.uk/42002/">https://clock.uclan.ac.uk/42002/</a>
DOI	
Date	2022
Citation	Hill, James Edward, Harrison, Joanna, Christian, Danielle, Reed, Janet, Clegg, Andrew, Duffield, Stephen J., Goodson, Nicola and Marson, Tony (2022) The prevalence of comorbidity in rheumatoid arthritis: a systematic review and meta-analysis. British Journal of Community Nursing, 27 (5). ISSN 1462-4753
Creators	Hill, James Edward, Harrison, Joanna, Christian, Danielle, Reed, Janet, Clegg, Andrew, Duffield, Stephen J., Goodson, Nicola and Marson, Tony

It is advisable to refer to the publisher's version if you intend to cite from the work.

For information about Research at UCLan please go to <http://www.uclan.ac.uk/research/>

All outputs in CLOK are protected by Intellectual Property Rights law, including Copyright law. Copyright, IPR and Moral Rights for the works on this site are retained by the individual authors and/or other copyright owners. Terms and conditions for use of this material are defined in the <http://clock.uclan.ac.uk/policies/>

# **The prevalence of comorbidities in epilepsy: a systematic review**

## **Abstract**

Comorbidities are associated with adverse patient outcomes. We conducted a systematic review according to a pre-determined protocol (PROSPERO 2019 CRD42019125550) and established PRISMA guidelines and reporting standards to estimate the prevalence of common comorbidities in people with epilepsy, and to explore whether the burden is greater in more deprived populations. Findings from the review's 107 included studies indicate that the most common comorbidities in people with epilepsy are anxiety (19.2%) and major depressive disorder (17.4%). Among adults with epilepsy, common comorbidities include: hypertension (18.2%), stroke (14.5%), heart disease (11%), diabetes (10.2%) and arthritis (9.2%). There was no evidence that a country's income status was a moderating factor for the prevalence of anxiety and depression. However, prevalence rates for hypertension and stroke were lower for lower-income-countries where epilepsy is more commonly symptomatic of brain infection or injury. The analyses were affected by the studies' heterogeneity and should be interpreted cautiously.

**Keywords:** epilepsy; comorbidity; prevalence; epidemiology, deprivation.

## **Full Text**

### **INTRODUCTION**

For people with epilepsy (PWE), the occurrence of another medical condition or conditions (comorbidities) impacts on their quality of life, care, and medical management (1-5). Previous studies have identified a high risk of comorbid mental health conditions in PWE, including anxiety and depression (6-8), and suicide (9). There is also evidence of comorbid physical health conditions in PWE including: strokes (10), migraine (11), brain tumours (1), and other cancers (12,13). However, whilst these studies provide some measure of an association between epilepsy and another medical condition, little is known about the prevalence of

comorbidity rates in PWE (14,15). The burden of comorbidities may also be greater for deprived populations (16,17).

## **AIMS**

This systematic review aimed to estimate the prevalence of common comorbidities in PWE, and to explore whether the burden associated with comorbidities is greater in more deprived populations of PWE. The identification, prevention, and treatment of comorbid conditions in PWE should be an important part of epilepsy care and management (18). This review's findings are expected to provide a better understanding of the prevalence of common types of comorbid conditions in PWE which, in turn, may inform the care, management and health-related quality of life for this population.

## **METHODS**

We conducted a systematic review according to a pre-determined protocol registered on PROSPERO (Registration number: CRD42019125550), established guidelines and reporting standards (19,20). Studies were identified through searches of electronic databases including MEDLINE (Ovid), Embase (Ovid), The Cochrane Library, and PsycINFO (EBSCO). The search included studies that reviewed point prevalence of selected comorbidities amongst PWE. Non-English language studies were excluded due to a lack of resources for translation purposes. Studies published before 1987 were excluded as the clinicians involved in this review considered studies published over 30 years ago to be out-of-date. Reviews were included as a source for cross-checking reference lists of primary (prevalence) studies.

Our first search was conducted on 04.03.2019, with an updated search conducted on 18.09.2020 in accordance with Cochrane review standards and other recognised guidelines (19-22). The search strategy, which was developed iteratively with input from the co-authors, key articles, and consultation with information specialists (JR/CH), is outlined within the published protocol.

### **Inclusion and exclusion criteria**

We included studies if they were original investigations of comorbidity or multimorbidity prevalence in epilepsy populations. These comprised studies with consecutively sampled epilepsy patients, studies using probability sampling of a broader representative epilepsy population (i.e. representative samples of all PWE in the general population), studies of entire epilepsy populations, or studies of all PWE in a representative sub-population of known size. For inclusion, epilepsy must have been clinically diagnosed by a physician or derived from clinical databases where participants have been diagnosed with epilepsy by a physician (using diagnostic codes). Studies utilising self-reported diagnoses of epilepsy were excluded. Studies focusing solely on sub-groups of PWE and another condition (such as a learning disability or cerebral palsy) were excluded as being non-representative of all PWE in the general population. The comorbidity or multimorbidity condition(s) included must have been derived from clinical records, a physician diagnosis, a validated questionnaire or multimorbidity score/index. Studies must have also reported which selected conditions were used to define multimorbidity or comorbidity.

Our conditions of interest included anxiety, major depression disorders (MDD), hypertension, asthma, coronary heart disease, ischemic heart disease (IHD), stroke, transient ischaemic

attack (TIA), atrial fibrillation (AF), heart failure (HF), diabetes, thyroid problems, arthritis, cancer or neoplasms, hearing loss or deafness, migraine, chronic obstructive pulmonary disease (COPD), and painful conditions (e.g. back pain, fibromyalgia). These conditions were selected from an initial set of terms which had been used in previous reviews in this area, together with further suggestions from clinicians in this field and the research team.

The income status of the study population's country was included, recorded and classified as: High-Income-Countries (HIC), Upper-Middle-Income-Countries (UMICs), Low-Middle-Income Countries (LMICs), or Low-Income-Countries (LIC) using The World Bank Economies rankings (23). The study population's socioeconomic status data such as education and income were also included and recorded to assess, if available data permitted, whether prevalence of certain comorbid conditions varies across socioeconomic strata and, therefore, whether the comorbidity burden is greater in more deprived populations with epilepsy.

### **Study selection**

Duplicates from the original and updated searches were removed. Study selection involved two stages. Firstly, titles and abstracts of papers from the searches were screened independently by four reviewers (JHa, AJD, PB, DC), using a predetermined and piloted screening tool. Secondly, full-text manuscripts of studies that met the criteria at the first stage were retrieved and screened independently by three reviewers (JHa, DC, PB) using the same screening tool. Any discrepancies during any stage of the study selection process were resolved through discussion between the reviewers or with another independent reviewer (AJD/AJC).

## **Data extraction**

We extracted data from the included studies independently using a pre-piloted data extraction form (AMS, DC, PB). The data was checked by two independent reviewers (AJD, JHa). Data extracted included: study (first author); publication year; study design; country; country income status (measured by HIC, UMIC, LMIC and LIC classification); setting (hospital / non-hospital setting); participant characteristics (numbers, percentage male / female, population of participants by age grouping); prevalence of co-morbidity by type; and socioeconomic data (e.g. education and income). Data extracted for each of the individual included studies were collated, combined, and narratively synthesised by the reviewers (AJD, PB, DC). Microsoft Excel 2015 was used to support the data extraction and quality assessment processes.

## **Quality assessment**

We assessed the included studies' quality independently (AMS, DC, PB) and analyses were checked independently by two other reviewers (AJD, JHa). The studies' quality was assessed using an adaptation of the 'Hoy' quality assessment checklist for prevalence studies (24). Any discrepancies in decision-making were resolved through discussions or through discussions involving a third reviewer (AJC).

## **Data analysis**

To enable a meaningful summary of the prevalence across each of the comorbidities of interest, meta-analysis was only considered where: (i) there was sufficient quality of data; and (ii) the included studies were homogeneous in terms of the classification used for the comorbidity of interest. A random effects meta-analysis (Der Simonian-Laird) was

undertaken by a reviewer (JH) to compute pooled prevalence estimates and 95% CIs (25). A random effects model was used due to the high likelihood of substantial heterogeneity (I-squared >50%). Heterogeneity across studies was assessed using the I-squared statistic. A meta-regression was undertaken for the comorbidities of major depression and anxiety disorders in PWE. These comorbidities were identified a priori as we had anticipated both to be the most prevalent comorbidities studied in PWE. Subgroup analyses were undertaken for comorbidities: hypertension, stroke, asthma, diabetes, and cancer in PWE where there was available data. The potential moderating variables of country income and age were assessed. The remaining comorbidities were not analysed due to the limited number of studies for each comorbidity. The software package of 'OpenMetaAnalyst' was used for both meta-analysis and meta-regression (26).

