Depression in epilepsy

A systematic review and meta-analysis

Kirsten M. Fiest, BSc
Jonathan Dykeman, BSc
Scott B. Patten, MD, PhD
Samuel Wiebe, MD, MSc
Gilaad G. Kaplan, MD, MSc
Colleen J. Maxwell, PhD
Andrew G.M. Bulloch, PhD
Nathalie Jette, MD, MSc

Correspondence to Dr. Jette: Nathalie.Jette@albertahealthservices.ca

ABSTRACT

Objective: To estimate the prevalence of depression in persons with epilepsy (PWE) and the strength of association between these 2 conditions.

Methods: The MEDLINE (1948–2012), EMBASE (1980–2012), and PsycINFO (1806–2012) databases, reference lists of retrieved articles, and conference abstracts were searched. Content experts were also consulted. Two independent reviewers screened abstracts and extracted data. For inclusion, studies were population-based, original research, and reported on epilepsy and depression. Estimates of depression prevalence among PWE and of the association between epilepsy and depression (estimated with reported odds ratios [ORs]) are provided.

Results: Of 7,106 abstracts screened, 23 articles reported on 14 unique data sources. Nine studies reported on 29,891 PWE who had an overall prevalence of active (current or past-year) depression of 23.1% (95% confidence interval [CI] 20.6%–28.31%). Five of the 14 studies reported on 1,217,024 participants with an overall OR of active depression of 2.77 (95% CI 2.09–3.67) in PWE. For lifetime depression, 4 studies reported on 5,454 PWE, with an overall prevalence of 13.0% (95% CI 5.1–33.1), and 3 studies reported on 4,195 participants with an overall OR of 2.20 (95% CI 1.07–4.51) for PWE.

Conclusions: Epilepsy was significantly associated with depression and depression was observed to be highly prevalent in PWE. These findings highlight the importance of proper identification and management of depression in PWE. *Neurology*® 2013;80:590–599

GLOSSARY

CCHS = Canadian Community Health Survey; **CES-D** = Center for Epidemiologic Studies–Depression Scale; **CI** = confidence interval; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; **HADS** = Hospital Anxiety and Depression Scale; **HPA** = hypothalamic-pituitary-adrenal; **ICD** = International Classification of Diseases; **ICPC** = International Classification of Primary Care; **K-6** = Kessler-6; **OR** = odds ratio; **PWE** = persons with epilepsy; **WMH-CIDI** = World Mental Health–Composite Diagnostic Interview.

Depression is the leading cause of years lived with disability and the fourth leading cause of disability-adjusted life-years worldwide.[1] It is often under-recognized and improperly managed in persons with epilepsy (PWE), and can interfere with treatment outcomes and quality of life.[2] Undermanaged depression in epilepsy is associated with work absenteeism, increased health care system utilization, and direct medical costs.[3] The reported prevalence of depression in PWE varies between 12% and 37% in community settings.[4,5] This wide range of estimates may be attributed to heterogeneity in study design, population demographics, or the method of diagnosing depression or epilepsy. A systematic review and meta-analysis could help explain the variability in the existing literature and through pooling, produce more precise estimates.

The purpose of this systematic review was to estimate the prevalence of depression in PWE and to determine the strength of the association between epilepsy and depression. The second objective was to assess the nature and importance of heterogeneity between estimates. We hypothesized that reported differences in estimates of depression in epilepsy would be largely attributable to variations in depression ascertainment methods (e.g., self-report vs screening questionnaire).

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Supplemental data at www.neurology.org

From the Departments of Community Health Sciences (K.M.F., J.D., S.B.P., S.W., G.G.K., C.J.M., A.G.M.B., N.J.), Psychiatry (S.B.P., A.G.M.B.), Clinical Neurosciences (S.W., N.J.), and Medicine (G.G.K.), University of Calgary, Canada; the Hotchkiss Brain Institute and Institute of Public Health, University of Calgary (K.M.F., J.D., S.B.P., S.W., A.G.M.B., N.J.); and School of Public Health and Health Systems & School of Pharmacy (C.J.M.), University of Waterloo, Canada.

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METHODS

Search strategy. We conducted the systematic review and meta-analysis according to a predetermined protocol and established guidelines (MOOSE).[6] The search strategy (appendix e-1 on the *Neurology*® Web site at www.neurology.org) was based on input from the coauthors, key articles, and consultation with a medical librarian with systematic review expertise. No restrictions were placed on time of publication or language. The search was executed on January 16, 2012, in the electronic databases MEDLINE, EMBASE, and PsycINFO, and references were exported and managed using EndNote X5.[7] Bibliographies of included articles and proceedings from the past 3 years of relevant conferences (American Psychiatric Association, American Academy of Neurology, and American Epilepsy Society) were manually searched for additional articles. Experts in psychiatry (S.P.) and epileptology (N.J. and S.W.) were asked to identify any missing key publications and provide information on unpublished or ongoing studies.

