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Risk factors for anxiety in patients with epilepsy: A meta-analysis

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ABSTRACT

Background: Epilepsy is a very common neurological disease, and it is important to focus on both controlling seizures and alleviating the psychological problems associated with this disease.Anxiety is an important risk factor for epilepsy and seriously affects the quality of life of patients with epilepsy (PWE). However, several risk factors for anxiety in PWE are relatively controversial and understudied. This meta-analysis was performed to identify potential risk factors for anxiety in PWE with the aim of reducing the incidence of anxiety and improving the quality of life among the individuals.

Method: The PubMed, Embase and Cochrane Library databases were systematically searched up to July 2023 to find eligible original English studies. All the search results were reviewed based on our inclusion and exclusion criteria. We calculated the combined odds ratios (ORs), standard mean differences (SMDs) and their corresponding 95% confidence intervals (CIs) to evaluate the effect of the included risk factors on anxiety in PWE.

Results: Twenty-four studies involving 5,403 PWE were ultimately included. The pooled results of our meta-analysis showed that female sex (OR = 1.67; 95 % CI: 1.30,2.15; $p < 0.001$), unmarried/divorced/widowed (OR = 0.83; 95 % CI: 0.72,0.96; $p = 0.011$), low socioeconomic status (OR = 0.47; 95 % CI: 0.33,0.67; $p < 0.001$), education levels below high school (OR = 1.74; 95 % CI: 1.36,2.23; $p < 0.001$), a history of trauma (OR = 2.53; 95 % CI: 1.69,3.78; $p < 0.001$), monotherapy (OR = 0.49; 95 % CI: 0.39,0.62; $p < 0.001$), AED-induced psychiatric side effects (OR = 2.45; 95 % CI: 1.20,4.98); $p = 0.014$), depression (OR = 5.45 95 % CI: 2.49,11.94; $p < 0.001$), a history of suicide (OR = 3.56; 95 % CI: 1.72,7.38; $p = 0.001$), and illness-related shame (OR = 2.76; 95 % CI: 2.17,3.52; $p < 0.001$) were risk factors for anxiety.

Conclusion: This meta-analysis showed that female, unmarried, low socioeconomic status, education level below senior high school, a history of trauma, monotherapy, AED-induced psychiatric side effects, depression, a history of suicide, and shame were risk factors for anxiety in PWE. However, further research is needed to determine the effect of other potential risk factors on anxiety in PWE. In addition, most of the studies included in this meta-analysis were not uniform in scale, and the risk factors were not comprehensive; therefore, larger prospective studies in different countries are needed to further investigate these risk factors.

1. Introduction

Epilepsy is a chronic neurological disorder that affects more than 50 million people worldwide [1]. In addition to the physical effects of seizures, epilepsy has important neurobiological, cognitive, and psychosocial consequences [2]. The incidence of psychiatric disorders is 2–3 times greater in patients with epilepsy (PWE) than in the general population [3]. Depression and anxiety are the most prevalent psychiatric disorders, with reported lifetime incidence rates of 30–35 % and 22.8 %[4], respectively. Although the psychiatric comorbidities of epilepsy are increasingly understood, most related research has focused on depression, which is very common and is influenced by age, education level, employment status, use of antiepileptic drugs, etc. [56].

However, many important outcomes, including quality of life, epileptic state, subjective cognitive state, economic cost and mortality, are significantly affected by epilepsy comorbid with anxiety [7]. Many

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PWE have undiagnosed anxiety, as they should be or are compounded by potential drug interactions that aggravate seizures or anxiety. Anxiety has been shown to reduce compliance with epileptic drugs, thereby causing more serious emotional problems. The latest evidence from epidemiological studies suggests that there is a two-way association between anxiety and epilepsy [8], especially during major social events, such as the COVID-19 pandemic [9]. PWE are more prone to anxiety problems, while patients with anxiety have a greater risk of seizures. There is increasing evidence that anxiety and epilepsy may have a common pathophysiology, including a common genetic basis and neurobiological hypotheses [10]. Therefore, to improve the quality of life and treatment efficiency of PWE, screening for anxiety and identifying its possible causes are necessary parts of clinical practice. Unfortunately, anxiety is often not recognized or treated in PWE.

Several studies have investigated which factors increase the risk of anxiety in PWE. Previous studies have shown that possible risk factors for comorbid anxiety include demographic factors (female, older age), psychosocial factors (unemployment, shame) and epileptic factors (increased frequency of seizures, hippocampal sclerosis) [11–13]. Although some studies have reached similar conclusions on the risk factors for anxiety in PWE, some factors are still unclear [14]. As anxiety has a serious impact on quality of life and seizures in PWE, it has received increasing attention worldwide; therefore, a meta-analysis on this topic has important clinical value.

