

Psychiatric comorbidities in persons with epilepsy compared to persons without epilepsy – A systematic review and meta-analysis

Short Title: Psychiatric Comorbidities in Epilepsy

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Abstract

Importance: Several psychiatric disorders have been found to occur more frequently in persons with epilepsy (PwE) than in persons without epilepsy.

Objective: We summarize the prevalence of 20 psychiatric disorders in PwE compared to persons without epilepsy.

Data Sources: The search included records from inception to February 2024 in Ovid® MEDLINE, Embase®, and PsycINFO.

Study Selection: We systematically reviewed published epidemiological studies examining the prevalence of psychiatric disorders among PwE compared to persons without epilepsy. We followed the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). There were no restrictions on language or publication date.

Main Outcomes and Measures: Data were recorded on the prevalence of 20 psychiatric disorders among PwE compared to persons without epilepsy. Meta-analyses were performed along with descriptive analyses.

Data Extraction and Synthesis: Abstracts were reviewed in duplicate and data were extracted using standard proforma. Descriptive statistics and meta-analyses are presented.

Results: The systematic search identified 10,392 studies, 27 of which met eligibility criteria. Our meta-analyses include 565,443 PwE and 13,434,208 persons without epilepsy. The odds of most psychiatric disorders studied were significantly increased in PwE compared to those without, including: anxiety (odds ratio; 95% confidence interval) 2.1; 1.73-2.58, depression (2.45; 1.94-3.09), bipolar disorder (3.2; 2.23-4.36), suicidal ideation (2.25; 1.75-2.88) and attempt (3.2; 0.49-20.46), psychotic disorder (4.0; 2.57-6.15), schizophrenia (3.7; 2.44-5.67), obsessive compulsive disorder (2.7; 1.76-4.15), post-traumatic stress disorder (1.8; 1.14-2.73), eating disorders (OR: 1.9; 1.73-2.01), alcohol misuse (3.4; 2.27-5.83), abuse (2.1; 0.60-7.37), and dependence (4.9; 3.50-6.96), substance use disorder (2.75; 1.61-4.72), autism spectrum disorder (10.7; 6.35-17.91), and attention deficit/hyperactivity disorder (3.3; 3.80-4.08).

Conclusions and Relevance: In this comprehensive study, most psychiatric comorbidities examined were significantly more prevalent in PwE than in those without. These findings show the high burden of psychiatric comorbidities in PwE. This in turn underscores the need for appropriately identifying and treating psychiatric comorbidity in epilepsy to manage patients effectively and improve quality of life.

Keywords: comorbidity, psychiatric, mental health, epilepsy.

Key Points

Question

Are persons with epilepsy (PwE) significantly more likely to experience psychiatric disorders compared to those without epilepsy? There are a very few systematic reviews and meta-analyses on the epidemiology of psychiatric disorders in PwE and all have focused on 1 or 2 specific psychiatric conditions.

Findings

This is the most comprehensive systematic review and meta-analysis of the prevalence of psychiatric disorders in PwE compared to those without epilepsy. Most psychiatric comorbidities investigated in this study were significantly more prevalent in PwE compared to individuals without epilepsy.

Meaning

Given the significant impact and high burden of psychiatric comorbidities in PwE on morbidity and quality of life, appropriate identification and effective management of psychiatric comorbidity in epilepsy should be considered.

Introduction

Many psychiatric disorders have been found to occur more frequently in persons with epilepsy (PwE) than in the general population. The presence of psychiatric disorders and epilepsy is associated with a higher impact on patients, their families, and society than in epilepsy without psychiatric disorders. Previous systematic reviews have identified a high prevalence of psychiatric comorbidities in PwE, including anxiety, depression, and suicide.¹⁻³ However, less is known about the prevalence of other types of psychiatric disorders among persons with epilepsy compared to those without.

This systematic review and meta-analysis aims to estimate the prevalence of common psychiatric disorders in PwE compared to those without epilepsy. The results are expected to improve understanding of the prevalence of common types of comorbid psychiatric conditions in PwE which may, in turn, inform the care and management and improve health-related quality of life for this population.

Methods

Search strategy

We systematically reviewed published epidemiological studies examining the occurrence of psychiatric disorders among PwE compared to persons without epilepsy. This study followed the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).⁴ A protocol for this systematic review and meta-analysis was established a priori and registered with PROSPERO (registration number CRD42024500147). A systematic search strategy (Supplementary Table S1) was developed by experts in epilepsy, psychiatric comorbidity, and epidemiology and a librarian with systematic review expertise. The main search terms included 'epilepsy', 'psychiatric comorbidity', 'mental health', and specific psychiatric disorders (available in Supplementary Table S1). To ensure no eligible study was missed from our review, a manual search of the references of the included articles was also performed. The following databases were queried: MEDLINE (via Ovid), Embase (via Ovid), and PsycINFO from inception to February 1, 2024 (via Ovid).

Study selection

After duplicate removal, two reviewers independently screened all abstracts to identify population-based epidemiological studies focusing on a single psychiatric disorder in PwE compared with persons without epilepsy. A full-text review of the selected studies was then performed in duplicate. Articles were included if they met the following criteria: 1) reported original data, 2) investigated the following psychiatric disorders: anxiety, depression, bipolar disorder, obsessive-compulsive disorder [OCD], eating disorders, alcohol misuse, abuse, and dependence, substance disorder, psychotic disorder, schizophrenia, suicide ideation and attempt, attention-deficit/hyperactivity disorder [ADHD], autism spectrum disorder [ASD] (as listed in Supplementary Table S2), 3) used a validated symptom measure (e.g., Neurological Disorders Depression Inventory in Epilepsy (NDDIE)), clinical interview, or standardized interview (e.g., Mini International Neuropsychiatric Interview [MINI]), or validated self-report questionnaires to determine the psychiatric diagnosis and/or symptoms, 4) included controls (epilepsy versus no epilepsy), 5) reported prevalence of a single psychiatric disorder. Exclusion criteria were: 1) non-peer-reviewed literature, case reports, abstracts, conference proceedings, or reviews, and 2) studies with less than 30 participants in each group. There were no exclusions for language. Any disagreement at the abstract or full text review stage were resolved by consensus, or involvement of a third reviewer if needed.