Study selection. Two reviewers (J.D. and K.F.) independently screened titles and abstracts to identify those reporting on original research that involved people with epilepsy and depression or psychiatric comorbidities. Abstracts that were clearly not population-based (e.g., case series and clinic-based) were excluded at this stage. The initial screen was intentionally broad to capture all relevant literature.

Two reviewers (J.D. and K.F.) independently screened the full-length articles of abstracts identified in the first screen. Articles were included if they met the following criteria: 1) original research, 2) cohort or cross-sectional design, 3) population-based (probability sampling, survey of entire population, or included all health care providers of a specific population of known size [e.g., all general practitioners in Cardiff]), 4) reported an odds ratio (OR) (or sufficient information to calculate an OR) of depression in PWE relative to those without epilepsy, and 5) reported a prevalence of depression in PWE or sufficient information to calculate an estimate. Articles solely using drug prescriptions to ascertain depression or epilepsy were excluded as antiepileptic and antidepressant drugs are both used in the treatment of unrelated conditions and would not provide a reliable estimate.[8,9] All non-English articles were screened in the same fashion using Google Translate[10] and colleagues fluent in the respective language were involved as necessary. Abstracts and unpublished studies were also considered. Disagreements of eligibility were resolved through discussion and involvement of a third party (S.P., N.J., and S.W.) as necessary.

Data extraction and study quality. Two reviewers (J.D. and K.F.) extracted and reached agreement on data from included articles using a standard electronic data form. Information from multiple articles reporting on the same data source was combined. For example, numerous studies reported on the Canadian Community Health Survey (CCHS); study characteristics and estimates were abstracted from all articles reporting on the CCHS to ensure the most comprehensive assessment. Studies reporting the most detailed description of methodology and results were extracted; other studies reporting on the same data source were used to ensure consistency and accuracy. The following data were extracted: study information (author, year), population demographics (age, location, time of data collection), condition information (data sources, condition definition, total number of participants), population size, and reported estimates (prevalence, OR) or the information needed to calculate an estimate. Indicators of study quality, which informed the assessment of condition heterogeneity, were extracted relating to sample representativeness, condition assessment, and statistical methods (table e-1).

Data synthesis and analysis. To assess for significant between-study heterogeneity, the Cochrane Q statistic was calculated and I^2 was used to quantify the magnitude of between-study heterogeneity. When statistically significant heterogeneity (Q statistic p value of <0.05) was absent, the pooled estimate and 95% confidence intervals (CIs) were calculated using a fixed-effect model. When significant heterogeneity was present a random-effects model was used. Publication bias was investigated visually using funnel plots and statistically using Begg's, Egger's, and the trim and fill tests.[11–14] The trim and fill method identifies funnel plot asymmetry by imputing the effect estimates of potentially missing studies and assessing the influence of these studies on the pooled estimate.[12,13]

Current depression and depression in the past 12 months were combined representing a measure of active depression. Lifetime depression was considered separately. Due to the limited number of studies on lifetime depression, only studies reporting active depression were investigated for potential sources of heterogeneity by stratifying on the method for ascertaining depression and how epilepsy was diagnosed. When studies provided estimates that were both not adjusted and adjusted for confounders, the unadjusted estimate was used due to the variability in confounders.

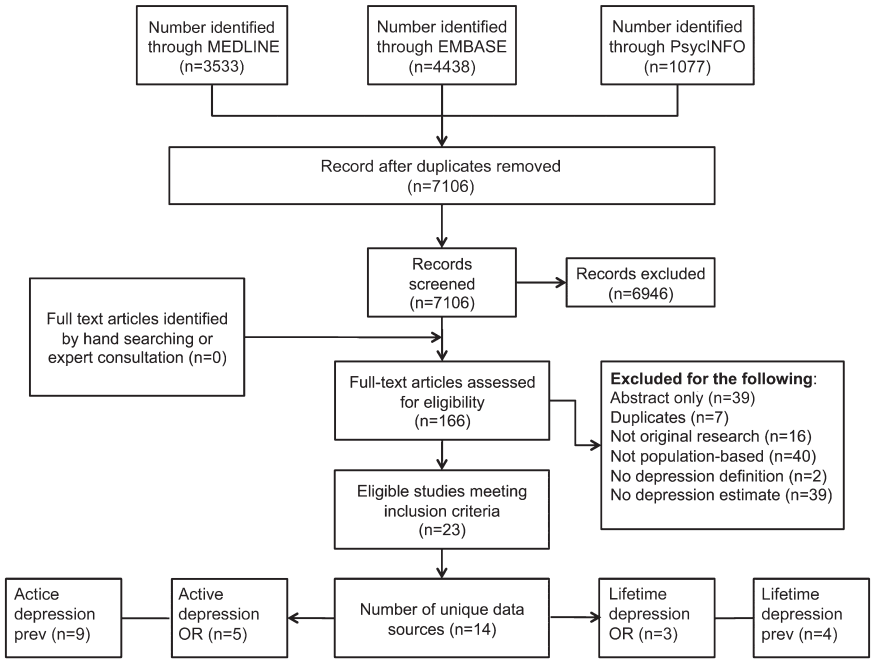
For all tests, $p < 0.05$ was deemed to be significant. Combined OR, prevalence, and 95% CIs were calculated separately for lifetime and active depression. All statistical analyses were carried out in *R* version 2.14.[15] The meta package was used to produce the pooled estimates, forest plots, and publication bias assessment.[16] The metafor package was used to conduct the meta-regression using restricted maximum likelihood estimation.[17]