## **FINDINGS**

The search yielded a total of 2,756 records and total of 2,356 after duplicate records were removed. A total of 2,055 records were excluded after title and abstract screening (abstract only, not prevalence, not population of interest). After initial title and abstract screening, 301 met the criteria for full-text screening, of which 157 were excluded (abstract-only, not prevalence studies, not population of interest). A further 33 articles were identified from other sources (reviews). Of the 144 full-text articles and 33 other articles screened, a further 70 were excluded (not prevalence studies, not population of interest, or information from multiple articles reporting on the same data sources). A total of 107 studies were included in the synthesis for this review (27-133). The included studies were assessed as either being low risk, (n=93) or moderate risk (n=14) of bias. None of the studies were assessed as being of high risk of bias. All studies used standardized methods to collect data. Figure 1 PRISMA

diagram details the selection process for the included studies. Appendix A: Table S1 provides a summary of the included studies.

*Insert Figure 1: PRISMA Diagram - near here*

The types of studies identified were either cross-sectional (n=93) or cohort studies (n=14). Settings were either hospital (n=70) or non-hospital-based settings (n=24), or both (n=2) (73;134). Settings were not reported in eight studies and three studies' settings were unclear.

Studies' dates of publications returned ranged from 1993 to 2020 (the earliest paper identified was published in 1993). Studies were conducted in: USA (n=20); Nigeria (n=10); India (n=8); Brazil (n=7); Turkey (n=7); China (n=6); Ethiopia (n=5); UK (n=5); Poland (n=4); and Italy (n=3). The remainder were one or two individual studies conducted in a further 27 different countries: Australia (n=1); Canada (n=1); Croatia (n=1); Finland (n=1); France (n=1); Gaza (n=1); Germany (n=2); Greece (n=1); Hong Kong (n=2); Iran (n=1); Malaysia (n=1); Mexico (n=1); Montenegro (n=1); North Korea (n=1); Norway (n=1); Portugal (n=1); Republic of Korea (n=1); Rwanda (n=1); Sierra Leone (n=1); Sweden (n=1); Switzerland (n=1); Taiwan (n=2); Thailand (n=2); The Netherlands (n=1); Togo and Benin (n=1); United Arab Emirates (n=2); and Zambia (n=1). Fifty-five of these studies were conducted in High-Income-Countries (HIC), 24 in Upper-Middle-Income Countries (UMICs), 21 in Lower-Middle-Income-Countries (LMICs), and seven in Low-Income-Countries (LIC).

The number of participants with epilepsy involved in each of the studies varied (range: 35 – 6,107,678). Twelve studies involved only children with epilepsy (aged  $\geq 2$  to 12 years). Five



studies involved only adolescents with epilepsy (aged  $\geq 13$  to 15 years). Most studies involved adult participants with epilepsy (aged  $<60$  years) (n=72). Five studies involved older adults only (aged  $>60$  years) with epilepsy. The remaining studies involved a combination of participants e.g. adults and adolescents with epilepsy; adults and older adults with epilepsy; or children, adolescents and adults with epilepsy (combined) or age-related data was unavailable (n=2). Most studies involved both male and female participants (n=99/92.5%). Two studies involved either male-only. One study included female-only participants. Gender related data was not available for five studies.

The types of epilepsy and seizures reported within the studies varied, including: broad populations with focal or generalised epilepsy, specific epilepsy syndromes or epilepsy types such as refractory temporal epilepsy with mesial temporal sclerosis, juvenile myoclonic epilepsy, extra-temporal lobe epilepsy, temporal lobe epilepsy (TLE). Epilepsy sub-populations described included adults, children and adolescents (varied age ranges), older people (varied age ranges), females (only), males (only), pre-surgical patients, new on-set epilepsy populations, and epilepsy populations treated for many years.

Seventy studies provided some form of socio-economic data such as employment, education, ethnicity, marital status, and residency data. However, the data and outcome measures used by the studies were different and data was insufficient to enable a comparative analysis of the relationship between health inequalities and the prevalence of comorbidities in PWE from different socioeconomic backgrounds.

The types of mental health related comorbidities reported by the prevalence studies included: depression (n=95/107 studies) and anxiety (n=69/107). Physical health related comorbidities included: diabetes (n=15/107), stroke (n=13/107), AF (n=4/107), TIA (n=1/107), IHD (n=2/107), HF (n=5), other vascular conditions (n=6/107), hypertension (n=14/107), migraine (n=12/107), cancer (n=11/107), asthma (n=11/107), hearing loss or deafness (n=5/107), thyroid problems (n=5/107), arthritis (n=3/107), and other (n=2/107 - lung disorders). Twenty-four studies reported data for more than one comorbidity.

### **Prevalence of comorbidities**

#### **Meta-analysis**

The most common comorbidities in PWE were anxiety disorders (19.2%; 95% CI: 17.2% - 21.1%), hypertension (18.2%; 95% CI: 14.3% - 22%), and Major Depressive Disorder (MDD) (17.4%; 95% CI: 15.6%, - 19.3%). The comorbidities of asthma (13.4%; 95% CI: 3.8%, - 22.9%), diabetes (10.2%; 95% CI: 6.3%, - 14.2%) and arthritis (9.2%; 95% CI: 1.2%, - 17.2%) were also common in PWE. Certain types of circulatory system comorbidities were common in PWE, including stroke (14.5%; 95% CI: 8.7%, - 20.3%) and heart disease (11%; 95% CI: 8%, - 13.9%). Other circulatory system comorbidities of Atrial Fibrillation (AF) (5.9%; 95% CI: 3.6%, - 8.2%), Myocardial Infarction (MI) (4.9%; 95% CI: 2%, - 7.9%) and Heart Failure (HF) (4.1%; 95% CI: 2.7%, - 5.5%) were less common in PWE. The prevalence rates for the comorbidities of thyroid disorders and cancer in PWE were 6.9% (95% CI: 3.9%, - 9.9%) and 6.7% (95% CI: 4.9%, - 8.4%) respectively. The prevalence rates for migraine and hearing loss in PWE were 10.7% (95% CI: 8%, - 13.4%) and 6.3% (95% CI: 3.9%, - 8.7%). See Table 1 for pooled prevalence estimates. All the meta-analyses were affected by considerable heterogeneity ( $I^2 > 75\%$ ) and should be interpreted cautiously (19).

### **Meta-regression (*Major Depressive Disorder and Anxiety*)**

A meta-regression was undertaken for the most prevalent comorbidities of Major Depressive Disorder (MDD) and anxiety disorders in PWE, examining the moderating factors of a country's income and age group. Using the most common subgroup of adults with epilepsy as a reference point, it was evident that children with epilepsy had a lower prevalence of MDD (-10.8%, 95% CI: -17.3%, -4.2%,  $P=0.001$ ) and a lower prevalence of anxiety disorders (-10.4%, 95% CI: -20.5%, -0.2%,  $P=0.046$ ) (See Table 2). A country's income appeared to have a limited influence on the prevalence of MDD and anxiety disorders in PWE.

### **Subgroup analysis**

Upon visual inspection of the subgroup analysis for country income, the estimated prevalence rates for hypertension in PWE were significantly lower for both LMIC (6.2%; 95% CI: 3.5%, - 8.9%) and UMIC (8.9%; 95% CI: 2%, - 15.9%) compared to HIC (23.1%; 95% CI: 16.1%, - 30.1%). Similarly, a significantly lower prevalence rate was also observed for stroke when comparing LMIC (1.8%; 95% CI: 0.0%, - 3.9%) and UMIC (2.9%; 95% CI: 2.8%, - 3%) compared to HIC (18%; 95% CI: 10.8%, - 25.2%) (See Appendix B: hypertension and stroke supplementary data).