Data extraction and study risk of bias assessment

The risk of bias of the eligible studies was assessed independently by two reviewers using two risk of bias assessment tools: 1) the Newcastle-Ottawa scale (NOS)⁵ and 2) the criteria comparably applied in other systematic reviews by the International League Against Epilepsy (ILAE) Commission on Epidemiology.⁶⁻⁸ The evaluations were based on consistency with the following criteria: i) sensitivity of identifying epilepsy and psychiatric cases (i.e., Reviewer's judgment of the sensitivity of methods of epilepsy diagnosis or psychiatric comorbidity ascertainment), ii) precision of epilepsy and psychiatric diagnoses (i.e., Reviewer's judgment of the accuracy of diagnoses of epilepsy or psychiatric comorbidity ascertainment), and iii) representativeness of the study population (identified based on the source of study subjects, e.g., population-based, clinic-based, or poorly defined). Each criterion was assessed and scored separately using a Likert-type scale of 'high,' 'good,' 'fair,' or 'poor' (specific explanations in Table 3). The overall ILAE risk of bias score of each study was assigned as the lowest rating among those for the individual criteria (e.g. if one item was rated as poor, the ILAE overall risk of bias score for that study would be poor). Discrepancies between the reviewers regarding data extraction and the overall risk of bias assessment were resolved

through discussions until an agreement was reached or using a third reviewer. A minimum overall risk of bias rating of 'fair' or better was required to include studies in our report. Cohen's kappa coefficient (inter-rater reliability) was 0.86 at the full text review stage, showing excellent agreement.⁹

The data were extracted in duplicate from the included studies using a standardized electronic form. In addition to rating studies' risk of bias score, when available, data extraction included: demographic characteristics of the study (author, publication year, study design, ILAE region), number of PwE and persons without epilepsy in the study, age group, data source (e.g., hospital, administrative database), diagnostic criteria and method for classification of epilepsy and psychiatric comorbidities reported, and inpatient vs. outpatient.

Statistical analysis

Analyses were performed using R, version 4.2.1 (R Foundation for Statistical Computing).

Descriptive analysis was used to report the study characteristics (Table 1).

Within each study, the odds ratio (OR) for the prevalence of each psychiatric disorder in PwE vs. persons without epilepsy, with 95% confidence interval (CI), was calculated using the Mantel-Haenszel method. The meta-analysis was performed with the 'metabin' function, and the results were demonstrated using forest plots. Higgin's I-squared (I^2) test and Cochran's Q statistic based on the DerSimonian-Laird estimator were utilized to assess the between-study heterogeneity. The studies were pooled using the common-effects model unless the $I^2 \geq 50\%$, showing a high heterogeneity, in which case, the random-effects model was used.

A meta-regression was conducted to see how different variables influenced the overall effect size. The variables included in the meta-regression were: outpatient vs. inpatient setting, age group (<18 vs. ≥ 18 years), diagnosis method for epilepsy (healthcare professional; administrative database; self-report; mail survey), diagnostic criteria for epilepsy (International Classification of Diseases [ICD]; read code; self-report) diagnosis method for psychiatric comorbidity (structured clinical interview/questionnaire; administrative database; self-report), diagnostic criteria for psychiatric comorbidity (ICD; Diagnostic and Statistical Manual of Mental Disorders [DSM]), and the ILAE region. Funnel plots were drawn to visualize publication bias, and asymmetry was tested using Egger's and Begg's tests. The level of significance was considered at a two-tailed p -value < 0.05.

Results

Study selection and characteristics

A summary of the process of study inclusion is depicted in the PRISMA flow diagram in Supplementary Figure S1. Among 10,392 records identified through the systematic search, 2,342 were duplicates. The remaining 8,050 were screened with titles and abstracts, and 400 remained for full-text review. After the full-text review, 371 were excluded. The reasons for exclusions are shown in the PRISMA flow diagram in Supplementary Figure S1. Finally, a total of 27 studies¹⁰⁻³⁶ were included in the systematic review. The characteristics of the included studies are summarized in Table 1. These 27 studies were conducted in different ILAE regions as follows: 14 were from Europe^{10,11,13,16,22,24-29,32,34,36}, 10 were from North America^{12,14,15,17,18,20,21,23,31,33}, two were from Asia and Oceania^{30,35}, and one was from Latin America.¹⁹ There were no studies from the ILAE African or Eastern Mediterranean regions.

Risk of bias assessment

The risk of bias in the included studies evaluated using the ILAE Commission on Epidemiology Standards varied from good (n=17^{10,11,13,18,20,23,24,26-30,32-36}) to fair (n=10^{12,14-17,19,21,22,25,31}) quality (Table 1). Furthermore, all studies scored 7 and higher out of 10 according to the NOS, meaning an acceptable methodological risk of bias. The results of the risk of bias assessment are shown in Supplementary Table S3.

Meta-analysis results

The results of the meta-analysis are represented in the subsequent subsections. A summary of the meta-analysis results is demonstrated in Figure 1 and Supplementary Figures.

Anxiety Disorders

Fifteen studies^{13,15-19,22,23,26,27,30,31,34-36} reported the prevalence of any anxiety disorder in 174,378 PwE and 6,094,835 persons without epilepsy. The pooled analysis showed a significantly higher prevalence of anxiety disorders in PwE than in persons without epilepsy (8.4% vs. 5.7%; OR: 2.11 95% CI: 1.73-2.58, p-value<0.0001, I²=99%, τ²=0.16, Cochran's Q p-value for heterogeneity<0.01; forest plot in Figure S2). In the subgroup analysis, structured clinical interview using a questionnaire (24% vs. 8%; OR: 2.43 95% CI: 1.48-4.00, p-value<0.01, I²=81%, τ²=0.20) and administrative databases (8.3% vs. 5.7%; OR: 2.01 95%

CI: 1.60-2.52, p-value<0.01, $I^2=99\%$, $\tau^2=0.16$), all indicated significantly higher prevalence in PwE than in persons without epilepsy. The meta-regression showed no significant moderator to the overall effect.

Separate forest plots were drawn for each anxiety disorder. Significantly higher prevalence of psychiatric comorbidities was observed in PwE compared to persons without epilepsy for Generalized Anxiety disorder (GAD) ^{22,23} (10.7% vs. 4.9%; OR: 2.34 95% CI: 1.14-4.79, $I^2=0\%$, p-value=0.02, $\tau^2=0.16$, Cochran's Q p-value for heterogeneity=0.12; Figure S4), specific phobia ^{22,23} (11.2% vs. 6.1%; OR: 1.73 95% CI: 1.08-2.77, p-value=0.02, $I^2=0\%$, $\tau^2=0$, Cochran's Q p-value for heterogeneity=0.84; Figure S6). However, for social phobia ^{22,23} (11.2% vs. 5.8%; OR: 3.00 95% CI: 0.56-16.12, p-value=0.2, $I^2=91\%$, $\tau^2=1.34$, Cochran's Q p-value for heterogeneity<0.01; Figure S8) and agoraphobia ^{22,23} (3% vs. 1.3%; OR: 2.17 95% CI: 0.29-16.27, p-value=0.45, $I^2=72\%$, $\tau^2=1.57$, Cochran's Q p-value for heterogeneity=0.06; Figure S10), no significant difference was observed.