We conducted a comprehensive and systematic review of the prevalence and reported risk factors for anxiety in PWE. We further studied the direct relationship between anxiety and epilepsy, which provides a strong basis for clinicians to specify new prevention and treatment strategies.

2. Method

A systematic review and meta-analysis were carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic review [15] and meta-analysis and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [16]. Approval from the Ethics Committee was not required for this study. This review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42023464424) [17].

2.1. Sources and searches

From the beginning to July 1, 2023, four databases were searched, including, PubMed, Cochrane Library, Embase and Web of Science. The search terms included epilepsy and anxiety. For example, we used the following keywords to search for articles in PubMed: “epilepsy”, “anxiety”, “generalized anxiety disorder”, “panic attacks”, “social anxiety disorder”, “agoraphobia”, “separation anxiety”, “specific phobia”, and “selective mutism”. The search language was English. EndNote X9 is used to export documents and manage citations.

2.2. Selection and exclusion criteria

According to the retrieval strategy, a researcher identified all the relevant articles in the four databases and eliminated duplicate articles. The two researchers independently reviewed the title, abstract and full text of the articles and included the articles according to the following criteria. The differences between the two sets of data were resolved through discussion. If no agreement could be reached, a third party was left to make a decision.

The inclusion criteria for the meta-analysis were as follows: 1) published in English; 2) case-control studies, cohort studies or cross-sectional studies; 3) met the diagnostic criteria for epilepsy and anxiety; 4) had epidemiological evidence of risk factors for PWE with anxiety; and 4) had original text with available original data. The exclusion criteria were as follows: reviews, single case reports, conference abstracts, articles with insufficient data or irrelevant results, animal experiments and low-quality literature.

2.3. Data extraction and quality assessment

For each study, the two researchers extracted the following data: 1) general information:first author, year of publication, country, study design, prevalence of PWE with anxiety, age range, and anxiety diagnostic criteria; and 2) demographic information: age, sex, marital status, socioeconomic status, place of residence (rural/urban), level of employment,education level, and history of trauma. 3) Epilepsy-related factors: age of onset of epilepsy, course of epilepsy and classification of epilepsy; 4) use of antiepileptic drugs (AEDs): quantity, whether there are psychiatric side effects; and 5) use of psychiatric factors: depression, history of suicide, and sense of shame.We have clarified the reference for each variable in supplementary Table 1.

The evidence review assessed and examined possible risk factors for anxiety in PWE, following the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews[18] (full details can be found in the online Appendix)[19]. The quality scores of the included cross-control studies ranged from 7 to 10 (the maximum AHRQ score was 11; low quality: 1–3; moderate quality: 4–7; high quality: 8–11).

2.4. Statistical analysis

Stata 17.0 was used for the statistical meta-analysis. The prevalence of anxiety in PWE was evaluated. The Cochrane Q test was used to determine whether there was significant heterogeneity between studies, and I^2 was used to quantify heterogeneity. When $I^2 > 50\ \%$, the random-effects model would be used for meta-analysis; otherwise, the fixed-effects model would be adopted [20]. We calculated OR or SMD using 95 % CI for dichotomous and continuous outcomes. Sensitivity analyses were performed to further confirm the stability of the overall effect. To assess the publication bias of each risk factor, we used Egger’s test [21]. $P < 0.05$ was considered to indicate a significant difference.

3. Results

3.1. Study selection

According to the previous retrieval strategy, a total of 14,051 related studies were detected.A total of 1971 duplicates were excluded.Then, 335 articles with relevant titles and abstracts were selected for full-text review. Finally, a total of 24 articles met our inclusion criteria [11,22–44]. A flow diagram of the included and excluded studies is shown in Fig. 1.

3.2. Characteristics of the studies and qualitative assessment

The 24 included studies were published between 2007 and 2022 and had sample sizes ranging from 57 to 574. Most of the participants were older than 18 years, 5 were about minors, and the youngest subject was 12 years old. The median incidence of anxiety in PWE was 34.62 % (range: 15.89 %-67.10 %). All 24 articles were cross-sectional studies. The details of the 24 articles included are shown in Table 1. We present the specific diagnostic criteria for each article in supplementary Table 2. The median AHRQ score of the studies included was seven (range: 7 to 10).