The comorbidities among most age groups were similar: anxiety and MDD; although the rates varied. The three most common comorbidities in children with epilepsy were anxiety disorders (9.8%; 95% CI: 5.5%, - 14%), MDD (7%; 95% CI: 2.4%, - 11.5%), and asthma (3%; 95% CI: 1%, - 5%) (See Table 3). The two most common comorbidities in adolescents with epilepsy were anxiety disorders (32.7%; CI: 28.4%, - 37.1%) and MDD: (20.1%; CI: 7.3%, - 32.8%) (See Table 4). Anxiety disorders (21.7%; 95% CI: 19.2%, - 24.3%), MDD (18.9%; 95% CI: 15.5%, -

22.3%) and asthma (16.3%; 95% CI: 1.5%, - 31.1%) were the three most commonly reported comorbidities in adults with epilepsy (See Table 5). However, the three most commonly reported comorbidities in the elderly with epilepsy group were hypertension (65%; 95% CI: 61.3%, - 68.6%), stroke (37%; 95% CI: 28.6%, - 45.4%) and diabetes (19%; 95% CI: 13.6%, - 24.5%) (See Table 6).

*Insert Tables 1-6 here*

## **DISCUSSION**

Anxiety disorders and MDD are common in PWE for all ages although rates vary. The income status of the study population's country appeared to have only a limited influence on the prevalence of anxiety disorders and MDD in PWE. This suggests that anxiety and MDD are common in PWE in all countries. The common prevalence of anxiety and MDD in PWE has been observed previously (134-136), and that the prevalence may be more common in PWE than in the general population (3, 137). The lifetime prevalence of overall anxiety in PWE has previously been estimated to be as high as 22% (95% CI 14.8%, -30.9%) (138) compared to 5.6% in the general population (73). The interplay between epilepsy, anxiety and depression are complex. Whilst anxiety and depression may occur as a consequence of having a chronic medical condition, there are also biological mechanisms that make PWE more susceptible to mental health disorders (139). Depression may be three to ten times more common in PWE compared to the general population (140). However, anxiety and depression may still be under-recognised in PWE in clinical practice (18, 108), and when recognised there may be a reluctance to initiate pharmacological treatment due to fear that antidepressants might theoretically worsen seizure control even though the evidence of an important effect in

clinical practice is scarce (141). Failure to recognise or diagnose depression in PWE, or delayed or inadequate treatment, may lead to worsening mental health conditions and poorer health-related quality of life for those affected (142-144). Depression may even increase the risk for suicide ideation and suicide attempts in PWE (145). There are also healthcare resource implications as evidence suggests that people with untreated depression use significantly more health resources, particularly in lower-income-countries (146).

Certain physical health related comorbidities are also common in PWE including hypertension and stroke. The prevalence rates for these circulatory system comorbidities are significantly lower for those PWE living in lower-income-countries compared to those in high-income-countries. This may be due to the fact that in lower-income-countries epilepsy is more likely to be associated with brain infections and brain injury and that the population structure is different with fewer elderly people in lower income countries, whilst in high income countries there are more elderly people and the incidence of epilepsy is now higher in the elderly than in children, in part due to vascular disease (147).

Our review also found that asthma, arthritis, and diabetes are common in PWE. These findings are supported by similar studies' findings: a Californian study found that PWE self-reported higher rates of Type 2 diabetes, asthma, heart disease, arthritis, and stroke than the population without epilepsy (146). Prior reviews of comorbidity in PWE have suggested a causal association between hypertension and diabetes – both of which are risk factors for stroke (18). However, few studies appear to have systematically assessed the prevalence of such comorbid conditions in PWE and / or conducted comparisons between different HIC, UMIC, LMIC and LIC countries. Our findings suggest that these physical health related

comorbidities in PWE (including their underlying factors) warrant further investigation. Findings from future studies may inform opportunities to intervene earlier and / or treat these common comorbid conditions in PWE.

### **Strengths & limitations**

The strengths of this review were the large number of studies included from different countries, the wide range of (both mental health and physical health related) comorbid conditions examined, the inclusion of different age groups, the comprehensive data searches, and analyses conducted. The review included all types of studies including all types of settings i.e. hospital and non-hospital-based settings which may have biased findings. The comorbidities included in the studies must have been derived from clinical records, physical diagnosis or a validated questionnaire / score / index. However, it is acknowledged that the diagnostic accuracy of conditions (particularly for psychiatric conditions) varies depending upon the method, as well as the availability of a physician. The review's included studies had a low risk of bias. However, the prevalence estimates of the different types of comorbid conditions experienced by PWE varied amongst studies that were available; and studies mainly reported on findings for adults with epilepsy with limited available data for children and adolescents. It was not possible to conduct an analysis of the relationship between health inequalities and the prevalence of comorbidities in PWE as originally planned due to studies' lack of comparative socioeconomic data. Therefore, we were unable to ascertain whether the burden of comorbidities is greater in more deprived populations with epilepsy. Whilst reference checks of included studies were undertaken, forward citation searches of the included studies were not undertaken as indicated in the original published protocol due

to staffing constraints. The search was limited to studies published in the English language and studies may be available in other languages.

## **CONCLUSIONS**

Anxiety and depression are common in PWE across all age groups, although rates vary. Certain circulatory system conditions and physical health conditions including hypertension, stroke, heart disease, diabetes, arthritis, and asthma are also common in PWE. There is no evidence that a country's income is a moderating factor for anxiety and depression. However, there is evidence to show that it is a moderating factor for hypertension and stroke, as rates for these comorbidities were significantly lower for lower-income countries compared to high-income-countries. Further international research is needed to confirm findings and to inform appropriate interventions.

## **KEY POINTS**

- Comorbidities impact detrimentally on people's health & wellbeing
- The prevalence of comorbidities in people with epilepsy were reviewed
- Anxiety and depression are common in all people with epilepsy and rates vary with age
- Certain circulatory and physical health comorbidities are also common in epilepsy
- Further studies are needed including those from lower-income-countries

## **REFLECTIVE QUESTIONS**

- Anxiety and depression may still be under-recognised in people with epilepsy in clinical practice. *How do we improve healthcare professionals' awareness and care management of anxiety and depression in people with epilepsy of all ages?*
- Certain circulatory and physical health related comorbidities are also common in people with epilepsy including hypertension, stroke, asthma, arthritis, and diabetes. *How do we best address the circulatory and physical health related support needs of people with epilepsy?*
- *What kinds of studies involving people with epilepsy warrant further investigation?*

## REFERENCES

1. Forsgren L, Nystrom L. An incident case-referent study of epileptic seizures in adults. *Epilepsy Res.* 1990;6(1):66-81. [https://doi.org/10.1016/0920-1211\(90\)90010-s](https://doi.org/10.1016/0920-1211(90)90010-s)
2. Gijzen R, Hoeymans N, Schellevis FG, Ruwaard D, Satariano WA, van den Bos GA. Causes and consequences of comorbidity: a review. *J Clin Epidemiol.* 2001 Jul;54(7):661-74. doi: 10.1016/s0895-4356(00)00363-2. PMID: 11438406.
3. Boro A, Haut S. Medical comorbidities in the treatment of epilepsy. *Epilepsy Behav.* 2003;4:2-12. <https://doi.org/10.1016/j.yebeh.2003.07.002>
4. Seidenberg M, Pulsipher DT, Hermann B. Association of epilepsy and comorbid conditions. *Future Neurol.* 2009;4(5):663-8. <https://dx.doi.org/10.2217%2Ffnl.09.32>
5. Ertem DH, Dirican AC, Aydın A, Baybas S, Sözmen V, Ozturk M, et al. Exploring psychiatric comorbidities and their effects on quality of life in patients with temporal lobe epilepsy and juvenile myoclonic epilepsy. *Psychiatry Clin Neurosci.* 2017 Apr;71(4):280-288. doi: 10.1111/pcn.12499. Epub 2017 Feb 8. PMID: 28025856.
6. Jacoby A, Baker GA, Steen N, Potts P, Chadwick DW. The Clinical Course of Epilepsy and Its Psychosocial Correlates: Findings from a U.K. Community Study. *Epilepsia.* 1996;37(2):148-61. <https://doi.org/10.1111/j.1528-1157.1996.tb00006.x>
7. Collings JA. Psychosocial Well-Being and Epilepsy: An Empirical Study. *Epilepsia.* 1990;31(4):418-26. <https://doi.org/10.1111/j.1528-1157.1990.tb05497.x>
8. Mula M. Chapter 16 - Epilepsy and mood disorders. In: Mula M, editor. *The Comorbidities of Epilepsy*. Academic Press; 2019. p. 299-314
9. Thurman DJ, Logroscino G, Beghi E, Hauser WA, Hesdorffer DC, Newton CR, et al. The burden of premature mortality of epilepsy in high-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy. *Epilepsia.* 2017;58(1):17-26. <https://doi.org/10.1111/epi.13604>
10. Li X, Breteler MM, de Bruyne MC, Meinardi H, Hauser WA, Hofman A. Vascular determinants of epilepsy: the Rotterdam Study. *Epilepsia.* 1997;38(11):1216-20. <https://doi.org/10.1111/j.1528-1157.1997.tb01219.x>
11. Ottman R, Lipton RB. Comorbidity of migraine and epilepsy. *Neurology.* 1994;44(11):2105-10. <https://doi.org/10.1212/wnl.44.11.2105>