Depression

Depression was reported in 16 ^{12,13,15,18-20,22-24,26,27,30,33-36} studies. The pooled analysis compared 417,208 PwE and 10,870,521 persons without epilepsy. The prevalence of depression was significantly higher in PwE than in persons without epilepsy (13.7% vs. 9.3%; OR: 2.45 95% CI: 1.94-3.09, p-value<0.0001, $I^2=100\%$, $\tau^2=0.26$, Cochran's Q p-value for heterogeneity=0; forest plot in Figure S12). The subgroup analysis also showed a significantly higher prevalence for PwE compared to persons without epilepsy as follows: structured clinical interview using a questionnaire (17.7% vs. 9%; OR: 1.91 95% CI: 1.05-3.48, p-value<0.01, $I^2=67\%$, $\tau^2=0.18$), administrative databases (13.7% vs. 9.3%; OR: 2.43 95% CI: 1.87-3.16, p-value<0.01, $I^2=100\%$, $\tau^2=0.26$), and validated self-report (36.3% vs. 15.3%; OR: 3.55 95% CI: 2.43-5.18, p-value<0.01, $I^2=55\%$, $\tau^2=0.04$). The meta-regression showed no covariate to moderate the overall effect significantly.

Bipolar Disorder

Bipolar disorder was reported in 4 ^{14,18,23,36} studies. A total of 60,816 PwE and 2,200,233 persons without epilepsy were compared in this meta-analysis. The pooled analysis showed a significantly higher prevalence of bipolar disorder PwE compared to persons without epilepsy (1.2% vs. 1%; OR: 3.12 95% CI: 2.23-4.36, p-value<0.0001, $I^2=90\%$, $\tau^2=0.10$, Cochran's Q p-value for heterogeneity<0.01; forest plot in Figure S14). Similarly, a

significant result was also yielded in the administrative database subgroup (1.1% vs. 1%; OR: 2.42 95% CI: 1.89-3.09, p-value<0.01, I²=84%, τ²=0.04). The meta-regression showed the following significant moderators to the overall effect: age group>18 years old (p-value<0.0001), diagnosis method for psychiatric comorbidity (p-value<0.0001), diagnosis criteria for psychiatric comorbidity (p-value<0.0001), and diagnosis method for epilepsy (p-value<0.0001).

Suicide Ideation and Attempt

Three ^{17,19,22} studies reported suicide ideation in 500 PwE and 43,952 persons without epilepsy. The prevalence of suicide ideation was higher in PwE compared to persons with epilepsy (20% vs. 11.7%; OR: 2.25 95% CI: 1.75-2.88, p-value<0.0001, I²=0%, τ²=0, Cochran's Q p-value for heterogeneity=0.47; forest plot in Figure S16). No significant moderator to the overall effect was found in the meta-regression.

The suicide attempt was reported in two ^{19,22} studies including 247 PwE and 7225 persons without epilepsy. Suicide attempt was not significantly more prevalent in PwE than in persons without epilepsy (3.2% vs. 0.65%; OR: 3.17 95% CI: 0.49-20.46, p-value=0.22, I²=79%, τ²=1.44, Cochran's Q p-value for heterogeneity=0.03; forest plot in Figure S18). No study met the eligibility criteria on comparing the prevalence of completed suicide between PwE and those without epilepsy.

Any Psychotic Disorder and Schizophrenia

Eight ^{10,13,16,18,20,22,31,33} studies reported psychotic disorders. The pooled analysis included 151,235 PwE and 4,404,204 persons without epilepsy. The prevalence of any psychotic disorders was shown to be significantly higher in PwE compared to persons without epilepsy (14.8% vs. 6.3%; OR: 3.98 95% CI: 2.57-6.15, p-value<0.0001, I²=99%, τ²=0.44, Cochran's Q p-value for heterogeneity<0.01; forest plot in Figure S20). The diagnosis method for epilepsy (p-value<0.0001) and inpatient vs. outpatient (p-value=0.036) were found to be a significant moderator to the overall effect in the meta-regression.

Schizophrenia was reported in six ^{10,13,21,27,35,36} studies, accounting for 147,677 PwE and 4,665,066 persons without epilepsy. Schizophrenia was reported to be more prevalent in PwE than in persons without epilepsy (3.3% vs. 0.85%; OR: 3.72 95% CI: 2.44-5.67, p-

value<0.0001, $I^2=99%$, $\tau^2=0.28$, Cochran's Q p-value for heterogeneity<0.01; forest plot in Figure S22). No significant moderator to the overall effect was found in the meta-regression.

Obsessive Compulsive Disorders

OCD was reported in two ^{13,22} studies and was compared between 5928 PwE and 1,042,880 persons without epilepsy. The prevalence of OCD in pooled analysis was significantly higher in PwE than in persons without epilepsy (0.35% vs. 0.12%; OR: 2.71 95% CI: 1.76-4.15, p-value<0.0001, $I^2=0%$, $\tau^2=0$, Cochran's Q p-value for heterogeneity=0.87; forest plot in Figure S24). No covariate was found to be a significant moderator to the overall effect in the meta-regression.

Trauma- and Stressor-Related Disorders

Post-traumatic stress disorder (PTSD) ^{22,23} were compared between 2039 PwE and 1,036,037 persons without epilepsy. PTSD was significantly more frequent in PwE than those without epilepsy (5.6% vs. 3.7%; OR: 1.76 95% CI: 1.14-2.73, p-value=0.01, $I^2=56%$, $\tau^2=0.08$, Cochran's Q p-value for heterogeneity=0.10; Figure S26).

Eating Disorders

Three ^{22,31,36} studies accounting for 59,162 PwE and 1,178,543 persons without epilepsy were pooled in the meta-analysis. The meta-analysis indicated that eating disorders were significantly more prevalent in PwE than persons without epilepsy (1.2% vs. 0.67%; OR: 1.87 95% CI: 1.73-2.01, p-value<0.0001, $I^2=0%$, $\tau^2=0$, Cochran's Q p-value for heterogeneity=0.53; forest plot in Figure S28). In the meta-regression, no covariate was found to be a significant moderator to the overall effect.