3.3. Risk factors for anxiety among PWE

The following risk factors were statistically analysed: demographic factors (age, sex, marital status, socioeconomic status, place of residence

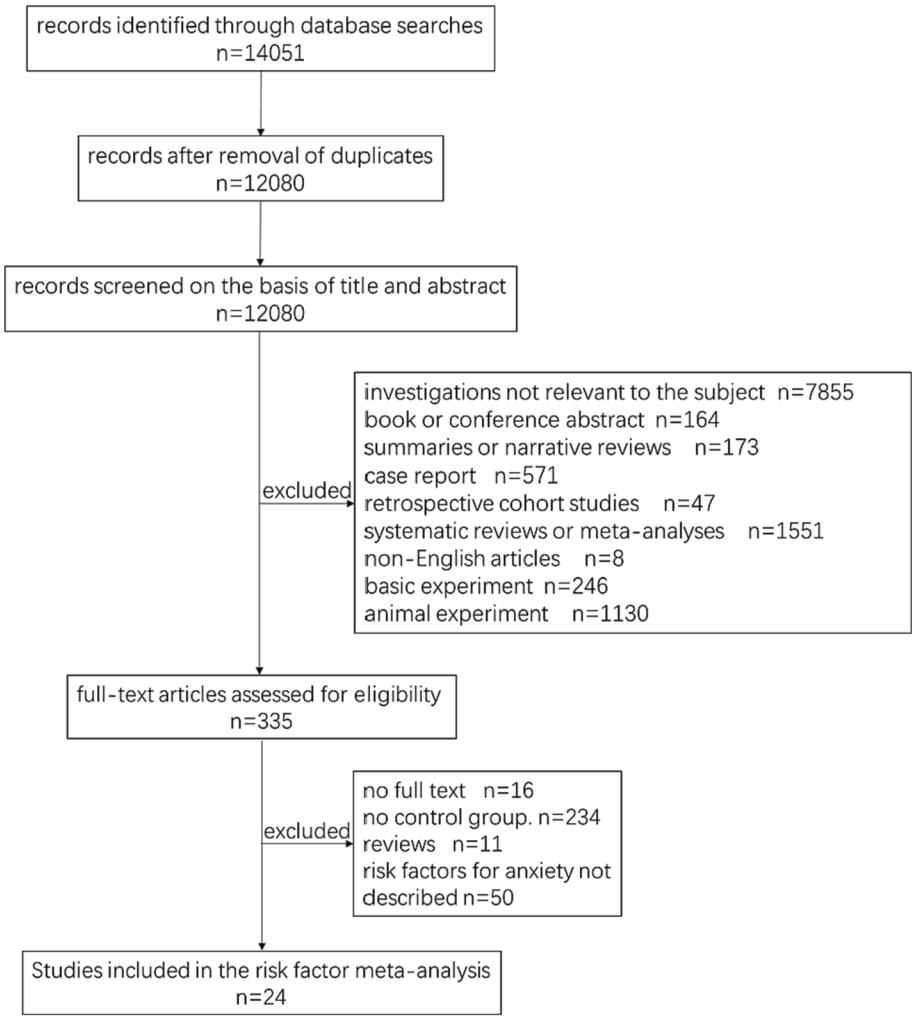

Fig. 1. Flow diagram of the retrieved, screened, and included studies.

(rural/urban), employment level, education level, history of trauma), factors related to epilepsy (age of onset, course, classification), antiepileptic drug (AED)-related factors (quantity, psychiatric side effects) and psychiatric factors (depression, history of suicide, sense of shame). Heterogeneity and significant differences were also analysed. The results are shown in Table 2.

3.3.1. Social demographic factors

Eight studies [22,25,31,34,35,36,11,43] investigated the relationship between age and anxiety in PWE, for a total of 1335 patients. The level of heterogeneity between the included studies was low ($I^2 = 12.90$ %, $p = 0.329$), and a fixed effects model was used. The model showed that age had no significant effect on the incidence of anxiety in PWE (SMD = -0.09; 95 % CI: −0.22, 0.03; $p = 0.140$).

Fifteen studies[22,23,25,26,28,31,33,34,36,38,11,40,41,43,44] were conducted to investigate the relationship between sex and anxiety in PWE. A total of 3379 patients were investigated. The incidence of anxiety in male PWE was 29.97 % (493/1645), and that in female PWE was 42.68 % (740/1734). The level of heterogeneity between the included studies was significant ($I^2 = 56.90$ %, $p = 0.003$), and a random effects model was used. The model showed that the incidence of anxiety in women with epilepsy was greater than that in men, and there was a significant difference between the two groups (OR = 1.67; 95 % CI:1.30, 2.15; $p < 0.001$).

Eleven studies [26,27,28,29,31,33,36,38,11,40,44] investigated the relationship between marital status and anxiety in PWE. A total of 3447 patients were investigated. The incidence of anxiety in married PWE was 32.20 % (604/1876). The incidence of anxiety in unmarried/divorced/widowed PWE was 37.94 % (596/1571). The heterogeneity between the included studies was significant ($I^2 = 37.70$ %, $p = 0.098$) using a fixed effect model. The model showed that the incidence of anxiety in married PWE was lower than that in unmarried/divorced/widowed PWE, and there was a significant difference between the two groups (OR = 0.83; 95 % CI: 0.72, 0.96; $p = 0.011$).