RESULTS

Identification and description of studies. The results of the search strategy yielded a total of 9,048 citations: 3,533 from MEDLINE, 4,438 from EMBASE, and 1,077 from PsycINFO (a total of 7,106 after duplicates removed) (figure 1). After the initial screen, 166 articles met the criteria for full-text review, of which 143 were excluded (39 abstract only, 7 duplicate studies, 16 not original research, 40 not population-based, 2 no depression definition, and 39 no depression estimate). This meta-analysis included 14 unique data sources from the 23 eligible articles. For active depression, 5 studies reported an OR and 9 reported prevalence. For lifetime depression, 3 studies reported an OR and 4 reported prevalence.

Table 1 presents characteristics of the 14 included studies. Four studies reported lifetime depression, 6 reported depression in the past 12 months, and 4 reported on current (past 30 days) depression. Dates of publication ranged from 1996 to 2011. Seven of 14 studies reported summary data on age, with the mean age of participants ranging from 37.2 to 52.4 years. Eight studies were based in North America, 4 in Europe, and one each in Asia and South America. Diagnosis of epilepsy varied with studies using self-report (whether diagnosed by health professional or not), chart review, or administrative data codes. Depression was diagnosed by one of 3 different scales: self-report, administrative data codes, or clinical assessment. Three data sources employed the Hospital Anxiety and Depression Scale (HADS),[18–24] one used the Center for Epidemiologic Studies–Depression Scale (CES-D),[3,4,25,26] and a final study used the

Figure 1 Flow chart of studies



OR = odds ratio; prev = prevalence.

Kessler-6 (K-6).[27] The K-6 was included with the remaining data sources, as it has a question specific to feeling depressed in the past 30 days.[28] Two studies using self-report of depression included one with[29] and one without[2] a clarifier of health professional diagnosis.

The administrative data codes used to determine depression diagnosis varied widely, with 4 studies using International Classification of Diseases codes (ICD-9 or ICD-10), International Classification of Primary Care (ICPC) codes, or read codes.[30–33] Three studies used a clinical assessment to ascertain depression status: the CCHS 1.1[34] used the World Mental Health–Composite Diagnostic Interview (WMH-CIDI) Short Form, the CCHS 1.2[35,36] employed a Canadian adaptation of the WMH-CIDI, and the study of the Iranian population[5] used the Structured Clinical Interview for *DSM-IV*.

Study quality assessment. The quality of the included studies varied (table e-1). Seven of 10 eligible studies reported a response rate ≥70% and only 2 studies clearly described nonresponders. All studies used standardized methods to collect data on depression, with 10 using validated criteria to assess the presence of depressive symptoms. Thirteen studies (1 was unclear) used standardized methods for data collection and 9 used a standard accepted classification of epilepsy.[37] Only 5 studies adjusted for potential confounders and the number of confounders varied (table 1).

Active depression in persons with epilepsy. The prevalence of active depression in PWE across the 9 studies reporting on 29,891 persons ranged from 13.2% to 36.5% (figure 2). The overall pooled prevalence of active depression was 23.1% (95% CI 19.8%–27.0%) (figure 2). In the 5 studies that reported on the OR of active depression (odds of active depression in PWE relative to the odds of active depression in persons without epilepsy), the number of participants was 1,217,024, with an estimated pooled OR of 2.77 (95% CI 2.09–3.67) using a random-effects model (figure 3). Four studies reported an adjusted OR of active depression varying in magnitude and in adjustment for various confounders. Adjusting for age and sex, the CCHS 1.2 reported an OR of 2.3 (95% CI 0.99–5.23)[36]; the CCHS 1.1[34] adjusted for gender, education level, marital status, race, immigration status, and food security, and reported an adjusted OR of 1.43 (95% CI 1.13–1.82); the California Health Interview Survey[27] reported 2 adjusted models: model 1 reported an OR of 3.49 (95% CI 2.96–4.12), after adjusting for gender, age, race/ethnicity, annual household income, education attainment, and urban/rural living status, and model 2 adjusted for all model 1 factors, as well as numerous comorbid health conditions, with an OR of 3.14 (95% CI 2.42–4.07); and the HealthStyles Survey[2] adjusted for income and race/ethnicity, with a reported OR of 2.40 (95% CI 1.40–4.30).