12. Lamminpää A, Pukkala E, Teppo L, Neuvonen PJ. Cancer incidence among patients using antiepileptic drugs: a long-term follow-up of 28,000 patients. *Eur J Clin Pharmacol*. 2002;58(2):137-41. <https://doi.org/10.1007/s00228-002-0429-6>
13. Nuyen J, Schellevis FG, Satariano WA, Spreeuwenberg PM, Birkner MD, van den Bos GA, et al. Comorbidity was associated with neurologic and psychiatric diseases: a general practice-based controlled study. *J Clin Epidemiol*. 2006;59(12):1274-84. <https://doi.org/10.1016/j.jclinepi.2006.01.005>
14. Velioglu SK, Boz C, Ozmenoglu M. The impact of migraine on epilepsy: a prospective prognosis study. *Cephalalgia*. 2005;25(7):528-35. <https://doi.org/10.1111/j.1468-2982.2005.00912.x>
15. Taylor RS, Sander JW, Taylor RJ, Baker GA. Predictors of health-related quality of life and costs in adults with epilepsy: a systematic review. *Epilepsia*. 2011;52(12):2168-80. <https://doi.org/10.1111/j.1528-1167.2011.03213.x>
16. Macleod U, Mitchell E, Black M, Spence G. Comorbidity and socioeconomic deprivation: an observational study of the prevalence of comorbidity in general practice. *Eur J Gen Pract*. 2004 Mar;10(1):24-6. doi: 10.3109/13814780409094223. PMID: 15060478. <https://doi.org/10.3109/13814780409094223>
17. Pathirana TI, & Jackson CA. Socioeconomic status and multimorbidity: a systematic review and meta-analysis. *Aust N Z J Public Health*. 2018. 42:186-194. <https://doi.org/10.1111/1753-6405.12762>
18. Gaitatzis A, Sisodiya SM, Sander JW. The somatic comorbidity of epilepsy: a weighty but often unrecognized burden. *Epilepsia*. 2012;53(8):1282-93. <https://doi.org/10.1111/j.1528-1167.2012.03528.x>
19. Higgins J, Chandler J, Cumpston M, Li T, Page M, Welch V. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.0 (updated July 2019). 2019. <https://training.cochrane.org/handbook>
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine*. 2009;6(7):e1000097. <https://doi.org/10.1136/bmj.b2535>
21. Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. *Ann Intern Med*. 2007 Aug 21;147(4):224-33. doi: 10.7326/0003-4819-147-4-200708210-00179. Epub 2007 Jul 16. PMID: 17638714.
22. Stovold E, Beecher D, Foxlee R, Noel-Storr A. Study flow diagrams in Cochrane systematic review updates: an adapted PRISMA flow diagram. *Syst Rev* 3, 54 (2014). <https://doi.org/10.1186/2046-4053-3-54>
23. *The World Bank Annual Report 2018 (English)*. Washington, D.C. : World Bank Group. <http://documents.worldbank.org/curated/en/630671538158537244/The-World-Bank-Annual-Report-2018>
24. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol*. 2012;65(9):934-9. <https://doi.org/10.1016/j.jclinepi.2011.11.014>
25. Viechtbauer W. Conducting Meta-Analyses in R with the Metafor Package. *Journal of Statistical Software*, 2010.36(3), 1 - 48. doi:<http://dx.doi.org/10.18637/jss.v036.i03>
26. Wallace BC, Dahabreh IJ, Thomas A, Trikalinos JL, Trow P, Schmid CH. Closing the Gap between Methodologists and End-Users: R as a Computational Back-End. *Journal of Statistical Software* 49 (2012): 5.
27. Aaberg KM, Bakken IJ, Lossius MI, Lund Soraas C, Haberg SE, Stoltenberg C, et al. Comorbidity and Childhood Epilepsy: A Nationwide Registry Study. *Pediatrics*. 2016;138(3). DOI: [10.1542/peds.2016-0921](https://doi.org/10.1542/peds.2016-0921)
28. Abadiga M, Mosisa G, Amente T, & Oluma A. Health-related quality of life and associated factors among epileptic patients on treatment follow up at public hospitals of Wollega

- zones, Ethiopia, BMC Res Notes. 2019; 12(1), 679. <https://doi.org/10.1186/s13104-019-4720-3>
29. Adebayo PB, Akinyemi RO, Oluwole F, Ogun SA, Ogunniyi A. Impact of somatic comorbidities on quality of life of patients living with epilepsy in Sagamu, Nigeria. *Acta Neurol Scand*. 2014;130(6):387-93. <https://doi.org/10.1111/ane.12281>
  30. Adewuya A, Ola BA, & Okeniyi J. Psychiatric morbidity in Nigerian adolescents with epilepsy. *J Pediatr Neurol: JPN*. 2005a; 3, 153-158.
  31. Adewuya AO, Ola BA. Prevalence of and risk factors for anxiety and depressive disorders in Nigerian adolescents with epilepsy. *Epilepsy Behav: E&B*. 2005b;6(3):342-7. <https://doi.org/10.1016/j.yebeh.2004.12.011>
  32. Afifi T, Elessi K, Samaan M, Alaqad A, Abu Elhatal H, & Abu-Lamzi, A. Management of Epilepsy among Children in the Gaza Strip: A Multicenter Clinical Audit. *Dubai Medical Journal*. 2019; 2(3), 90-98. <https://doi.org/10.1159/000503028>
  33. Ajinkya S, Fox J, Lekoubou A. Trends in prevalence and treatment of depressive symptoms in adult patients with epilepsy in the United States. *Epilepsy Behav*. 2020 Apr;105:106973. doi: 10.1016/j.yebeh.2020.106973. Epub 2020 Mar 9. PMID: 32163889.
  34. Almane DN, Jones JE, McMillan T, Stafstrom CE, Hsu DA, Seidenberg M, et al. The Timing, Nature, and Range of Neurobehavioral Comorbidities in Juvenile Myoclonic Epilepsy [Research Support, N.I.H., Extramural]. *Pediatr Neurosci*. 2019; 101, 47-52.
  35. Alsaadi T, El Hammami K, Shahrour TM, Shakra M, Turkawi L, Nasreddine W, et al. Depression and Anxiety among Patients with Epilepsy and Multiple Sclerosis: UAE Comparative Study. *Behav Neurol*. 2015;2015:196373. <https://doi.org/10.1155/2015/196373>
  36. Alsaadi T, Kassie S, Ali OM, Mozahem K, Al Fardan S, & Ahmed AM. Psychiatric comorbidity in neurological disorders: Towards a multidisciplinary approach to illness management in the United Arab Emirates. *Front Psychiatry*. 2019;10(APR), Article 263. <https://dx.doi.org/10.3389%2Ffpsy.2019.00263>
  37. Amruth G, Praveen-Kumar S, Nataraju B, Kasturi P. Study of psychiatric comorbidities in epilepsy by using the Mini International Neuropsychiatric Interview. *Epilepsy Behav: E&B*. 2014;33:94-100. <https://doi.org/10.1016/j.yebeh.2014.02.001>
  38. Ayanda KA, & Sulyman D. The predictors of psychiatric disorders among people living with epilepsy as seen in a Nigerian Tertiary Health Institution. *Niger Med J*. 2016;57(1), 24-30. <https://dx.doi.org/10.4103%2F0300-1652.180559>
  39. Baca CB, Vickrey BG, Caplan R, Vassar SD, Berg AT. Psychiatric and Medical Comorbidity and Quality of Life Outcomes in Childhood-Onset Epilepsy. *Pediatrics*. 2011;128(6):e1532. <https://doi.org/10.1542/peds.2011-0245>
  40. Balibey H, Yasar H, Tekeli H, Bayar N. Frequency of Anxiety and Depression in Epileptic Patients. *Klinik Psikofarmakol Bülteni*. 2015;25(2):136-40. <https://doi.org/10.5455/bcp.20130429122553>
  41. Bandyopadhyay S, Bangalore-Vittal N, Arain AM. Management outcome in elderly adults with epilepsy in a tertiary care epilepsy center. *J Am Geriatr Soc*. 2016;64(11):e216-7. <https://doi.org/10.1111/jgs.14413>
  42. Begasse de Dhaem OAJ, French J, Morrison C, Meador KJ, Hesdorffer DC, Cristofaro S, et al. Migraine comorbidity and cognitive performance in patients with focal epilepsy. *Epilepsy Behav*. 2019; 97, 29-33. DOI: 10.1016/j.yebeh.2019.05.008
  43. Beghi E, Roncolato M, Visonà G. Depression and Altered Quality of Life in Women with Epilepsy of Childbearing Age. *Epilepsia*. 2004;45(1):64-70. <https://www.researchgate.net/deref/http%3A%2F%2Fdx.doi.org%2F10.1111%2Fj.0013-9580.2004.56502.x>
  44. Biftu BB, Dachew BA, Tiruneh BT, & Birhan Tebeje N. Depression among people with epilepsy in Northwest Ethiopia: a cross-sectional institution based study. *BMC Res Notes*. 2015;8(1). <https://doi.org/10.1186/s13104-015-1515-z>