Four studies [23,28,34,44] investigated the relationship between socioeconomic status and anxiety in PWE. A total of 794 patients were investigated. The incidence of anxiety in patients with medium–high socioeconomic status was 42.13 % (198/470). The incidence of anxiety in PWE with low socioeconomic status was 59.88 % (194/324). The level of heterogeneity between the included studies was significant ($I^2 = 14.40$ %, $p = 0.320$), and a fixed effects model was used. The model showed that the incidence of anxiety in PWE with middle and high socioeconomic status was lower than that in PWE with low socioeconomic status, and there was a significant difference between the two groups (OR = 0.47; 95 % CI: 0.33, 0.67; $p < 0.001$).

Eight studies [25,26,27,28,31,32,36,43] investigated the relationship between employment level and anxiety in PWE. A total of 1711 patients were investigated. The incidence of anxiety in PWE with unemployment/unemployment was 40.85 % (297/727). The incidence of anxiety in PWE with employment was 39.89 % (290/984). The heterogeneity between the included studies was significant ($I^2 = 78.40$ %, $p < 0.001$) using a random effect model. The model showed that

Table 1
Basic characteristics of the patients included in the meta-analysis.

	Author	Year	Design	Country	Sample	Age	Prevalence	Diagnostic criteria of anxiety	AHQR score
1	Ciaran Lane	2018	cross sectional study	Canada	57	> 18	22.81 %	GAD-7	7
2	Stijn Van Hees	2020	cross sectional study	Belgium	342	> 18	51.75 %	HADS	8
3	Deniz Ertan	2021	cross sectional study	France	87	> 18	52.87 %	MINI	7
4	Milena Gandy	2015	cross sectional study	Australia	147	≥18	29.93 %	MINI, HADS	10
5	Seth A Mensah	2007	cross sectional study	UK	515	> 18	39.40 %	HADS	7
6	Minale Tareke Tegegne	2015	cross sectional study	Ethiopia	415	≥18	33.50 %	HADS	8
7	Sabrina Stefanello	2011	cross sectional study	Brazil	127	≥13	39.37 %	HADS	8
8	Kabtamu Nigussie	2021	cross sectional study	Ethiopia	556	≥18	37.05 %	HADS	8
9	Agata M Grzegorzewska	2021	cross sectional study	Poland	96	18–65	16.67 %	DSM-IV-TR	7
10	Rui Zhong	2021	cross sectional study	Tianjin	157	≥18	23.57 %	GAD-7	7
11	Jemal Seid	2022	cross sectional study	Ethiopia	300	≥12	38.33 %	GAD-7	9
12	Hai-Jiao Wang	2018	cross sectional study	Sichuan	458	≥18	33.40 %	GAD-7	8
13	Abiodun O Adewuya	2005	cross sectional study	Nigeria	102	12–18	31.37 %	DISC-IV	7
14	Christian Brandt	2010	cross sectional study	Germany	97	≥18	19.59 %	SCID-I	8
15	Mariusz S Wiglusz	2017	cross sectional study	Poland	96	18–65	16.67 %	SCID-I	9
16	Cristina Maria Duarte Wigg	2014	cross sectional study	Brazil	98	≥18	46.94 %	BAI	7
17	C L Peterson	2014	cross sectional study	Australia	162	≥18	46.91 %	HADS	7
18	Rui Zhong	2021	cross sectional study	Changchun	574	≥18	28.20 %	GAD-7	7
19	M López-Gómez	2008	cross sectional study	Mexico	196	28 ± 7	38.78 %	HAMA	7
20	Taoufik Alsaadi	2015	cross sectional study	United Arab Emirates	186	18–65	25.81 %	GAD-7	8
21	Kanitpong Phabphal	2007	cross sectional study	Thailand	126	15–50	39.68 %	HADS	7
22	Melissa L Engel	2021	cross sectional study	USA	179	13–24	35.20 %	GAD-7	7
23	Yen-Cheng Shih	2022	cross sectional study	China	107	≥20	15.89 %	GAD-7	8
24	Bilal Hadi Jawad	2022	cross sectional study	Iraq	225	≥18	67.10 %	GAD-7	7

GAD-7, the 7-item Generalized Anxiety Disorder Questionnaire; HADS, Hospital Anxiety and Depression Scale; MINI, the MINI-International Neuropsychiatric Interview; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders; DISC-IV, Diagnostic Interview Schedule for Children Version IV; SCID-I, the Structured Clinical Interview for DSM-IV Axis I Disorders; BAI, Beck Anxiety Inventory; HAMA, Hamilton Anxiety Scale.

employment status had no significant effect on the incidence of anxiety in PWE (OR = 1.30; 95 % CI: 0.79, 2.13; p = 0.305).