Alcohol Misuse, Abuse, and Dependence

Alcohol disorders are reported in three subsections: alcohol misuse, alcohol abuse, and alcohol dependence. Alcohol misuse was reported in seven ^{10,18,24,27,35,36} studies, accounting for 212,071 PwE and 4,490,629 persons without epilepsy. The pooled analysis showed that the prevalence of alcohol misuse was more prevalent in PwE compared to persons without epilepsy (6.8% vs. 2.6%; OR: 3.64 95% CI: 2.27-5.83, p-value<0.0001, $I^2=100%$, $\tau^2=0.39$, Cochran's Q p-value for heterogeneity=0; forest plot in Figure S30). The meta-regression showed no significant moderator to the overall effect.

Alcohol abuse was reported in three ^{20,23,33} studies. A total of 141,727 PwE and 2,339,311 persons without epilepsy were compared in the pooled analysis. The meta-analysis indicated no significant difference in the prevalence of alcohol abuse between PwE and persons without epilepsy (10.3% vs. 9.6%; OR: 2.10 95% CI: 0.60-7.37, p-value=0.24, I²=100%, τ^2 =1.12, Cochran's Q p-value for heterogeneity<0.01; forest plot in Figure S32). No significant moderator to the overall effect was observed for the overall effect in the meta-regression.

Alcohol dependence was reported in two ^{13,21} studies. In this meta-analysis, 7444 PwE and 1,858,682 persons without epilepsy were compared. According to the pooled analysis, the prevalence of alcohol dependence was significantly higher in PwE compared to persons without epilepsy (3.3% vs. 1.1%; OR: 4.94 95% CI: 3.50-6.96, p-value<0.0001, I²=81%, τ^2 =0.11, Cochran's p-value for heterogeneity<0.01; forest plot in Figure S34). The meta-regression showed that the age group>18 years old (p-value<0.0001) is a significant moderator to the overall effect.

Substance Disorder

A total of nine ^{16,20,21,23,24,27,32,33,36} studies reported substance disorders, accounting for 412,446 PwE and 6,874,067 persons without epilepsy. The prevalence of substance disorder was significantly higher in PwE than in persons without epilepsy (6.4% vs. 5.2%; OR: 2.75 95% CI: 1.61-4.72, p-value=0.0002, I²=100%, τ^2 =0.74, Cochran's Q p-value for heterogeneity=0; forest plot in Figure S36). The diagnosis method for psychiatric comorbidity (p-value=0.036) was indicated as a significant moderator to the overall effect in the meta-regression.

Autism Spectrum Disorders

In six ^{11,22,25,26,28,31} studies, ASD was reported in 7941 PwE and 1,192,423 persons without epilepsy. ASD was observed to be significantly more prevalent in PwE compared to persons without epilepsy (10.9% vs. 1%; OR: 10.67 95% CI: 6.35-17.91, p-value<0.0001, I²=93%, τ^2 =0.29, Cochran's Q p-value for heterogeneity<0.01; forest plot in Figure S38). The effect remained significant in two subgroups of structured clinical interview using a questionnaire (8.9% vs. 7.1%; OR: 11.86 95% CI: 8.39-16.79, p<0.01, I²=16%, τ^2 =0.02) and administrative databases (11% vs. 1%; OR: 8.65 9% CI: 3.87-19.35, p<0.01, I²=97%, τ^2 =0.37). The meta-regression showed no significant moderator to the overall effect.

Attention Deficit Hyperactive Disorder

ADHD was reported in six ^{11,22,23,26,29,31} studies. The pooled analysis compared 27,862 PwE and 3,024,942 persons without epilepsy. ADHD was observed significantly more in PwE than in persons without epilepsy (13% vs. 3.4%; OR: 3.93 95% CI: 3.80-4.08, p-value<0.01, I²=98%, τ²=0.23, Cochran's Q p-value for heterogeneity<0.01; forest plot in Figure S40). ADHD was also more prevalent in PwE than in persons without epilepsy in both subgroups of structured clinical interview using a questionnaire (8.7% vs. 4.7%; OR: 1.73 95% CI:1.12-2.69, p=0.01, I²=0%, τ²=0) and admin database (13% vs. 3.4%; OR: 4.57 95% CI: 2.55-8.20, p<0.01, I²=99%, τ²=0.23). The meta-regression showed the following significant moderators of the overall effect: diagnosis method for epilepsy (p-value=0.03), diagnosis method for psychiatric comorbidity (structured clinical interview) (p-value=0.01), and diagnosis criteria for psychiatric comorbidity (p-value<0.0001).

Publication bias

No publication bias was found in any of the meta-analyses as assessed with Egger's and Begg's tests' p-values in all meta-analyses to be >0.05. Asymmetry is visualized using funnel plots in Supplementary Figures S3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, and 41.

Discussion

The objective of this systematic review and meta-analysis was to determine the prevalence of psychiatric disorders in individuals with epilepsy compared to those without epilepsy. PwE have higher odds of experiencing psychiatric disorders compared to those without epilepsy, likely attributed to shared risk factors encompassing neurobiology, psychosocial aspects, bidirectional influences, medication effects, and common genetic predispositions (Figure 1).

Very few systematic reviews have compared the risk of psychiatric comorbidities in PwE to persons without epilepsy.^{1,37-39} Previous meta-analyses comparing PwE to those without epilepsy found: 1) an overall OR of depression of 2.77 (95%CI 2.09-3.67; five population-based studies)¹; 2) significantly higher anxiety ($d = 0.57$, 95%CI 0.32–0.83, $p < .0001$) and depressive ($d = 0.42$, 95% CI 0.16–0.68, $p < .0001$) symptomatology reported (11 hospital setting studies in those <18 years of age)³⁷; 3) significantly higher risk of suicidal ideation (OR 2.70, 95%CI 2.21-3.30, 11 studies from mixed settings and study types) and suicidal attempts (OR 2.74, 95%CI 2.08-3.61, 14 studies from mixed settings and study types)³⁸; 4) significantly higher odds of psychosis (OR 7.83, 95%CI 2.81-21.79, 4 studies from mixed settings)³⁹. All these studies have reported estimates including validated and unvalidated diagnostic methods, as well as varying study settings and study types. The only previous study that included only population-based data for their analysis compared depression in PwE to those without, with similar estimates reported to our larger study (current study: OR 2.45, 95% CI 1.94-3.0 vs. earlier study with search performed January 2012: OR 2.77, 95% CI 2.09-3.67).¹ Our study also delineates population-based studies that used validated structured clinical interviews and administrative databases, resulting in similar pooled estimates (for depression: structured clinical interview: OR 1.91 95% CI: 1.05-3.48,) vs. administrative databases: OR 2.43, 95% CI 1.87-3.16). We further present estimates of population-based studies of 20 psychiatric disorders subcategorizing into those that used validated structured clinical interviews, administrative databases, and validated self-report (Figure 1), with overwhelming evidence of increased odds of having a psychiatric comorbidity in PwE compared to persons without epilepsy.