Lifetime depression in persons with epilepsy. Four studies reported prevalence of lifetime depression in PWE ranging from 4.1% to 32.5%. Overall, there were 5,454 PWE, with an overall prevalence of 13.0%

Table 1 Characteristics of included studies

Study	Country, continent	Data source	Depression diagnosis	Depression time period	Epilepsy diagnosis	Sample size	Reports OR	Reports prevalence	Reports adjusted OR	Adjusted for
CCHS 1.2[35,36]	Canada, North America	Two-stage stratified random sampling of Canadian population	WMH-CIDI	Lifetime	Self-report of diagnosis by a health professional	Epilepsy: 253; no epilepsy: 36,984	Y	Y	Y	Age and sex
LHS[33]	USA, North America	Veterans Health Administration Database	At least 2 outpatient visits or 1 inpatient visit coded with ICD-9 296.2 or 296.3	12-month (fiscal year of 1999)	At least one inpatient or outpatient visit coded with ICD-9 345.xx or 780.3 and AED at least once during the year	Epilepsy: 13,699	N	Y	N	
Dutch National Survey of General Practices[31]	Netherlands, Europe	134 GPs working in 75 general practices	ICPC Code P76	Lifetime	ICPC Code N88	Epilepsy: 1,259	Y	Y	N	
Iranian Nationwide Study[5,38]	Iran, Asia	Randomized cluster sampling of Iranian population	Schedule for Affective Disorders and Schizophrenia (SADS) and *DSM-IV* criteria applied by clinical psychologist during structured interview	Lifetime	Epilepsy Questionnaire: 2 or more unprovoked nonfebrile seizures	Epilepsy: 454; no epilepsy: 24,727	Y	Y	N	
GPRD[30]	England/Wales, Europe	211 General practices	Read code equivalent of ICD-9 311	12-month (previous 6 months)	Read code equivalent of ICD-9 345	Epilepsy: 5,834; no epilepsy: 1,035,809	Y	Y	N	
EPIC Survey[29]	USA, North America	Mailed questionnaire to households randomly sampled from maintained survey panels	Self-report of diagnosis by a health professional	Lifetime	Self-report of diagnosis by a health professional	Epilepsy: 3,488; no epilepsy: 169,471	Y	Y	N	
CCHS 1.1[34]	Canada, North America	Multistage stratified cluster sampling of Canadian population	CIDI-SF	12-month	Self-report of diagnosis by a health professional	Epilepsy: 835; no epilepsy: 126,104	Y	Y	Y	Gender, education level, marital status, race, immigration status, food security
CHIS[27]	California, USA, North America	Geographically stratified, random-digit dialed, multistage telephone survey	Kessler-6	Current (past 30 days)	Self-report of diagnosis by a health professional	Epilepsy: 604; no epilepsy: 42,416	Y	N	Y	A1: gender, age, race/ethnicity, annual household income, education attainment, urban/rural; A2: A1 + comorbid health conditions
Health Styles Survey[2]	USA, North America	Mailed survey using stratified random sampling from maintained survey panels	Self-report	12-month	Self-report of diagnosis by a health professional	Epilepsy: 131; no epilepsy: 4,154	Y	Y	Y	Income, race/ethnicity
NFO Survey[4,25,26,50]	USA, North America	Mailed survey to representative sample of panel held by NFO	Center for Epidemiology Studies–Depression Scale (CES-D) score of 15 or above	12-month	Self-report of diagnosis by a health professional	Epilepsy: 775; no epilepsy: 362	Y	Y	N	
Brazilian Community Survey[23]	Brazil, South America	Target population door-to-door survey screening with confirmation of cases by neurologist	HADS with 7 positive items	Current	Diagnosis by neurologist	Epilepsy: 153	N	Y	N	

Continued

Table 1 Continued

Study	Country, continent	Data source	Depression diagnosis	Depression time period	Epilepsy diagnosis	Sample size	Reports OR	Reports prevalence	Reports adjusted OR	Adjusted for
Mersey General Practices[18–20]	England, Europe	31 general practices randomly selected to be representative of the Mersey region	HADS score of 8 or above	Current	Seizure in the past 2 years or seizure-free and on AEDs	Epilepsy: 696	N	Y	N	
Calgary Administrative Databases[32]	Alberta, Canada, North America	5 Linked databases (Discharge Abstract Database, Ambulatory Care Classification System, Alberta Physicians Claims Database, Alberta Healthcare Insurance Plan Registry)	ICD-9 codes 296.2, 296.3, 296.5, 300.4, 309.x, 311. x or ICD-10 codes F20.4, F31.3-F31.5, F32.x, F33. x, F34.1, F41.2, F43.2	12-month	ICD-9 code 345 or ICD-10 codes G40-G41	Epilepsy: 7,253	N	Y	N	
Cardiff general practices[21,22,24]	Wales, Europe	40 General practices from Cardiff region used to identify patients who then completed mailed surveys	HADS score of 8 or higher	Current	Read codes identifying recurrent seizures and AED prescription in the past 6 months	Epilepsy: 515	N	Y	N	