Seven studies [22,25,26,27,31,33,44] investigated the relationship between education level and anxiety in PWE. A total of 1931 patients with anxiety were investigated. The incidence of anxiety in PWE below senior high school was 40.20 % (550/1368). The incidence of anxiety in PWE above senior high school was 27.71 % (156/563). The level of heterogeneity among the included studies was low (I^2 = 41. 10 %, p = 0.117) using a fixed-effect model. The model showed that the incidence of anxiety in PWE with an education level below senior high school was greater than that above senior high school, and there was a significant difference between the two groups (OR = 1.74; 95 % CI: 1.36, 2.23; p < 0.001).

Two studies [24,32] investigated the relationship between trauma history and anxiety in PWE, with a total of 337 patients. The incidence of anxiety in PWE with a history of trauma was 54.60 % (95/174), while the incidence of anxiety in PWE without a history of trauma was 28.22 % (46/163). The level of heterogeneity among the included studies was low (I^2 = 0.00 %, p = 0.879), and a fixed-effect model was used. The model showed that PWE with a history of trauma had a greater incidence of anxiety than those without a history of trauma, and there was a significant difference between the two groups (OR = 2.53; 95 % CI: 1.69, 3.78; p < 0.001).

Two studies [31,11] investigated the relationship between residence and anxiety in PWE, with a total of 731 patients. The incidence anxiety among PWE who live in rural areas was 30.39 % (86/283), and the incidence anxiety among PWE who live in urban areas was 25.22 % (113/448). The level of heterogeneity among the included studies was poor (I^2 = 0.00 %, p = 0.789), and a fixed-effect model was used. The model showed that residence had no significant effect on the incidence of anxiety in PWE (OR = 1.29; 95 % CI = 0.93, 1.80; p = 0.130).

3.3.2. Factors related to epilepsy

Six studies [24,25,34,35,36,43] investigated the relationship between the age of onset of epilepsy and anxiety in PWE. The level of heterogeneity between the included studies was low (I^2 = 6.70 %; p = 0.374). A fixed effect model was used. The model showed that age of onset had no significant effect on the incidence of anxiety in PWE (SMD = 0.05; 95 % CI: −0.13, 0.23; p = 0.608).

Six studies [24,25,34,35,36,43] investigated the relationship between the course of epilepsy and anxiety in PWE. The level of heterogeneity among the included studies was low (I^2 = 26.90 %; p = 0.233). A fixed effect model was used. The model showed that the course of disease had no significant effect on the incidence of anxiety in PWE (SMD = -0.09; 95 % CI: −0.27, 0.09; p = 0.321).

Eight studies [22,25,28,31,34,40,43,44] investigated the relationship between epilepsy classification and anxiety in PWE, for a total of 1106 patients. The incidence of anxiety in PWE with focal epilepsy was 28.62 % (186/650). The incidence of anxiety in PWE with other types of epilepsy (generalized epilepsy/epilepsy of unknown origin) was 41.23 % (118/456). The level of heterogeneity between the included studies was low (I^2 = 52.10 %; p = 0.041), and a random effect model was used. The model showed that the type of epilepsy had no significant effect on the incidence of anxiety in PWE (OR = 1.00; 95 % CI: 0.64, 1.56; p = 0.985).

3.3.3. Factors related to AED use

Eight studies [27,28,29,31,33,34,40,44] with 2,090 patients investigated the relationship between the number of AEDs used and anxiety in PWE. The incidence of anxiety in PWE treated with a single drug was 29.68 % (436/1469). The incidence of anxiety in PWE with multidrug-treated was 47.02 % (292/621). The level of heterogeneity between the included studies was low (I^2 = 21.40 %, p = 0.259), and a fixed effects model was used. The model showed that the incidence of anxiety in PWE treated with a single drug was lower than that in PWE treated with multiple drugs, and there was a significant difference between the two groups (OR = 0.49; 95 % CI: 0.39, 0.62; p < 0.001).

Three studies [23,27,32] with 1,057 patients investigated the relationship between the psychiatric side effects of AEDs and anxiety in PWE. The incidence of anxiety in PWE with psychiatric side effects of AEDs was 51.90 % (191/368). The incidence of anxiety in PWE without psychiatric side effects of AEDs was 34.83 % (240/689). The level of heterogeneity between the included studies was significant (I^2 = 84.70 %, p = 0.001), and a random effects model was used. The model showed that the incidence of anxiety in PWE with psychiatric side effects of AEDs was greater than that in PWE without psychiatric side effects, and

Table 2
Meta-analysis and characteristics of every risk factor for anxiety in PWE.

