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 for 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 ≥ 2 to 12 years). Five

studies involved only adolescents with epilepsy (aged ≥ 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?*

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Supplementary data

Appendix A: Table S1: Summary of included studies

Appendix B: Sub-group analyses for hypertension and stroke