Our study searched three large databases, with no restrictions on language or publication date and our meta-analyses include over 2 million PwE and 45 million persons without epilepsy. Population-based studies with strict inclusion criteria are included e.g., studies with high sensitivity of identifying epilepsy and psychiatric cases, precision of epilepsy, and psychiatric

diagnoses. Funnel plots across all diseases found no strong evidence of publication bias in the included studies. However, the strength of the inference afforded by our analysis may be limited by some of the following factors. There is heterogeneity across studies, and in meta-regression, it is associated to diagnostic methodology, diagnostic criteria, age group, and inpatient vs. outpatient settings. Differences in the diagnostic methodology make it difficult to generalize findings across studies, which was the reason for our strict inclusion criteria. The use of self-rating psychiatric instruments may identify psychiatric symptoms but not establish necessarily a psychiatric diagnosis, which requires further investigations to be established. To ensure the heterogeneity arising from psychiatric comorbidity diagnosis does not reduce the accuracy of the meta-analyses, for each meta-analysis we performed a subgroup analysis and reported the results of pool analysis separately for the following subgroups: structured clinical interview/questionnaire; administrative database; and self-report. Enhanced diagnostic categorization could improve our understanding of prevalence. However, current standardized criteria for psychiatric disorders, such as ICD-10 or DSM-V, may not facilitate this improvement. Moreover, several relatively common psychiatric disorders are yet to be recognized by these classifications (e.g., interictal dysphoric disorder or postictal psychosis). Additional population-based studies are needed to attain a more precise prevalence at the population level. Furthermore, family-based studies are essential to explore potential patterns of clustering of psychiatric disorders and epilepsy within families. These studies lack information on the etiology of the psychiatric comorbidities of the study subjects and the potentially shared etiology of epilepsy and the comorbid condition, the ILAE standards for reporting epilepsy epidemiology only make a short reference to the evidence that epilepsy and psychiatric comorbidities might share a common etiology ⁸. These studies also lack information about management, the diagnostic gap, the therapeutic gap, and other unmet healthcare needs that need to be captured and screened for. Population-based studies are lacking from the African or Eastern Mediterranean regions which is a priority.

With the bidirectional nature of epilepsy and psychiatric comorbidities becoming more evident⁴⁰, further research is needed on: 1) whether epilepsy is more common among individuals with the comorbidity in question than in the general population? (relies upon cross-sectional studies in adults and children), 2) whether epilepsy and psychiatric comorbidities share a common etiology? 3) whether the comorbidity studied is associated with an increased risk for developing epilepsy or a first unprovoked seizure? (best evaluated using longitudinal incident studies of epilepsy and controls, or prospective or retrospective

cohort studies of comorbidity (exposure) where epilepsy is an outcome),⁴ whether epilepsy or first unprovoked seizure is associated with an increased risk for developing the comorbidity in question? (relies upon prospective or retrospective cohort studies of epilepsy compared to controls where the comorbidity is the outcome or studies of prevalent epilepsy where incident comorbidity is the outcome), 5) whether the comorbidity in persons with epilepsy is different from comorbidity in persons without epilepsy? Is epilepsy in persons with comorbidity different from epilepsy in persons without the comorbidity? (relies upon casecontrol studies or cross-sectional studies in the general population or prospective/retrospective cohort studies), 6) does the comorbidity occur during the preictal or postictal period more than during other periods? (Relies upon crosssectional studies of epilepsy or prospective/retrospective cohort studies of epilepsy specifically examining the preictal or postictal period), 7) does the psychiatric comorbidity have a negative impact on the pharmacologic response of the seizure disorder or the prognosis of the seizure disorder? 8) does the psychiatric comorbidity have a negative impact on the mortality and morbidity of somatic disorders (e.g., cardiovascular disorders)?, 9) Last but not least, updating the reporting guidelines and standards for epilepsy epidemiologic research with new evidence of the etiology of the psychiatric comorbid condition that helps us to discover specific network derangements associated with epilepsy and the concurrent psychiatric comorbidity.

Appropriate identification and treatment of psychiatric comorbidity in epilepsy is crucial to manage patients effectively, given the significant impact on morbidity and quality-of-life ^{26,27}. In this study we identified the prevalence of single psychiatric disorders in PWE. Yet, a significant number of these patients suffer from more than one psychiatric comorbidity, including mood and anxiety disorders, ADHD and substance abuse, etc. Recognition of the comorbid occurrence of these psychiatric disorders has a significant impact on their management and potential risk for more severe psychiatric complications (e.g., suicidality). As PwE with psychiatric comorbidities such as depression and anxiety experience a higher risk of poor quality of life and encounter a higher burden of adverse events, routine screening with reliable and validated tools for psychiatric comorbidities has been suggested by the guidelines of the American Academy of Neurology (AAN)⁴¹, the National Institute for Health and Care Excellence (NICE)⁴², and the Scottish Intercollegiate Guidelines Network (SIGN)⁴³. The identification of psychiatric comorbidity in PwE in this review underscores the importance of providing support to clinicians involved in the care of PwE who have neuropsychiatric symptoms. A survey conducted by the Task Force on Education of the ILAE

Commission on Neuropsychiatry, which involved clinicians from 36 countries, addressed crucial areas for skills enhancement and their preferred educational format for skill improvement.⁴⁴ The surveyed clinicians highlighted the importance of screening for neuropsychiatric conditions and expressed a need for education on managing specific scenarios.⁴⁴

Conclusion

The findings from this review suggest that the training curriculum for epilepsy care should incorporate validated psychiatric screening tools. Additionally, resources for information and care referral related to other common conditions e.g., PTSD and substance abuse disorders should be readily accessible to neurology specialists treating individuals with epilepsy.