Item	study (n)	OR/SMD (95 % CI)	heterogeneity test	
			p	I^2
Social demographic factors				
age	8	−0.09(-0.22,0.03) p = 0.140	0.329	12.90 %
famale***	15	1.67 (1.30,2.15) p < 0.001	0.003	56.90 %
married *	11	0.83(0.72,0.96) p = 0.011	0.098	37.70 %
middle and high socioeconomic status ***	4	0.47(0.33,0.67) p < 0.001	0.320	14.40 %
Unemployment	8	1.30 (0.79,2.13) p = 0.305	<0.001	78.40 %
education level below senior high school ***	7	1.74(1.36,2.23) p < 0.001	0.117	41.10 %
trauma history***	2	2.53(1.69,3.78) p < 0.001	0.879	0.00 %
residence in rural areas	2	1.29(0.93,1.80) p = 0.130	0.789	0.00 %
Factors related to epilepsy				
age of onset of epilepsy	6	0.05(-0.13,0.23) p = 0.608	0.374	6.70 %
course of epilepsy	6	−0.09(-0.27,0.09) p = 0.321	0.233	26.90 %
focal epilepsy	8	1.00 (0.64.1.56) p = 0.985	0.041	52.10 %
Factors related to AED use				
monotherapy***	8	0.49(0.39,0.62) p < 0.001	0.259	21.40 %
the psychiatric side effects of AEDs*	3	2.45(1.20,4.98) p = 0.014	0.001	84.70 %
Psychiatric factors				
depression***	7	5.45(2.49,11.94) p < 0.001	<0.001	84.40 %
a history of suicide**	3	3.56(1.72,7.38) p = 0.001	0.457	0.00 %
shame***	3	2.76 (2.17,3.52) p < 0.001	0.387	0.00 %

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
ORs or SMDs were calculated with 95 % confidence intervals (CIs) for dichotomous and continuous outcomes.

there was a significant difference between the two groups (OR = 2.45; 95 % CI: 1.20, 4.98; p = 0.014).

3.3.4. Psychiatric factors

Seven studies [24,28,30,31,32,11,40] investigated the relationship between depression and anxiety in PWE. The incidence of anxiety in PWE with depression was 60.45 %. The incidence of anxiety in PWE without depression was 24.44 %. The level of heterogeneity between the included studies was significant ($I^2 = 84.40$ %, $p < 0.001$), and a random effects model was used. The model showed that the incidence of anxiety in patients with depression was greater than that in patients without depression, and there was a significant difference between the two groups (OR = 5.45 95 % CI: 2.49,11.94; $p < 0.001$).

Three studies [24,28,32] investigated the relationship between a history of suicide and anxiety in PWE. The incidence of anxiety in PWE with a history of suicide was 71.05 %, and that in PWE without a history of suicide was 38.66 %. The level of heterogeneity between the included studies was low ($I^2 = 0.00$ %, p = 0.457) using a fixed-effect model. The model showed that the incidence of anxiety in PWE with a history of suicide was greater than that in PWE without a history of suicide, and there was a significant difference between the two groups (OR = 3.56; 95 % CI: 1.72, 7.38; p = 0.001).

Three studies [27,29,32] investigated the relationship between shame and anxiety in PWE. A total of 1271 patients were investigated. The incidence of anxiety in PWE with shame was 49.24 % (226/459), and the incidence of anxiety without shame was 26.11 % (212/812). The level of heterogeneity between the included studies was low ($I^2 = 0.00$ %, p = 0.387) using a fixed effect model. The model showed that the incidence of anxiety in PWE with a history of shame was greater than that in PWE without a history of shame, and there was a significant difference between the two groups (OR = 2.76; 95 % CI: 2.17, 3.52; $p < 0.001$).

3.4. Publication bias

According to the Egger test, the p values of all the research factors were > 0.05. Table 3 shows that no publication bias was detected.

3.5. Sensitivity analyses

Overall, there were no differences in the outcomes of any risk factor investigated. The results are shown in supplementary Fig. 1.

4. Discussion

Epidemiological studies have shown that, compared with the general population, PWE are more than twice as likely to develop anxiety, and some studies have reported that up to 30 % of PWE have anxiety [3,45]. Anxiety has a significant impact on PWE, including quality of life, seizure control, the use of health care systems, and other psychosocial problems [46]. Park and colleagues reported that emotional symptoms were most closely related to and the strongest predictor of quality of life, followed by seizure control. The influence of emotional symptoms was almost twice as great as that of seizure control [47]. Anxiety aggravates AED-related adverse events, including headaches and memory problems, in PWE [48]. Therefore, early identification and management of anxiety symptoms in PWE may provide benefits beyond the relief of psychiatric symptoms. However, there are still some disputes about the risk factors for anxiety prediction in PWE. A total of 24 articles were included in our meta-analysis. Female sex, unmarried/divorced/widowed status, low socioeconomic status, education level below high school, history of trauma, multidrug treatment, psychotic side effects of AEDs, depression, shame, and history of suicide were found to be risk factors of anxiety among PWE.