45. Bosak M, Dudek D, Siwek M, Szczudlik A. Subtypes of interictal depressive disorders according to ICD-10 in patients with epilepsy. *Neurol Neurochir Pol.* 2015;49(2):90-4. <https://doi.org/10.1016/j.pjnns.2015.01.008>
46. Bosak M, Kowalik M, Molek P, & Slowik A. Somatic comorbidity in Polish patients with epilepsy. *Pol Arch Intern Med.* 2019;129(5), 303-307. <https://dx.doi.org/10.20452/pamw.14794>
47. Bragatti JA, Torres CM, Londero RG, Assmann JB, Fontana V, Martin KC, et al. Prevalence of psychiatric comorbidities in temporal lobe epilepsy: the value of structured psychiatric interviews. *Epileptic Disord.* 2010;Dec;12(4):283-91. doi: 10.1684/epd.2010.0345. Epub 2010 Nov 29. PMID: 21112827
48. Bragatti JA, Torres CM, Londero RG, Martin KC, Souza AC, Hidalgo MP, et al. Prevalence of psychiatric comorbidities in temporal lobe epilepsy in a Southern Brazilian population. *Arq Neuropsiquiatr.* 2011;69(2a):159-65. <https://doi.org/10.1590/S0004-282X2011000200003>
49. Brandt C, Schoendienst M, Trentowska M, May TW, Pohlmann-Eden B, Tuschen-Caffier B, et al. Prevalence of anxiety disorders in patients with refractory focal epilepsy--a prospective clinic based survey. *Epilepsy Behav.* 2010;17(2):259-63. <https://doi.org/10.1016/j.yebeh.2009.12.009>
50. Bruun E, Virta LJ, Kalviainen R, Keranen T. Co-morbidity and clinically significant interactions between antiepileptic drugs and other drugs in elderly patients with newly diagnosed epilepsy. *Epilepsy Behav.* 2017;73:71-6. <https://doi.org/10.1016/j.yebeh.2017.05.022>
51. Burkhardt M, Bacher M, Kornmeier R, Kurth C, Staack AM, Steinhoff BJ. The General and Social Health Long-Term Outcome of Adult Epilepsy Patients at the Kork Epilepsy Center. *Neurol Int Open.* 2018;2(02):131-5. DOI: 10.1055/a-0621-8559
52. Camara-Lemarroy CR, Hoyos M, Ibarra-Yruegas BE, Diaz-Torres MA, De Leon R. Affective symptoms and determinants of health-related quality of life in Mexican people with epilepsy. *Neurol Sci.* 2017;38(10):1829-34. <https://doi.org/10.1007/s10072-017-3075-6>
53. Chaka A, Awoke T, Yohannis Z, Ayano G, Tareke M, Abate A, et al. Determinants of depression among people with epilepsy in Central Ethiopia. *Ann Gen Psychiatry.* 2018;17:27. <https://doi.org/10.1186/s12991-018-0197-z>
54. Chandrasekharan SC, Menon V, Wadwekar V, Nair PP. High Frequency of Depressive Symptoms among Adults with Epilepsy: Results from a Hospital-based Study. *J Neurosci Rural Pract.* 2017;8(Suppl 1):S13-S9. [https://dx.doi.org/10.4103%2Fjnnp.jnnp\\_21\\_17](https://dx.doi.org/10.4103%2Fjnnp.jnnp_21_17)
55. Chang CS, Liao CH, Lin CC, Lane HY, Sung FC, Kao CH. Patients with epilepsy are at an increased risk of subsequent stroke: a population-based cohort study. *Seizure.* 2014;23(5):377-81. <https://doi.org/10.1016/j.seizure.2014.02.007>
56. Chen Z, Liew D, Kwan P. Excess mortality and hospitalized morbidity in newly treated epilepsy patients. *Neurology.* 2016;87(7):718-25. <https://dx.doi.org/10.1212%2FWNL.0000000000002984>
57. Chung MC, Allen RD, Dennis I. The impact of self-efficacy, alexithymia and multiple traumas on posttraumatic stress disorder and psychiatric co-morbidity following epileptic seizures: A moderated mediation analysis. *Psychiatry Res.* 2013;210(3):1033-41. <https://doi.org/10.1016/j.psychres.2013.07.041>
58. Çilliler AE, Güven B. Sleep quality and related clinical features in patients with epilepsy: A preliminary report. *Epilepsy Behav.* 2020 Jan;102:106661. doi: 10.1016/j.yebeh.2019.106661. Epub 2019 Nov 23. PMID: 31766003.
59. Cramer JA, Brandenburg N, Xu X. Differentiating anxiety and depression symptoms in patients with partial epilepsy. *Epilepsy Behav.* 2005;6(4):563-9. <https://doi.org/10.1016/j.yebeh.2005.02.017>
60. Dabla S, Juneja H, Singh P, & Bala K. Depression, anxiety and suicidal ideation/behaviour among persons with epilepsy: Common but underestimated comorbidities in Haryana, North India. *Neurology Asia.* 2020;25(1), 7-12.