Supplementary information

The supplementary materials are available at (link)

Author contribution

Churl-Su Kwon: conceptualization, formal analysis, investigation, data curation, methodology, visualization, wrote the original draft, project administration, supervised, validated, reviewed, and edited the manuscript.

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All authors read and approved the final manuscript.

Conflicts of interest

We declare no conflict of interest.

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Data availability

This study contains no original data to share. All analyses were performed on previously published data.

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Table 1-Characteristics of the studies reporting current psychiatric comorbidities in persons with or without epilepsy.

No.	Author, year, source	ILAE Study quality	ILAE region	Persons with epilepsy, n	Persons without epilepsy, n	Age group, year	Psychiatric comorbidity	Diagnosis method (epilepsy)	Diagnosis Criteria (epilepsy)	Diagnosis method (psychiatric morbidity)	Diagnosis Criteria (psychiatric morbidity)	Diagnosis type (psychiatric morbidity)	Inpatient vs. outpatient	
1.	Harnod et al.³⁰, 2018, Taiwan	Good	Asia and Oceania	9801	39,204	<18	Anxiety disorders; depression	administrative database	ICD	administrative database	ICD	ICD	both	
2.	Harnod et al.³⁵, 2018, Taiwan	Good	Asia and Oceania	68,543	137,086	>18	Alcohol disorder; anxiety disorders; depression; psychosis	administrative database	ICD	administrative database	ICD	ICD	both	
3.	Uepping et al.³⁴, 2021, Germany	Good	Europe	7942	7942	>18	anxiety disorders; dementia; depression; intellectual disability	administrative database	ICD	administrative database	ICD	ICD	both	
4.	Andersson et al.³², 2020, Sweden	Good	Europe	126,406	379,131	>18	intellectual disability; dementia; substance disorders	administrative database	ICD	administrative database	ICD	ICD	both	
5.	Gorton et al.³⁶, 2018, UK	CPRD	Good	Europe	44,678	891,429	>18	alcohol disorder; anxiety disorders; BD; depression; eating disorders; personality disorders; psychosis; substance disorders	administrative database	READ code	administrative database	READ code	READ code	both
		SAIL databank	Good	Europe	14,051	279,365	>18	alcohol disorder; anxiety disorders; BD; depression; eating disorders; personality disorders; psychosis; substance disorders	administrative database	READ code	administrative database	READ code	READ code	both
6.	Brikell et al.²⁹, 2018, Sweden	Good	Europe	20625	1876240	<18 and >18	ADHD	administrative database	ICD	administrative database	ICD	ICD	both	
7.	Weatherburn et al.²⁷, 2017, UK	Good	Europe	12720	1,498,022	<18	Alcohol disorder; anxiety disorders; dementia; depression; psychosis; substance disorders	administrative database	READ code	administrative database	READ code	READ code	both	
8.	Gillberg et al.²⁸, 2017, Sweden	Good	Europe	277	26390	<18	ASD	administrative database	ICD	structured clinical interview/questionnaire	DSM	A-TAC	both	
9.	Aaberg et al.²⁶, 2016, Norway	Good	Europe	6635	1,125,161	<18	ADHD; anxiety disorders; ASD; intellectual disability; depression	administrative database	ICD	administrative database	ICD	ICD	both	
10.	Jokiranta et al.²⁵, 2014, Finland	Fair	Europe	529	22921	<18	ASD	administrative database	ICD	administrative database	ICD	ICD	both	

No.	Author, year, source	ILAE Study quality	ILAE region	Persons with epilepsy, n	Persons without epilepsy, n	Age group, year	Psychiatric comorbidity	Diagnosis method (epilepsy)	Diagnosis Criteria (epilepsy)	Diagnosis method (psychiatric morbidity)	Diagnosis Criteria (psychiatric morbidity)	Diagnosis type (psychiatric morbidity)	Inpatient vs. outpatient
11.	Fazel et al.²⁴, 2013, Sweden	Good	Europe	69995	660869	<18 and >18	alcohol disorder; depression; substance disorders	administrative database	ICD	administrative database	ICD	ICD	both
12.	Rai et al.²², 2012, UK	Fair	Europe	94	7071	>18	ADHD; anxiety disorders; ASD; depression; eating disorders; OCD; psychosis; suicide	self-report	NA	structured clinical interview/questionnaire	ICD	CIS-R	both
13.	Nuyen et al.¹⁶, 2006, The Netherlands	Fair	Europe	1259	3067	<18 and >18	anxiety disorders; dementia; intellectual disability; psychosis; substance disorders	administrative database	ICD	administrative database	ICD	ICD	both
14.	Gaitatzis et al.¹³, 2004, UK	Good	Europe	2321	420,312	<18 and >18	alcohol disorder; anxiety disorders; dementia; depression; OCD; psychosis	administrative database	ICD	administrative database	ICD	ICD	both
15.	Davies et al.¹¹, 2003, UK	Good	Europe	67	10202	<18	ADHD; ASD	healthcare professional	NA	structured clinical interview/questionnaire	DSM	DAWBA	both
16.	Stefansson et al.¹⁰, 1998, Iceland	Good	Europe	241	482	<18 and >18	alcohol disorder; psychosis;	administrative database	ICD	administrative database	ICD	ICD	NA
17.	Stefanello et al.¹⁹, 2010, Brazil	Fair	Latin America	153	154	>18	anxiety disorders; depression; suicide	healthcare professional	NA	questionnaire	HADS	HADS	outpatient
18.	Kwon et al.³³, 2020, US	Good	North America	163,671	4,113,967	<18 and >18	alcohol disorder; depression; psychosis; substance disorders	healthcare professional	ICD	administrative database	ICD	ICD	inpatient
19.	Wirrell et al.³¹, 2020, US	Fair	North America	339	678	<18	anxiety disorders; ADHD; ASD; eating disorders; psychosis	healthcare professional	ILAE	administrative database	NA	NA	both
20.	Kessler et al.²³, 2012, US	Good	North America	102	5590	<18 and >18	alcohol disorder; anxiety disorders; BD; depression; ADHD; substance disorders	self-report	NA	structured clinical interview/questionnaire	DSM	CIDI	both
21.	Kwon et al.²⁰, 2011, US	Good	North America	10,240	40,960	<18 and >18	alcohol disorder; depression; psychosis; substance disorders	administrative database	ICD	administrative database	ICD	ICD	both
22.	Copeland et al.²¹, 2011, US	Fair	North America	1610	822873	>18	alcohol disorder; psychosis; substance disorders	administrative database	ICD	administrative database	ICD	ICD	both
23.	Ettinger et al.¹⁸, 2010, US	Good	North America	1843	1,023,376	>18	alcohol disorder; anxiety disorders; BD; depression; psychosis	administrative database	ICD	administrative database	ICD	ICD	both
24.	Tellez-Zenteno et	Fair	North	253	36727	<18	anxiety disorders;	self-report	NA	structured clinical	DSM	WMH-CIDI	both