Abbreviations: AED = antiepileptic drug; CCHS = Canadian Community Health Survey; CHIS = California Health Interview Survey; CIDI-SF = Composite International Diagnostic Interview Short Form; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; EPIC = Epilepsy Comorbidities and Health; GP = general practitioners; GPRD = General Practice Research Database; HADS = Hospital Anxiety and Depression Scale; ICD = International Classification of Diseases; ICPC = International Classification of Primary Care; LHS = Large Health Survey of VA Enrollees; NFO = National Family Opinion; OR = odds ratio; WMH-CIDI = World Mental Health–Composite Diagnostic Interview.

(95% CI 5.1%–33.1%) (figure e-1). Three studies reported the OR of lifetime depression in PWE at 1.48[29] (95% CI 1.37–1.59), 1.80[36] (95% CI 1.01–3.20), and 3.96[5,38] (95% CI 2.96–5.29) (figure e-2). Overall, these studies reported on 4,195 persons with an OR of lifetime depression of 2.20 (95% CI 1.07–4.51). Significant heterogeneity was found in the meta-analyses of lifetime depression for both OR and prevalence estimates. Only one study reported an OR of 1.80[36] (95% CI 1.1–3.2), adjusting for age and sex, and was not included in the meta-analysis.

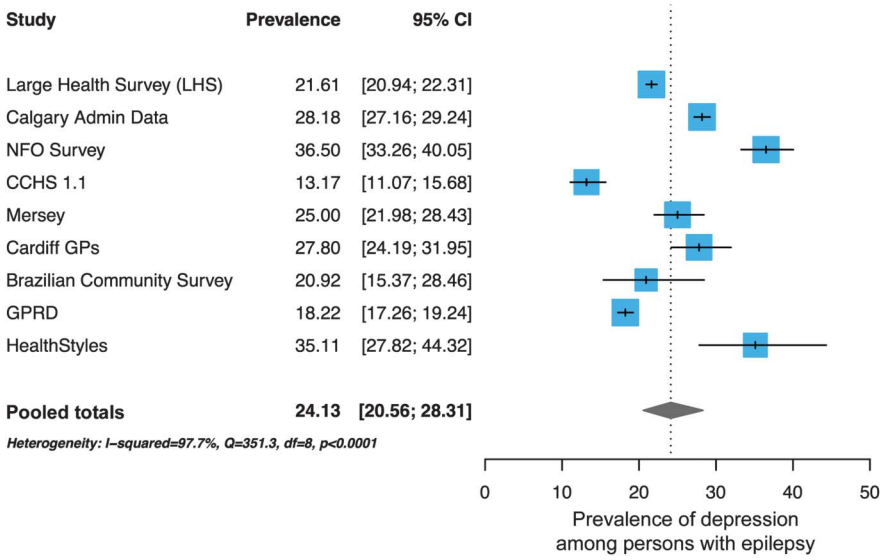
Sources of heterogeneity. Prevalence estimates, when stratified by method of depression diagnosis, were slightly greater when based on self-report and K-6 measures than in studies using validated depression scales or administrative data codes (figure 4, appendix e-2). When stratified by depression diagnostic method, OR estimates varied between methods (figure 5). The estimates for the CES-D and K-6 scales (which measure distress more broadly, with subelements related to depression) were slightly higher than those using validated depression-only scales.

The estimates of active prevalence of depression did not differ when stratified by method of epilepsy diagnosis (figure e-3). When stratified by the method of epilepsy diagnosis, the individual study estimates of the OR for active depression using administrative data codes of epilepsy diagnosis were slightly lower than those using self-report for epilepsy diagnosis (figure e-4).

Publication bias. Neither the overall OR nor prevalence estimates had significant publication bias detected by either Begg's or Egger's tests. However, on visual inspection, the funnel plot for the estimated OR appeared asymmetric. This was supported by the trim and fill method identifying 2 small missing studies with imputed ORs of 1.17 (95% CI 0.78–1.76) and 1.09 (95% CI 0.77–1.55). The pooled OR after the imputation using a random-effects model was 2.20 (1.48–3.27). On visual inspection the prevalence funnel plot appeared symmetric and no missing studies were found using the trim and fill method.