61. Dafoulis V, & Kalyva E. Factors associated with behavioral problems in children with idiopathic epilepsy. *Epilepsy Res.* 2012;100(1-2), 104-112.  
<https://doi.org/10.1016/j.eplepsyres.2012.01.014>
62. Dalmagro CL, Velasco TR, Bianchin MM, Martins AP, Guarnieri R, Cescato MP, et al. Psychiatric comorbidity in refractory focal epilepsy: a study of 490 patients. *Epilepsy Behav.* 2012;25(4):593-7.  
<https://www.researchgate.net/deref/http%3A%2F%2Fdx.doi.org%2F10.1016%2Fj.yebeh.2012.09.026>
63. De A Filho GM, Rosa VP, Lin K, Caboclo LO, Sakamoto AC, Yacubian EM. Psychiatric comorbidity in epilepsy: a study comparing patients with mesial temporal sclerosis and juvenile myoclonic epilepsy. *Epilepsy Behav.* 2008;13(1):196-201.  
<https://doi.org/10.1016/j.yebeh.2008.01.008>
64. De A Filho G, Mazetto L, Silva J, Caboclo L, Yacubian E. Psychiatric comorbidity in patients with two prototypes of focal versus generalized epilepsy syndromes. *Seizure.* 2011;20:383-6.  
<https://doi.org/10.1016/j.seizure.2011.01.007>
65. de Oliveira GNM, Kummer A, Salgado JV, Portela EJ, Sousa-Pereira SR, David AS, et al. Psychiatric disorders in temporal lobe epilepsy: An overview from a tertiary service in Brazil. *Seizure.* 2010;19(8):479-84. <https://doi.org/10.1016/j.seizure.2010.07.004>
66. Dhull P, Patnaik SK, Somasekharan M, & Kumar KVSH. Long-Term study about the incidence of epilepsy in male service personnel from india: A retrospective, cohort study. *J Neurosci Rural Pract.* 2019;10(4):588-591. <https://doi.org/10.1055/s-0039-1700792>
67. Ebong IM, Lopez MR, Kanner AM, Wallace DM. The relationship between mood disorder and insomnia depends on race in US veterans with epilepsy. *Epilepsy Behav.* 2017;70(Pt A):80-6.  
<https://doi.org/10.1016/j.yebeh.2017.02.004>
68. Ettinger AB, Weisbrot DM, Nolan EE, Gadow KD, Vitale SA, Andriola MR, et al. Symptoms of Depression and Anxiety in Pediatric Epilepsy Patients. *Epilepsia.* 1998;39(6):595-9.  
<https://doi.org/10.1111/j.1528-1157.1998.tb01427.x>
69. Fazel S, Wolf A, Langstrom N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. *Lancet (London, England).* 2013;382(9905):1646-54. [https://doi.org/10.1016/S0140-6736\(13\)60899-5](https://doi.org/10.1016/S0140-6736(13)60899-5)
70. Fela-Thomas A, Akinhanmi A, Esan O. Prevalence and correlates of major depressive disorder (MDD) among adolescent patients with epilepsy attending a Nigerian neuropsychiatric hospital. *Epilepsy Behav.* 2016;54:58-64. <https://doi.org/10.1016/j.yebeh.2015.11.008>
71. Fiordelli E, Beghi E, Bogliun G, Crespi V. Epilepsy and psychiatric disturbance. A cross-sectional study. *Br J Psychiatry* 1993;163:446-50. <https://doi.org/10.1192/bjp.163.4.446>
72. Gabriel, D., Ventura, M., Samões, R., Freitas, J., Lopes, J., Ramalheira, J., et al. Social impairment and stigma in genetic generalized epilepsies. *Epilepsy Behav.* 2020;104(Part A).  
<https://doi.org/10.1016/j.yebeh.2019.106886>
73. Gaitatzis A, Carroll K, Majeed A, W Sander J. The epidemiology of the comorbidity of epilepsy in the general population. *Epilepsia.* 2004;Dec;45(12):1613-22. doi: 10.1111/j.0013-9580.2004.17504.x. PMID: 15571520.
74. Gatta M, Raffagnato A, Mannarini S, Balottin L, Toldo I, BVecchi M, et al. Pediatric epilepsy and psychiatric comorbidity: preliminary observational data from a prospective study. *Minerva Pediatr.* 2018;70(6):501-12. <https://doi.org/10.23736/s0026-4946.17.04753-3>
75. Grahovac D, Ružić K, Grahovac T, Dadić-Hero E, Bajek S. Epilepsy in the elderly and depression. *Coll Antropol.* 2011;35 Suppl 2:179-81. <https://hrcak.srce.hr/72261>
76. Gulpek D, Bolat E, Mete L, Arici S, Celebisoy M. Psychiatric comorbidity, quality of life and social support in epileptic patients. *Nord J Psychiatry.* 2011;65:373-80.  
<https://doi.org/10.3109/08039488.2011.565798>



77. Gupta S, Sharma N, Bharti S, Sharma R, Kohli A, Agarwal A, et al. Depression and anxiety in patients with epilepsy. *IJAM*. 2018;5(5):6 <https://dx.doi.org/10.18203/2349-3933.ijam20183906>
78. Jansen C, Francomme L, Vignal JP, Jacquot C, Schwan R, Tyvaert L, et al. Interictal psychiatric comorbidities of drug-resistant focal epilepsy: Prevalence and influence of the localization of the epilepsy. *Epilepsy Behav*. 2019;94:288-96. <https://doi.org/10.1016/j.yebeh.2018.06.046>
79. Jones JE, Watson R, Sheth R, Caplan R, Koehn M, Seidenberg M, et al. Psychiatric comorbidity in children with new onset epilepsy. *Dev Med Child Neurol Suppl*. 2007;49(7):493-7. <https://doi.org/10.1111/j.1469-8749.2007.00493.x>
80. Kessler RC, Lane MC, Shahly V, Stang PE. Accounting for comorbidity in assessing the burden of epilepsy among US adults: results from the National Comorbidity Survey Replication (NCS-R). *Mol Psychiatry*. 2012;17(7):748-58. <https://doi.org/10.1038/mp.2011.56>
81. Kim J, Kim Y, Bae JS, Lee JH, & Song HK. Concomitant psychiatric symptoms in neurological outpatients. *Int J Environ Res Public Health*. 2019;16(5), Article 860. <https://dx.doi.org/10.3390%2Fijerph16050860>
82. Kuladee S, Prachason T, Srisopit P, Trakulchang D, Boongird A, Wisajan P, et al. Prevalence of psychiatric disorders in Thai patients with epilepsy. *Epilepsy Behav*. 2019;90:20-4. <https://doi.org/10.1016/j.yebeh.2018.11.004>
83. Kwon O-Y, Park S-P. Frequency of affective symptoms and their psychosocial impact in Korean people with epilepsy: A survey at two tertiary care hospitals. *Epilepsy Behav*. 2013;26(1):51-6. <https://doi.org/10.1016/j.yebeh.2012.10.020>
84. Kwong KL, Lam D, Tsui S, Ngan M, Tsang B, Lai TS, et al. Anxiety and Depression in Adolescents With Epilepsy. *J Child Neurol*. 2016;31(2):203-10. <https://doi.org/10.1177%2F0883073815587942>
85. LaGrant B, Marquis BO, Berg AT, & Grinspan ZM. Depression and anxiety in children with epilepsy and other chronic health conditions: National estimates of prevalence and risk factors. *Epilepsy Behav*. 2020;Part A. 103. Article 106828. <https://doi.org/10.1016/j.yebeh.2019.106828>
86. Lekoubou A, Fox J, Bishu KG, Ovbiagele B. Trends in documented cannabis use disorder among hospitalized adult epilepsy patients in the United States. *Epilepsy Res*. 2020 Jul;163:106341. doi: 10.1016/j.eplepsyres.2020.106341. Epub 2020 Apr 18. PMID: 32361206. <https://doi.org/10.1016/j.eplepsyres.2020.106341>
87. Li Q, Chen D, Zhu LN, Wang HJ, Xu D, Tan G, et al. Depression in people with epilepsy in West China: Status, risk factors and treatment gap. *Seizure*. 2019;66, 86-92. <https://doi.org/10.1016/j.seizure.2019.02.014>
88. Li T, Zhou H, Li Y, Li C, Zhang Y, Zhou Y, et al. Assessment of the neuropsychiatric comorbidities in Chinese children with epilepsy using the MINI-KID tool. *Epilepsy Res*. 2018;140:8-14. <https://doi.org/10.1016/j.eplepsyres.2017.11.011>
89. Lin CY, Harnod T, Lin CL, Shen WC, & Kao CH. Differences in Incidence and Risks of Suicide Attempt and Suicidal Drug Overdose between Patients with Epilepsy with and without Comorbid Depression [Research Support, Non-U.S. Gov't]. *Int J Environ Health Res*. 2019;16(22), 15. <https://dx.doi.org/10.3390%2Fijerph16224533>
90. Liu Z, Yin R, Fan Z, Fan H, Wu H, Shen B, et al. Gender differences in associated and predictive factors of anxiety and depression in people with epilepsy. *Front Psychiatry*. 2020 Jul 10;11:670. doi: 10.3389/fpsy.2020.00670. PMID: 32754069; PMCID: PMC7365887.
91. Maruzairi H, Jamil BYM, Salmi AR, Pridmore S. Spectrum of psychiatric disorders in children with epilepsy: a Malaysian sample. *IMJ*. 2009;16(2):113-6. [https://www.researchgate.net/publication/288806554\\_Spectrum\\_of\\_psychiatric\\_disorders\\_in\\_children\\_with\\_epilepsy\\_A\\_Malaysian\\_sample](https://www.researchgate.net/publication/288806554_Spectrum_of_psychiatric_disorders_in_children_with_epilepsy_A_Malaysian_sample)