No.	Author, year, source	ILAE Study quality	ILAE region	Persons with epilepsy, n	Persons without epilepsy, n	Age group, year	Psychiatric comorbidity	Diagnosis method (epilepsy)	Diagnosis Criteria (epilepsy)	Diagnosis method (psychiatric morbidity)	Diagnosis Criteria (psychiatric morbidity)	Diagnosis type (psychiatric morbidity)	Inpatient vs. outpatient
	al. ¹⁷ , 2007, Canada		America				suicide			interview/questionnaire			
25.	Kobau et al. ¹⁵ , 2006, US	Fair	North America	131	4154	<18	anxiety disorders; depression	mail survey	self-report	self-report	self-report	self-report	both
26.	Ettinger et al. ¹⁴ , 2005, US	Fair	North America	142	473	>18	BD	mail survey	Self-report	self-report	MDQ	MDQ	both
27.	Ettinger et al. ¹² , 2004, US	Fair	North America	775	362	>18	depression	mail survey	self-report	self-report	CES-D score	CES-D score	both

ADHD, Attention-deficit hyperactivity disorder; ASD, Autism spectrum disorder; A-TAC, ADHD and other Comorbidities inventory; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CSE-D, Center for Epidemiology Studies–Depression Scale; CIDI, Composite International Diagnostic Interview; CIS, Clinical Interview Schedule; CIS-R, The revised CIS; DAWBA, Development and Well-Being Assessment; DIGS, Diagnostic Interview for Genetic Studies; DSM, Diagnostic and Statistical Manual of Mental Disorders; GAD-7, Generalized Anxiety seven-item scale; HADS, Hospital Anxiety and Depression Scale; ICD, International Classification of Diseases; ILAE, International League Against Epilepsy; K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia; MDQ, Mood Disorder Questionnaire; MINI, Mini International Neuropsychiatric Interview; MINI-KID, MINI for children and adolescents; NA, not available; OCD, Obsessive compulsive disorder; PHQ-9, Patient Health Questionnaire nine-item depression scale; PSE, Present State Examination; PwE, Persons with epilepsy; SCID, Structured Clinical Interview for DSM-IV; SNAP-IV, Swanson, Nolan e Pelham-IV questionnaire; SWAN, Strengths and Weakness of ADHD Symptoms and Normal Behaviors.

Table 2- Summary of Meta-analyses.

Psychiatric comorbidity	No. of Studies	Prevalence in PwE, n	Prevalence in persons without epilepsy, n	Overall OR (95% CI, τ^2 , Cochran's Q p-value)	Structured clinical interview using questionnaire	Admin database	Self-report
Any anxiety disorder	15	14,607/174,378 (8.4%)	351,291/6,094,835 (5.7%)	2.11 (1.73-2.58, 0.16, <0.01)*	2.43 (1.72-4.81, 0.15, 0.02)*	2.01 (1.48-4.00, 0.20, <0.01)*	NA
GAD	2	21/196 (10.7%)	619/12,661 (4.9%)	2.34 (1.14-4.79, 0.15, 0.12)*	2.34 (1.14-4.79, 0.15, 0.12)*	NA	NA
Specific phobia	2	22/196 (11.2%)	775/12,661 (6.1%)	1.73 (1.08-2.77, 0, 0.84)*	1.73 (1.08-2.77, 0, 0.84)*	NA	NA
Social phobia	2	22/196 (11.2%)	743/12,661 (5.8%)	3.00 (0.56-16.12, 1.33, <0.01)	3.00 (0.56-16.12, 1.33, <0.01)	NA	NA
Agoraphobia	2	6/196 (3%)	161/12,661 (1.3%)	2.17 (0.29-16.27, 1.56, 0.06)	2.17 (0.29-16.27, 1.56, 0.06)	NA	NA
Depression	16	57,275/417,208 (13.7%)	1,009,400/10,870,521 (9.3%)	2.45 (1.94-3.09, 0.26, 0)*	1.91 (1.05-3.48, 0.18, 0.05)*	2.43 (1.87-3.16, 0.26, 0)*	3.55 (2.43-5.18, 0.04 0.14)*
Bipolar disorder^b	4	739/60,816 (1.2%)	23,572/2,200,233 (1%)	3.12 (2.23-4.36, 0.10, <0.01)*	NA	2.42 (1.89-3.09, 0.04, <0.01)*	NA
Suicidal ideation	3	100/500 (20%)	5172/43,952 (11.7%)	2.25 (1.75-2.88, 0, 0.47)*	2.25 (1.75-2.88, 0, 0.47)*	NA	NA
Suicide attempt	2	9/247 (3.2%)	47/7225 (0.65%)	3.17 (0.49-20.46, 1.44, 0.03)	3.17 (0.49-20.46, 1.44, 0.03)	NA	NA
Any psychotic disorder	8	22,411/151,235 (14.8%)	278,634/4,404,204 (6.3%)	3.98 (2.57-6.15, 0.43, <0.01)*	NA	3.98 (2.57-6.15, 0.43, <0.01)*	NA
Schizophrenia	6	4849/147,677 (3.3%)	39,991/4,665,066 (0.85%)	3.72 (2.44-5.67, 0.28, <0.01)*	NA	3.72 (2.44-5.67, 0.28, <0.01)*	NA
OCD	2	21/5928 (0.35%)	1310/1,042,880 (0.12%)	2.71 (1.76-4.15, 0, 0.87)*	NA	2.68 (1.69-4.24, 0, 0.74)*	NA
PTSD	3	114/2039 (5.6%)	38,183/1,036,037 (3.7%)	1.76 (1.14-2.73, 0.08, 0.10)*	2.34 (1.47-3.73, 0, 0.5)*	NA	NA
Eating disorders	3	736/59,162 (1.2%)	7990/1,178,543 (0.67%)	1.87 (1.73-2.01, 0, 0.53)*	NA	1.86 (1.72-2.01, 0, 0.74)*	NA
Alcohol misuse^c	6	14,413/212,071 (6.8%)	116,824/4,490,629 (2.6%)	3.64 (2.27-5.83, 0.38, 0)*	NA	3.64 (2.27-5.83, 0.38, 0)*	NA
Alcohol abuse	3	14,672/141,727 (10.3%)	225,660/2,339,311 (9.6%)	2.10 (0.60-7.37, 1.12, <0.01)	NA	2.31 (0.49-10.84, 1.24, <0.01)	NA
Alcohol dependence	2	247/7444 (3.3%)	21,554/1,858,682 (1.1%)	4.94 (3.50-6.96, 0.10, <0.01)*	NA	4.94 (3.50-6.96, 0.10, <0.01)*	NA
Any substance disorder^d	9	26,378/412,446 (6.4%)	356,186/6,874,067 (5.2%)	2.75 (1.61-4.72, 0.74, 0)*	NA	NA	NA