DISCUSSION This systematic review and meta-analysis of the association between depression and epilepsy revealed increased odds of depression in persons with epilepsy, with substantial heterogeneity between estimates. Subgroup analyses suggested the method of depression diagnosis drives the heterogeneity. The lifetime prevalence was high, approaching 13%. It should be noted that the ICPC codes used in the Nuyen et al.[31] study have not been validated in depression or epilepsy. When this study was excluded, the prevalence of lifetime depression in epilepsy was almost 20%. These population-based studies represent the burden of depression in

Figure 2 Overall prevalence of active depression among persons with epilepsy



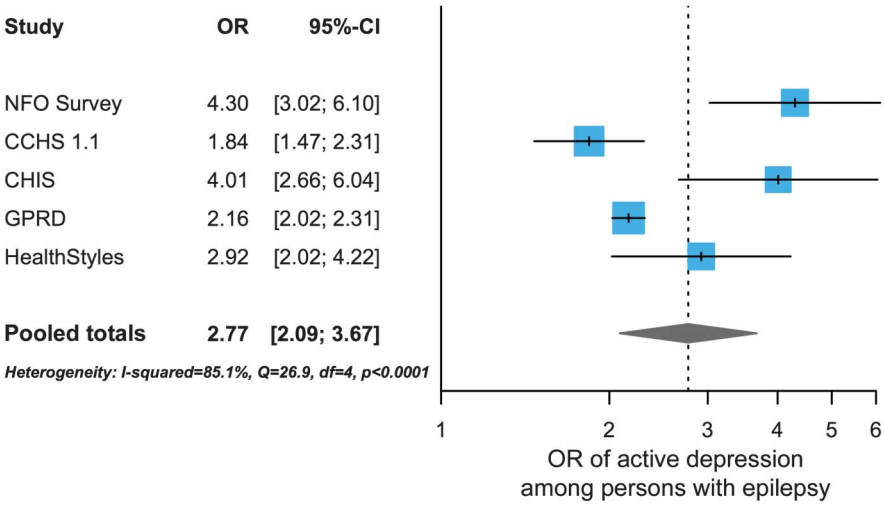
CCHS = Canadian Community Health Survey; CI = confidence interval; GP = general practitioners; GPRD = General Practice Research Database; NFO = National Family Opinion.

all patients with epilepsy rather than in any one selected clinical population.

Significant heterogeneity in depression ascertainment methods was identified. Three studies used a clinical assessment for the diagnosis of depression and there were 6 different methods of depression diagnosis across the 9 studies reporting a prevalence of active depression. The K-6[28] and CES-D[39] include measures of depressive symptoms, but are also considered to be broad measures of psychological distress, perhaps accounting for their relatively greater ORs and prevalence estimates. Differences in the method of depression diagnosis also makes it difficult to generalize findings across OR and prevalence estimates, as similarities between studies are lacking.

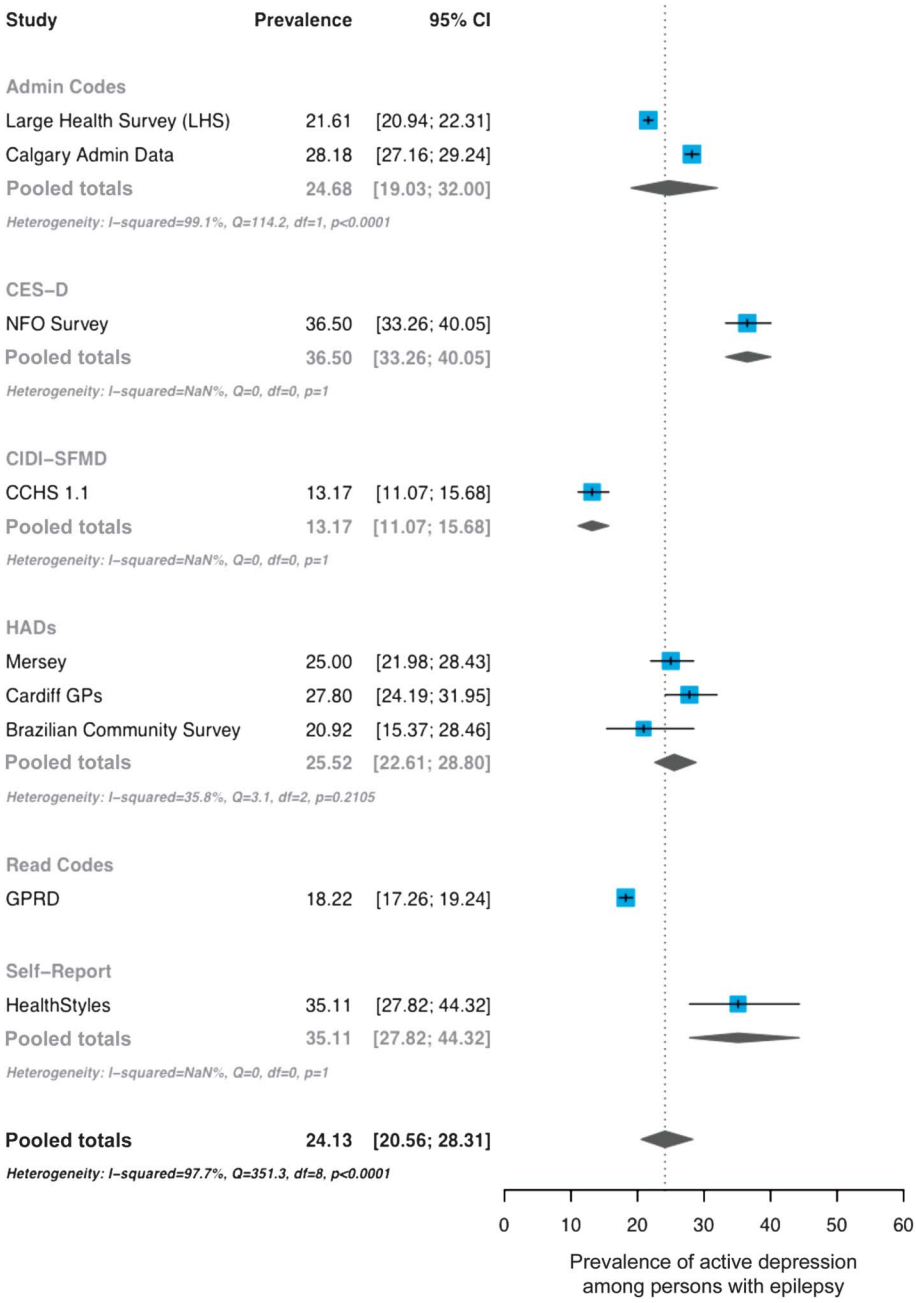
When comparing unadjusted vs adjusted OR estimates, the unadjusted estimates tended to be higher. It is possible that the studies that adjusted for over 4 confounding variables were actually removing the effect of some of the factors that would mediate the relationship between epilepsy and depression. That is, by adjusting for factors that may be more common in persons with epilepsy, or consequences of having epilepsy, the effect of epilepsy on depression may be masked. Some of the factors controlled for as confounders may in fact be on the causal pathway between