4.1. Social demographic factors

This meta-analysis revealed that the risk of anxiety is greater in women with epilepsy than in men with epilepsy, which is consistent with findings in the general population. In the general population, men and women exhibit obvious and consistent differences in anxiety, and anxiety is more common in women than in men [49]. This sex difference

Table 3
Assessment of publication bias.

Item	Study (n)	publication bias Egger's test
age	8	t = 0.60 p = 0.569
female	15	t = -0.42 p = 0.684
marital status	11	t = 0.30 p = 0.775
employment level	8	t = -2.42 p = 0.052
education level	7	t = 0.55 p = 0.608
age of onset of epilepsy	6	t = 0.43 p = 0.689
course of epilepsy	6	t = -0.21 p = 0.843
epilepsy classification	8	t = 1.66 p = 0.147
monotherapy	8	t = 0.44 p = 0.674
depression	7	t = 0.69 p = 0.522

* $p < 0.05$.

is more pronounced in people with other chronic diseases, such as coronary heart disease [50,51]. The sex difference in PWE can be explained by the following reasons [52]. A previous survey reported that most people in China have a negative attitude towards epilepsy and epilepsy patients [53]. Therefore, patients may be subjected to tremendous social and psychological pressure and social isolation. This shame may have a greater impact on the psychiatric health of female patients than on that of male patients because women are more likely than men to rely on social and religious support [54]. In addition, female patients exhibit more worries about the effects of AED treatment and seizures on the foetus during pregnancy and lactation. These concerns increase the likelihood of anxiety in females with epilepsy. Two recent studies aimed at identifying possible sex differences in PWE strikingly found that there was no increased risk of anxiety in women compared to men [13,55]. Our data do not support these results. The current study included more than 5000 people; thus, it has more power than previously published studies for confirming the incidence of anxiety, and another meta-analysis of more than 570 people confirmed our results [11].

Our study confirmed that there was no significant relationship between age and anxiety in epilepsy patients. However, previous studies have shown that the corresponding symptoms of anxiety are more often reported by young participants [56]. This may be due to the relatively small number of young people included in the population.

Marriage status and family are the main sources of social support and predictors of the health of patients with chronic diseases [57]. Our study showed that, compared with unmarried PWE, married adult patients had a lower incidence of anxiety. This is because marriage helps cultivate a sense of responsibility, promote healthy behaviour, reduce risk factors, and enhance compliance with medical programmes [58]. Married PWE have better epilepsy control and quality of life than unmarried patients. Emotional support from family members has a positive impact on psychiatric health [59], which suggests that marriage is very important for PWE and that the risk of anxiety in PWE with a stable marital status is also reduced.

In our study, we found that PWE with low socioeconomic status had a significantly increased risk of anxiety. This finding is consistent with previous studies [60]. In research conducted by Tibber et al., income inequality was also shown to be associated with negative psychiatric health. In this study, as the proportion of the rural population increased, so did the prevalence of anxiety and the years of life affected by anxiety. Rural communities have fewer psychiatric health services because they are less socioeconomically developed. As a result, a great proportion of people living in rural areas have unmet psychiatric health needs. However, our research showed that employment status and place of residence were not associated with the occurrence of anxiety.

Patients with a low education level in our study had higher rates of anxiety symptoms, which is consistent with the findings of previous studies [12]. This may be because highly educated patients have a better understanding of disease conditions and self-adjustment and actively seek help from doctors, friends and family.

Compared with patients without epilepsy-related injuries or accidents, patients with a history of epilepsy-related trauma have significantly reduced quality of life and increased anxiety [61]. This finding is consistent with our meta-analysis and may be related to the significant increase in trauma associated with the burden on PWE, their families, and society.

4.2. Seizure-related factors

In addition to the potential neuropsychiatric changes caused by epilepsy, a key area of concern is the psychosocial burden that accumulates in PWE over time [62]. However, most studies have shown little correlation between epilepsy-related factors (age of onset, course of epilepsy, and whether epilepsy is focal) and mood [12].

Age of seizure onset was found to be a nonsignificant predictor in our meta-analysis. The effect of age on the onset of anxiety is complex. Munger Clary HM showed that the age of seizure onset was not associated with the onset of anxiety [63], while Sang-ahm Lee et al [12]. reported that age of onset predicted high hospital anxiety (HDS-A) and depression scale scores 12 months after the first seizure and that patients with earlier onset of epilepsy were more likely to develop anxiety than were those with later onset.

The course of epilepsy and anxiety were not correlated in this meta-analysis, which is consistent with the fact that the course of epilepsy has not been previously reported to be a predictor of depression in PWE. A study showed that the course of epilepsy did not affect outcomes on the SAFA scale or subscale scores, and the course of epilepsy was not associated with abnormal anxiety or depression scores [64].