ASD	6	870/7941 (10.9%)	11,831/1,192,423 (1%)	10.67 (6.35-17.91, 0.29, <0.01)*	11.86 (8.65-18.85, 0.02, 0.31)*	8.65 (3.87-19.35, 0.37, <0.01)*	NA
ADHD	6	3625/27,862 (13%)	102,573/3,024,942 (3.4%)	3.93 (3.80-4.08, 0.23, <0.01)*	1.73 (1.12-2.69, 0, 0.60)*	4.57 (2.55-8.20, 0.23, <0.01)*	2.52 (2.13-2.98, 0.03, <0.01)*

*P-value<0.05

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; GAD, Generalized Anxiety disorder; NA, not applicable; OCD, obsessive-compulsive disorder; OR, odds-ratio; PTSD, Post-traumatic stress disorder; PwE, Persons with epilepsy.

Table 3-Study Eligibility and Study Quality Rating based on ILAE rating scale.

Report Type	
1	original research on population of ≥ 30 people with epilepsy or unprovoked seizure and > 30 people without epilepsy
2	meta-analysis
3	other (would exclude)
Psychiatric multimorbidity measured?	
Relevant multimorbidities of epilepsy are limited to psychiatric conditions (includes neurodevelopmental conditions e.g. autism, intellectual disability). Measures of risk include rates, proportions, and relative comparisons (e.g., RR, OR) or can be calculated	
0	no
1	yes
Proceed with rating quality?	
0	no (does not meet criteria above)
1	yes (If report type #1 or 2 and psychiatric multimorbidity measured)
QUALITY-OF-EVIDENCE RATING (The lowest ranking score from any category will be the ‘Calculated rating’ for the study)	
Study Type	
1	incidence (prospective or retrospective cohort study)
2	prevalence (cohort or cross-sectional)
3	case-control
4	other or mixed
Source of Study Subjects	
1	Population-based
2	Clinic-based, broad representation (e.g. all people with epilepsy in the practice)
3	Clinic-based, limited representation (e.g. only women with epilepsy, people with JME, people who had epilepsy surgery)
4	Other, <i>poorly defined, or highly skewed subject</i>
Completeness (Sensitivity) of Epilepsy Case-finding in Study Population	

Reviewer's judgment of the sensitivity of methods of epilepsy diagnosis: completeness of epilepsy case ascertainment in population-based studies of epilepsy incidence or prevalence:	
0	Not population-based/Not applicable. Clinic-based study where subjects are selected based on epilepsy diagnosis
1	High – nearly all cases. Methods appear likely to find nearly all cases of epilepsy in population (or sampled population)
2	Good – most. Screening methods appear likely to ascertain most (approx. 70 - 84%) cases in population
3	Fair – majority. Screening methods appear likely to ascertain majority (approx. 50 - 69%) of cases in population
4	Poor – minority. Screening methods appear unlikely to ascertain majority of cases in population, OR information published is insufficient to assess
Sensitivity of Comorbidity Determination	
Reviewer's judgment of the sensitivity of methods of comorbidity ascertainment	
1	High – nearly all cases evaluated and classified. Comorbidities appear likely to be recorded in nearly all ($\geq 85\%$) cases in the study population
2	Good – most cases evaluated and classified. Comorbidities appear likely to be recorded in most (70 - 84%) cases in the study population
3	Fair—majority of cases evaluated and classified. Comorbidities appear likely to be recorded in the majority (50 - 69%) of cases in the study population
4	Poor – majority not classified or insufficient. Comorbidities appear unlikely to be recorded in the majority of cases in study population, OR unable to determine
Accuracy of Epilepsy Diagnoses	
Reviewer's judgment of the accuracy of diagnoses of epilepsy:	
1	High -- specialist diagnosis or valid structured interview; ILAE def'n. Cases are diagnosed by specialist clinician (i.e., w/ neurologic training), AND ILAE case definition applied
2	Good - mainly non-specialist clinicians. Cases are diagnosed by non-specialist clinician, OR minor deviation from ILAE case definition, OR all or substantial proportion of cases diagnosed based on ICD codes
3	Fair - self-report; non-clinical sources. All or substantial proportion of cases diagnosed based on self-report or non-clinical sources with specified criteria judged to have fair ($>50\%$) positive predictive value (PPV)
4	Poor - ill-defined or unreliable sources. All or substantial proportion of cases diagnosed with poorly defined criteria from non-clinical sources; positive predictive value judged to be poor; OR unable to determine
Accuracy of Comorbidity Determination	
Reviewer's judgment of the accuracy of diagnoses of comorbidity:	
1	High - DSM-based from specialist diagnosis or valid structured interview. Determined mainly from either structured interview designed to make DSM diagnosis, or diagnosis by a psychiatrist, when such data are judged to have good-to-excellent positive predictive value for the specific comorbidity of interest
2	Good - not DSM-based, but derived from good quality administrative data, non-specialist diagnoses, or rating scales deemed to have good PPV ($>70\%$). Determined largely or wholly from ICD, READ, or other diagnostic coding, when such data are judged to have good positive predictive value for the specific comorbidity of interest.

3	Fair - only self -report without a structured interview or fair administrative data. Determined largely or wholly from rating scales where a diagnosis is not made but a continuous measure used, patient report, or symptoms (reported or in the medical record) but not diagnosis when such data are judged to have only fair to good positive predictive value for the specific comorbidity of interest; when such data are judged to have only fair positive predictive value for the specific comorbidity of interest.
4	Poor - ill-defined or unreliable sources. Poor quality data or unable to determine.

Figure Legends

Figure 1- Forest plot of the meta-analyses.

Caption: The figure demonstrates the results of meta-analyses for each psychiatric comorbidity. For each psychiatric comorbidity, the overall odds ratio with 95% CI is represented.