Figure 3 Overall odds ratio of active depression



CCHS = Canadian Community Health Survey; CHIS = California Health Interview Survey; CI = confidence interval; GP = general practitioners; GPRD = General Practice Research Database; NFO = National Family Opinion; OR = odds ratio.

Figure 4 Overall prevalence of active depression among persons with epilepsy by depression diagnostic tool

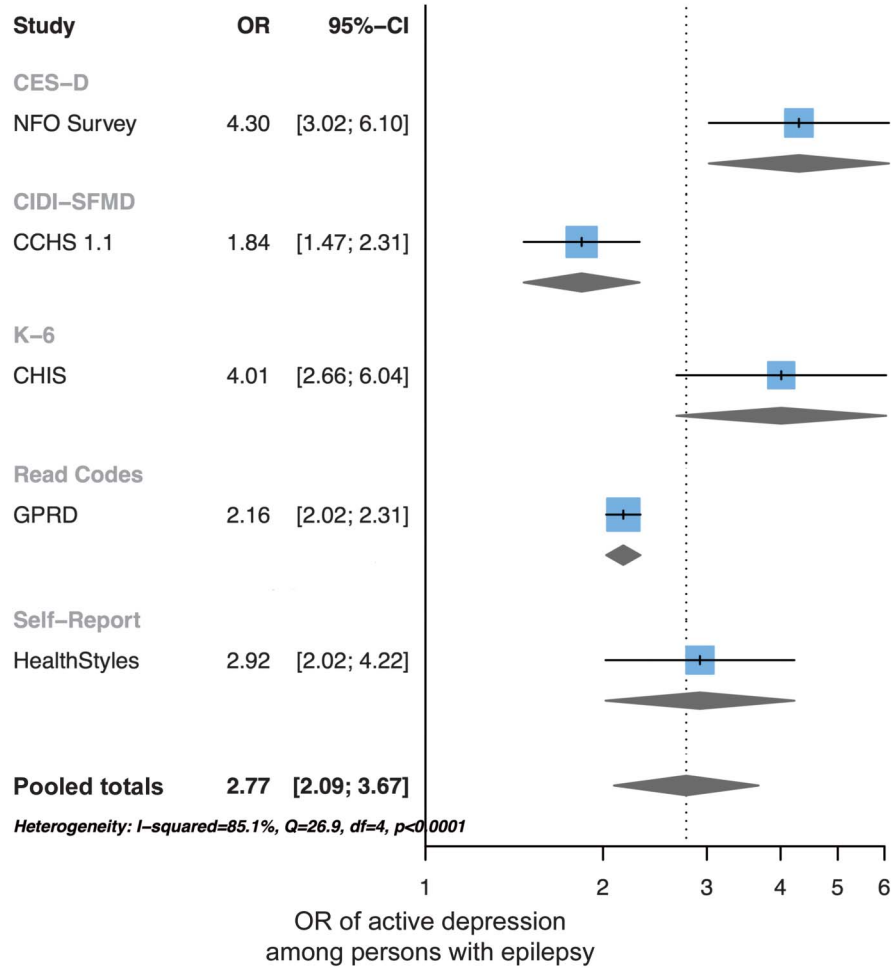


CCHS = Canadian Community Health Survey; CES-D = Center for Epidemiologic Studies-Depression Scale; CI = confidence interval; CIDI-SFMD = Composite International Diagnostic Interview Short Form for Major Depression; GPRD = General Practice Research Database; HAD = Hospital Anxiety and Depression Scale; NFO = National Family Opinion.

epilepsy and depression, and as such not true confounders. People with epilepsy may experience more of these factors (single marital status, lower education, less food security), and as such the relationship between epilepsy and depression is partially removed. Adjusted OR estimates may not represent the true population value, and should be interpreted separately.