92. M'bayo T, Tomek M, Kamara C, Lisk DR. Psychiatric comorbidity in African patients with epilepsy – Experience from Sierra Leone. *Int J Epilepsy*. 2017;04(01):026-30.  
<https://doi.org/10.1016/j.ijep.2016.12.002>
93. McLaughlin DP, Pachana NA, McFarland KJE, Behavior. Depression in a community-dwelling sample of older adults with late-onset or lifetime epilepsy. *Epilepsy Behav*. 2008;12(2):281-5.  
<https://doi.org/10.1016/j.yebeh.2007.10.005>
94. Mensah S, Beavis J, Thapar A, Kerr M. A community study of the presence of anxiety disorder in people with epilepsy. *Epilepsy Behav*. 2007;11:118-24.  
<https://doi.org/10.1016/j.yebeh.2007.04.012>
95. Mohammadi MR, Ghanizadeh A, Davidian H, Mohammadi M, Norouzzian M. Prevalence of epilepsy and comorbidity of psychiatric disorders in Iran. *Seizure*. 2006;15(7):476-82.  
<https://doi.org/10.1016/j.seizure.2006.05.011>
96. Mosaku KS, Fatoye FO, Komolafe M, Lawal M, & Ola BA. Quality of Life and Associated Factors among Adults with Epilepsy in Nigeria. *Int J Psychiatry Med*. 2006; 36(4), 469-481.  
<https://doi.org/10.2190/r80g-580x-x1h2-6936>
97. Munger Clary HM, Snively BM, Hamberger MJ. Anxiety is common and independently associated with clinical features of epilepsy. *Epilepsy Behav*. 2018;85:64-71.  
<https://doi.org/10.1016/j.yebeh.2018.05.024>
98. Nubukpo P, Preux PM, Houinato D, Radji A, Grunitzky EK, Avodé G, et al. Psychosocial issues in people with epilepsy in Togo and Benin (West Africa) I. Anxiety and depression measured using Goldberg's scale. *Epilepsy Behav*. 2004;5(5):722-7.  
<https://doi.org/10.1016/j.yebeh.2004.07.001>
99. Ogunrin OA, & Obiabo YO. Depressive symptoms in patients with epilepsy: analysis of self-rating and physician's assessment. *Neurol India*. 2010;58(4), 565-570.  
<https://www.neurologyindia.com/text.asp?2010/58/4/565/68679>
100. Oguz A, Kurul S, Dirik E, & Eylül D. Relationship of Epilepsy-Related Factors to Anxiety and Depression Scores in Epileptic Children. *J Child Neurol*. 2002;17(1), 37-40.  
<https://doi.org/10.1177%2F088307380201700109>
101. Oh A, Thurman DJ, Kim H. Comorbidities and risk factors associated with newly diagnosed epilepsy in the U.S. pediatric population. *Epilepsy Behav*. 2017;75:230-6.  
<https://doi.org/10.1016/j.yebeh.2017.07.040>
102. Okubadejo NU, Danesi MA, Aina OF, Ojini FI, Adeyemi JD, Olorunshola DA. Prospective case-control study of interictal depression and suicidal ideation in Nigerians with epilepsy. *Niger Postgrad Med J*. 2007 Sep;14(3):204-8. PMID: 17767203.
103. Owolabi SD, Owolabi LF, Udofia O, Sale S. Depression in patients with epilepsy in Northwestern Nigeria: Prevalence and clinical correlates. *Annals of African medicine*. 2016;15(4):179-84. <https://dx.doi.org/10.4103%2F1596-3519.194279>
104. Pham T, Sauro KM, Patten SB, Wiebe S, Fiest KM, Bulloch AGM, et al. The prevalence of anxiety and associated factors in persons with epilepsy. *Epilepsia*. 2017;58(8):e107-e10.  
<https://doi.org/10.1111/epi.13817>
105. Pranboon S, Tiamkao S, Thepsuthammarat K. Incidence and outcomes of Hospitalized in Adult Patients with Epilepsy: A national data report from Thailand. *J Med Assoc Thai* 2020;103:49. <http://www.jmatonline.com/index.php/jmat/article/view/10747#>
106. Rashid H, Katyal J, Tripathi M, Sood M, & Gupta YK. Validation of the Indian version of Neurological Disorders Depression Inventory for Epilepsy (NDDI-E). *Epilepsy Behav*. 2019;95:75-78. <https://doi.org/10.1016/j.yebeh.2019.03.048>
107. Rehman S, Kalita KK, Baruah A. A hospital based cross sectional study on comorbid psychiatric problems in persons with epilepsy from north eastern part of India. *Int J Epilepsy*. 2017;4:31-5. <https://doi.org/10.1016/j.ijep.2017.01.004>

108. Reilly C, Atkinson P, Das KB, Chin RFMC, Aylett SE, Burch V, et al. Neurobehavioral comorbidities in children with active epilepsy: a population-based study. *PEDIATRICS*. 2014;133(6), e1586-e1593. <https://doi.org/10.1542/peds.2013-3787>
109. Sahu PK, Mishra D, Juneja M, & Taneja K. Clinico-etiological Profile and Developmental Status of Infants Aged 1-24 months with Epilepsy. *Indian J Pediatr*. 2019;86(8): 681-685. <https://doi.org/10.1007/s12098-019-02943-2>
110. Selassie AW, Wilson DA, Martz GU, Smith GG, Wagner JL, Wannamaker BB. Epilepsy beyond seizure: A population-based study of comorbidities. *Epilepsy Res*. 2014;108(2):305-15. <https://doi.org/10.1016/j.epilepsyres.2013.12.002>
111. Sezibera V, & Nyirasafari D. Incidence of depression in Epilepsy patients. *Rwanda Journal*. 2013;1(1). <https://doi.org/10.4314/rj.v1i1.5f>.
112. Si Y, Xiao X, Sun H. Mortality-specific comorbidity among inpatients with epilepsy: A preliminary cross-sectional study in West China. *Epilepsy Behav*. 2018;84:70-3. <https://doi.org/10.1016/j.yebeh.2018.01.035>
113. Sperli F, Rentsch D, Despland PA, Foletti G, Jallon P, Picard F, et al. Psychiatric comorbidity in patients evaluated for chronic epilepsy: a differential role of the right hemisphere? *Eur Neurol*. 2009;61(6):350-7. <https://doi.org/10.1159/000210547>
114. Swinkels WA, Kuyk J, de Graaf EH, van Dyck R, Spinhoven P. Prevalence of Psychopathology in Dutch Epilepsy Inpatients: A Comparative Study. *Epilepsy Behav*. 2001;2(5):441-7. <https://doi.org/10.1006/ebep.2001.0242>
115. Taner Y, Erdoğan-Bakar E, Turanlı G, Topçu M. Psychiatric evaluation of children with CSWS (continuous spikes and waves during slow sleep) and BRE (benign childhood epilepsy with centrotemporal spikes/rolandic epilepsy) compared to children with absence epilepsy and healthy controls. *Turk J Pediatr*. 2007 Oct-Dec;49(4):397-403. PMID: 18246741.
116. Taskiran E, Matur Z, Gul G, Bebek N, Baykan B, Gokyigit A, et al. The impact of affective state on quality of life in focal epilepsy in Turkey. *J Neurosci Rural Pract*. 2019;10(2), 267-272. [https://dx.doi.org/10.4103%2Fjnnp.jnnp\\_324\\_18](https://dx.doi.org/10.4103%2Fjnnp.jnnp_324_18)
117. Tedrus Gloria Maria de Almeida Souza, Fonseca Lineu Correa, Carvalho Rachel Marin. Epilepsy and quality of life: socio-demographic and clinical aspects, and psychiatric co-morbidity. *Arq. Neuro-Psiquiatr*. [Internet]. 2013 June [cited 2021 Mar 18] ; 71( 6 ): 385-391. Available from: [http://www.scielo.br/scielo.php?script=sci\\_arttext&pid=S0004-282X2013000600385&lng=en](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004-282X2013000600385&lng=en). <http://dx.doi.org/10.1590/0004-282X20130044>
118. Tegegne MT, Muluneh NY, Wochamo TT, Awoke AA, Mossie TB, Yesigat MA, Assessment of Quality of Life and Associated Factors among People with Epilepsy Attending at Amanuel Mental Specialized Hospital, Addis Ababa, Ethiopia, *SJPH*. Vol. 2, No. 5, 2014, pp. 378-383. doi: 10.11648/j.sjph.20140205.12
119. Tegegne MT, Mossie TB, Awoke AA, Assaye AM, Gebrie BT, Eshetu D.A. Depression and anxiety disorder among epileptic people at Amanuel Specialized Mental Hospital, Addis Ababa, Ethiopia. *BMC psychiatry*. 15, 210 (2015). <https://doi.org/10.1186/s12888-015-0589-4>
120. Tosun A, Gokcen S, Ozbaran B, Serdaroglu G, Polat M, Tekgul H, et al. The effect of depression on academic achievement in children with epilepsy. *Epilepsy Behav*. 2008;13(3):494-498. <https://doi.org/10.1016/j.yebeh.2008.05.016>
121. Tunde-Ayinmode MF, Abiodun OA, Ajiboye PO, Buhari OI, Sanya EO. Prevalence and clinical implications of psychopathology in adults with epilepsy seen in an outpatient clinic in Nigeria. *Gen Hosp Psychiatry*. 2014;36(6):703-8. <https://doi.org/10.1016/j.genhosppsy.2014.08.009>
122. Venevivi L, Mbewe E, & Paul R. Determining treatment levels of comorbid psychiatric conditions in people with epilepsy attending selected local clinics in Lusaka, Zambia. *Med J Zambia*. 2016;43(4):184-190. <https://www.ajol.info/index.php/mjz/article/view/152148>