The types of seizures have been studied extensively in various articles. However, our meta-analysis, similar to previous reports, did not support an established link between the type of epilepsy and anxiety in PWE. Some studies have reported that the type of epilepsy was not associated with the occurrence of anxiety [65,66], but a cohort study showed that the type of seizure was significantly related to the occurrence of anxiety.

4.3. AED-related factors

Antiepileptic drugs are an essential part of the treatment of PWE; however, antiepileptic drugs profoundly affect the emotional state of patients, whether they are the emotional side effects of epilepsy or the amount of drugs taken.

PWE treated with multidrug therapy had a greater risk of anxiety than did those treated with a single AED. In general, patients treated with multiple drugs suffer from complex and drug-resistant epilepsy, and they also experience complex drug planning rules and adverse reactions. Therefore, the effect of multidrug therapy may be due to interactions among many factors.

It is well known that some AEDs, such as levetiracetam, perampanel, topiramate, zonisamide, and barbiturates, may induce negative psychiatric effects, especially depression, anxiety, or aggression. Conversely, other medications, such as sodium channel blockers, valproates, and benzodiazepines, produce positive mood or anti-anxiety effects. In our study, the psychiatric side effects of AEDs were not found to be risk factors for anxiety in PWE possibly because there is less research on this topic.

4.4. Psychological factors

Although anxiety and depression are considered two distinct entities according to diagnostic criteria, anxiety and depression are relatively common syndromes [67]. Similarly, as reflected in our meta-analysis, the highly prevalent comorbidity of depression and anxiety may be due to their mutual pathophysiological background, such as reduced quality of life; life stresses such as increased risk of unemployment; and progressive hypothalamic–pituitary–adrenal (HPA) axis dysfunction [68].

Previous studies have shown that suicide rates among PWE are at least three times and up to five times greater than those in the general population. The intersection of stress, anxiety and epilepsy is greater in these populations than in the general population [69]. Psychiatric comorbidities associated with epilepsy can seriously affect patients' quality of life. Among PWE, those who exhibited emotional disorders had a 32 times greater risk of suicide than did those with epilepsy who did not have a common emotional disorder [69]. Our research showed that PWE who had a history of suicide were more likely to have anxiety.

In addition to psychiatric illness, shame also surrounds neurological conditions such as epilepsy. Despite medical advances, there is still shame and misunderstanding about epilepsy. The shame associated with epilepsy includes that experienced by PWE and the attitudes of the community towards them. Shame is a risk factor for the development of psychiatric disorders such as anxiety and depression in PWE. According

to a recent study, 25 % of PWE perceive high shame, 61.0 % perceive stress, 55.0 % perceive anxiety and 47.5 % perceive extremely severe levels of depression. According to our regression analysis, overall perceived shame contributed to 32.9 % of the differences in stress, anxiety, and depression among PWE [70]. Our study also revealed that shame is significantly associated with anxiety in PWE. In addition, PWE who suffer from depression or anxiety often have a worse quality of life than PWE without these conditions [71], and depression and anxiety can lead to suicidal ideation or shame [71,72]. The psychological factors of PWE are interactive, so increasing attention is particularly important in improving the quality of life of PWE.

4.5. Limitation

Like with any literature review, this analysis is subject to limitations that affect its generality and interpretation. First, the scale and cut-off values used in each study were not consistent. Most of the included studies did not report potential confounding variables of risk factors for anxiety among PWE.The quality of the included studies was uneven. There were insufficient studies on potential risk factors (such as seizure control and location of epileptic foci); therefore, our results may reduce reliability to some extent. More high-quality original research is needed in the future. Second, because all the included studies were cross-sectional surveys, the results and variables were measured at the same time, so we cannot determine the temporal relationship between anxiety and epilepsy. Third, only five studies (5/24 20.8 %) examined minors, and only one of them included underaged patients aged 12–18 years. No conclusion can be drawn on the risk factors for anxiety in juvenile patients with epilepsy.

5. Conclusion

Our meta-analysis identified several factors associated with an increased risk of anxiety in PWE, including demographic factors, epileptic factors, factors associated with antiepileptic drugs, and psychiatric factors. These conclusions are helpful for improving the prevention and detection of anxiety attacks in PWE. The management of epilepsy involves not only controlling seizures but also paying attention to the psychological problems of patients and jointly improving the quality of life of PWE.

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CRediT authorship contribution statement

Cailang Niu: Writing – original draft, Visualization, Investigation, Formal analysis, Data curation, Conceptualization. **Penghong Li:** Investigation, Formal analysis, Data curation. **Xueqing Du:** Writing – original draft. **Mina Zhao:** Writing – original draft. **Haobo Wang:** Writing – original draft. **Debo Yang:** Writing – original draft. **Maolin Wu:** Writing – review & editing, Supervision. **Wei Jing:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2024.109665.

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