Depression is a broad and heterogeneous term that may include elevated symptoms as assessed by depression rating scales, depressive episodes (elevated symptoms associated with persistence and functional impairment), and depressive disorders. Major depressive disorder is defined by the occurrence of major depressive episodes in the absence of manic, hypomanic, or mixed episodes.[40] Episodes of the latter type signify a bipolar disorder. Elevated symptom ratings occur during major depressive episodes and are also common in anxiety disorders such as posttraumatic stress disorder. Depressive symptoms can also be self-limited, as in adjustment disorders. The distinction between major depressive disorder and bipolar disorder is a particularly critical one. Although

Figure 5 Overall odds ratio of active depression by depression diagnostic tool



CES-D = Center for Epidemiologic Studies-Depression Scale; CHIS = California Health Interview Survey; CI = confidence interval; CIDI-SFMD = Composite International Diagnostic Interview Short Form for Major Depression; GPRD = General Practice Research Database; K-6 = Kessler-6; NFO = National Family Opinion; OR = odds ratio.

each may present with major depressive episodes, antidepressant treatment can be problematic in bipolar disorder due to an increased risk of switching to a manic phase or of transitioning to a rapid cycling pattern.

It has been hypothesized that the relationship between epilepsy and depression is bidirectional.[41] Epilepsy may affect the development of depression through chronic stress exposure, in which stressful life events and inherent vulnerability affect the likelihood of developing depression.[42] The uncertainty and unpredictability of seizures may induce learned helplessness,[43] where persons with epilepsy report less personal control over their health than their peers.[44,45] Conversely, depression may facilitate the development of epileptic activity; proposed mechanisms of action for this association include hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and disturbances of glutamate and γ-aminobutyric acid neurotransmitters.[41] A hyperactive HPA axis has been found in both epilepsy and depression[46] and may lead to substantive cortical changes, particularly in the volume of the hippocampus and frontal lobes.[47,48] Social factors, such as a lack of occupational attainment, social engagement, or social support, may also influence the relationship between epilepsy and depression.[49]

Our study searched 3 large online databases, with no restrictions placed on language or date of publication. The meta-analysis included data from over 1 million participants and over 30,000 PWE. However, the strength of the inference afforded by our analysis may be limited by the following factors. First, the quality of the included studies was not always optimal, demonstrated by the lack of reporting of nonresponders and the lack of use of validated depression diagnostic criteria in some studies, though the magnitude of this problem may be small, and is unlikely to substantially alter our conclusion. Second, there was heterogeneity of OR and prevalence estimates across studies; this could be in part due to heterogeneity

in the method of diagnosis of both depression and epilepsy. Nevertheless the final stratified analysis showed pooled ORs consistently greater than one over numerous clinical factors. Third, there was a lack of consistency in terms of how depression and epilepsy were diagnosed. Finally, the funnel plots showed some asymmetry, indicating the possibility of publication bias. When the trim and fill analysis was conducted, the overall imputation did not change the general result (though the strength of the OR was attenuated), suggesting the results are robust to the possibility of unpublished negative studies. Though limitations are present, we do not believe they hinder the conclusion that epilepsy is associated with significantly increased odds of depression.

This systematic review and meta-analysis found significantly increased odds of active and lifetime depression in persons with epilepsy relative to those without epilepsy. These findings were consistent, regardless of the method of depression and epilepsy diagnosis. The focus on population-based studies allows for the results to be more applicable to primary care. Physicians responsible for the care of persons with epilepsy should be aware of the increased odds of depression and screen patients appropriately. Future research should focus on identifying the mechanisms of increased depression among persons with epilepsy and appropriate targeted interventions.

AUTHOR CONTRIBUTIONS

K.M. Fiest: study concept and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript. J. Dykeman: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript. S.B. Patten: study concept and design, interpretation of data, critical revision of the manuscript for important intellectual content. S. Wiebe: study concept and design, interpretation of data, critical revision of the manuscript for important intellectual content. G.G. Kaplan: study concept and design, interpretation of data, critical revision of the manuscript for important intellectual content, study supervision. C.J. Maxwell: critical revision of the manuscript for important intellectual content. A.G.M. Bulloch: critical revision of the manuscript for important intellectual content. N. Jette: study concept and design, interpretation of data, critical revision of the manuscript for important intellectual content.

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