123. Viguera AC, Fan Y, Thompson NR, Lapin B, Chaitoff A, Griffith SD, et al. Prevalence and Predictors of Depression Among Patients With Epilepsy, Stroke, and Multiple Sclerosis Using the Cleveland Clinic Knowledge Program Within the Neurological Institute [Research Support, Non-U.S. Gov't]. *Psychosomatics*. 2018;59(4):369-378.  
<https://doi.org/10.1016/j.psych.2017.12.003>
124. Vujisić S, Vodopić S, Radulović L, Injac-Stevović L. Psychiatric comorbidities among patients with epilepsy in Montenegro. *Acta Clin Croat*. 2014 Dec;53(4):411-6. PMID: 25868308. <https://pubmed.ncbi.nlm.nih.gov/25868308/>
125. Wannamaker BB, Wilson DA, Malek AM, Selassie AW. Stroke after adult-onset epilepsy: a population-based retrospective cohort study. *Epilepsy Behav*. 2015;43:93-9.  
<https://doi.org/10.1016/j.yebeh.2014.11.028>
126. Weatherburn CJ, Heath CA, Mercer SW, Guthrie B. Physical and mental health comorbidities of epilepsy: Population-based cross-sectional analysis of 1.5 million people in Scotland. *Seizure*. 2017;45:125-31. <https://doi.org/10.1016/j.seizure.2016.11.013>
127. Wiglusz MS, Landowski J, Michalak L, Cubala WJ. Reevaluating the prevalence and diagnostic subtypes of depressive disorders in epilepsy. *Epilepsy Behav*. 2015;53:15-9.  
<https://doi.org/10.1016/j.yebeh.2015.09.029>
128. Wiglusz MS, Landowski J, & Cubala WJ. Interictal dysphoric disorder of epilepsy: A continuing diagnostic challenge. *Epilepsy Behav*. 2019;95:34-38.  
<https://doi.org/10.1016/j.yebeh.2019.03.036>
129. Williams J, Steel C, Sharp GB, DelosReyes E, Phillips T, Bates S, et al. Anxiety in children with epilepsy. *Epilepsy Behav*. 2003;4(6):729-32.  
<https://doi.org/10.1016/j.yebeh.2003.08.032>
130. Wilner AN, Sharma BK, Soucy A, Thompson A, Krueger A. Common comorbidities in women and men with epilepsy and the relationship between number of comorbidities and health plan paid costs in 2010. *Epilepsy Behav*. 2014;32:15-20  
<https://doi.org/10.1016/j.yebeh.2013.12.032>
131. Xu X, Brandenburg NA, McDermott AM, & Bazil CW. Sleep disturbances reported by refractory partial-onset epilepsy patients receiving polytherapy [Comparative Study]. *Epilepsia*. 2006;47(7):1176-1183. <https://doi.org/10.1111/j.1528-1167.2006.00591.x>
132. Yang C, Hao Z, Mao Y, Xu Q, Zhao L, & Zhang LL. Depression in children with epilepsy from western China: A cross-sectional survey. *Medicine*. 2020;99(24):e20647. doi: 10.1097/MD.00000000000020647
133. Zheng Y, Ding X, Guo Y, Chen Q, Wang W, Zheng Y, et al. Multidisciplinary management improves anxiety, depression, medication adherence, and quality of life among patients with epilepsy in eastern China: A prospective study [Randomized Controlled Trial Research Support, Non-U.S. Gov't]. *Epilepsy Behav*. 2019;100(Pt A),106400.  
<https://doi.org/10.1016/j.yebeh.2019.07.001>
134. Tellez-Zenteno JF, Matijevic S, Wiebe S. Somatic comorbidity of epilepsy in the general population in Canada. *Epilepsia*. 2005;46(12):1955-62.  
<https://doi.org/10.1111/j.1528-1167.2005.00344.x>
135. Fiest KM, Dykeman J, Patten SB, Wiebe S, Kaplan GG, Maxwell CJ, et al. Depression in epilepsy: a systematic review and meta-analysis. *Neurology*. 2013;80(6):590-9.  
<https://doi.org/10.1212/wnl.0b013e31827b1ae0>
136. Josephson CB, Jette N. Psychiatric comorbidities in epilepsy. *Int Rev Psychiatry*. (Abingdon, England). 2017;29(5):409-24. <https://doi.org/10.1080/09540261.2017.1302412>
137. Kobau R, Gilliam F, Thurman DJ. Prevalence of self-reported epilepsy or seizure disorder and its associations with self-reported depression and anxiety: results from the 2004 HealthStyles Survey. *Epilepsia*. 2006;47(11):1915-21. <https://doi.org/10.1111/j.1528-1167.2006.00612.x>



138. Tellez-Zenteno JF, Patten SB, Jette N, Williams J, & Wiebe S. Psychiatric comorbidity in epilepsy: A population-based analysis. *Epilepsia*. 2007;48, 2336–2344.  
<http://dx.doi.org/10.1111/j.1528-1167.2007.01222.x>
139. Pineda E, Shin D, Sankar R, and Mazarati AM. (2010), Comorbidity between epilepsy and depression: Experimental evidence for the involvement of serotonergic, glucocorticoid, and neuroinflammatory mechanisms. *Epilepsia*, 51: 110-114.  
<https://doi.org/10.1111/j.1528-1167.2010.02623.x>
140. Lambert MV, and Robertson MM. Depression in Epilepsy: Etiology, Phenomenology, and Treatment. *Epilepsia*. 1999;40: s21-s47. <https://doi.org/10.1111/j.1528-1157.1999.tb00884.x>
141. Maguire MJ, Marson AG, Nevitt SJ. Antidepressants for people with epilepsy and depression. *Cochrane Database of Systematic Reviews* 2021, Issue 4. Art. No.: CD010682. DOI: 10.1002/14651858.CD010682.pub3. Accessed 09 June 2021.
142. Scott A, Sharpe L, Thayer Z, Miller L, Nikpour A, Parratt K. et al. How frequently is anxiety and depression identified and treated in hospital and community samples of adults with epilepsy? *Epilepsy & Behavior*. 2021;115. 107703. 10.1016/j.yebeh.2020.107703.
143. Cramer JA, Blum D, Reed M, Fanning K. The influence of comorbid depression on seizure severity. *Epilepsia*. 2003;44(12):1578-84. <https://doi.org/10.1111/j.0013-9580.2003.28403.x>
144. Mammen KA, Kumar S. A comprehensive review on comorbid depression in patients with epilepsy. *Asian J Pharm Clin Res*. 2017;10(12):30-5.  
<https://www.researchgate.net/deref/http%3A%2F%2Fdx.doi.org%2F10.22159%2Fajpcr.2017.v10i12.18938>
145. Jones JE, Hermann BP, Barry JJ, Gilliam FG, Kanner AM, Meador KJ. Rates and risk factors for suicide, suicidal ideation, and suicide attempts in chronic epilepsy. *Epilepsy Behav*. 2003 Oct;4 Suppl 3:S31-8. doi: 10.1016/j.yebeh.2003.08.019. PMID: 14592638.
146. Elliott JO, Lu B, Shneker B, Charyton C, & Layne Moore J. Comorbidity, health screening, and quality of life among persons with a history of epilepsy. *Epilepsy & Behavior*. 2009;14, 125–129. <https://www.sciencedirect.com/science/article/pii/S1525505008003466>
147. Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon CS, Dykeman J, Pringsheim T, Lorenzetti DL, Jetté N. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. *Neurology*. 2017 Jan 17;88(3):296-303. doi: 10.1212/WNL.0000000000003509. Epub 2016 Dec 16. Erratum in: *Neurology*. 2017 Aug 8;89(6):642. PMID: 27986877; PMCID: PMC5272794.

## Supplementary data

**Appendix A:** Table S1: Summary of included studies

**Appendix B:** Sub-group analyses for hypertension and stroke