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Suicidality and epilepsy: A systematic review and meta-analysis

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Background: We aimed to evaluate the association between epilepsy and suicidality, including suicidal ideation, attempts and completed suicide.

Methods: We systematically searched PubMed, Embase, Cochrane Online Library, and Clinicaltrials.gov from 1946 to June 21, 2021 and assessed the quality of the studies using the Newcastle–Ottawa Scale. We calculated the pooled OR and the crude rate for suicidal ideation, suicide attempts and completed suicide in patients with epilepsy (PWE).

Results: We screened 2,786 studies and included 88 articles with 1,178,401 PWE and 6,900,657 participants as controls. Search terms included epilepsy and suicide. The pooled rates of suicidal ideation, suicide attempts and completed suicide in PWE were 19.73% (95% CI: 17.00–22.62%), 5.96% (95% CI: 4.82–7.20%), and 0.24% (95% CI: 0.11–0.42%), respectively. Compared to the control group, PWE were at a significantly higher risk of total suicidality (pooled OR, 2.60; 95%: 2.13–3.18), including suicidal ideation (pooled OR, 2.70; 95% CI, 2.21–3.30), suicide attempts (pooled OR, 2.74; 95% CI, 2.08–3.61) and completed suicide (pooled OR, 2.36; 95% CI, 1.45–3.83). Subgroup analyses showed significant differences in the subgroups of the measurement of suicidality.

Conclusion: The rate of suicidal ideation, suicide attempts and completed suicide in PWE were about 19.73, 5.96, and 0.24%. And there was an increased risk of suicidality in PWE especially temporal lobe epilepsy and drug-resistant epilepsy. Clinicians need to be aware of this risk in PWE with early identification and prevention at the time of diagnosis.

Protocol Registration: PROSPERO CRD42021278220.

KEYWORDS

epilepsy, suicidal ideation, suicide attempt, completed suicide, incidence rate

1. Introduction

Epilepsy is a common chronic neurological disorder that affects approximately 50 million people worldwide (1), and nearly a quarter of them have emotional problems (2). Social distress, vulnerability, and reduced quality of life and stigma contributed to the overall profound psychosocial burden in patients with epilepsy (PWE) (2). The burden of suicide constitutes a serious public health issue worldwide. Approximately 800,000 people die from suicide annually according to a global estimate from the World Health

Organization (WHO) (3). Suicide is also a cause of premature mortality in PWE. The estimated lifetime prevalence of suicidal attempts among PWE ranged from 3.3 to 14.3%, whereas approximately 38% of PWE had suicidal ideation (4, 5).

In recent years, an increasing number of studies have focused on suicidality in PWE. Suicidality includes suicidal ideation, suicide attempts, and completed suicides (6). Most studies reported one or two components of suicidality in PWE (7-9). A recent meta-analysis only reported the comparison of suicide attempts among PWE and controls and did not report the risk of suicidal ideation and completed suicide (10). The result of the risk of completed suicide in PWE is inconsistent (11-13). It has been reported that 11.5% of all deaths in PWE are a result of suicide, which is 2.06–4.6 times higher than the rate of suicide in the general population (2, 14, 15). However, several studies found a higher risk of completed suicide in PWE than in controls, but the difference was not statistically significant (12, 13). Therefore, it is necessary to determine whether PWE have a higher risk of suicidality. We performed this systematic review and metaanalysis to determine the association between epilepsy and suicidality, including suicidal ideation, suicide attempts and completed suicide.

2. Materials and methods

2.1. Search strategy and selection criteria

We performed a systematic review and meta-analysis in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) principles to investigate the association between epilepsy and suicidality. We searched the online databases of PubMed, Embase, Cochrane Online Library, and Clinicaltrials.gov.¹ The last search was performed on June 21, 2021. Search terms included epilepsy and suicide. Two reviewers independently reviewed the titles and abstracts for any potentially relevant articles.

The two reviewers independently assessed the eligibility of potentially relevant studies according to the predesigned inclusion and exclusion criteria. Disputes about relevance were resolved by consensus among the investigators. The inclusion criteria were as follows.

Study design: English language articles; observational or controlled studies; population: study population identified with a clinical diagnosis of epilepsy with any age; outcomes: diagnosis of suicidality through medical records, interview, or questionnaire; suicidality studied in relation to epilepsy; and outcome measures reported. Animal studies, meta-analyses, reviews, case reports and conference abstracts without full articles to evaluate the quality of studies were excluded.

2.2. Data analysis

The two reviewers extracted data from the included studies using a data extraction form that included (1) general information: the first author, year of publication and country of study origin; (2) study characteristics: study design, number of individuals with epilepsy, number of individuals with epilepsy with suicidality, number of healthy controls, number of controls with suicidality, sexes and ages for both the epilepsy and control groups and follow-up; and (3) outcomes: the reviewers separately recorded suicidal ideation, suicide attempts and completed suicide. Suicidal ideation included suicidal risk, suicidal thoughts, suicidal tendencies, and suicidality without a defined attempt or behavior. Suicide attempts included suicidal behavior and suicide plans. In addition, the reviewers recorded the instruments used to measure suicidality and the association [hazard ratio (HR), odds ratio (OR), or risk ratio (RR)] between epilepsy and suicidality. If the patients from those studies were included with the same inclusion criteria in the same period and population, we extracted data from the most complete study if several studies had similar data resources or databases.

Two independent evaluators assessed the quality of the studies using the Newcastle–Ottawa Scale (NOS) from three aspects: the selection of the study groups, the comparability of the groups, and the ascertainment of the outcomes of the studies. The total score was 9; a score ≥ 6 indicated high-quality literature, and a score < 6 indicated low-quality literature.²

All statistical analyses were performed using R 4.1.0. We calculated pooled OR in the studies with a control group for suicidal ideation, suicide attempts and completed suicide. We also calculated the crude rates for suicidal ideation, suicide attempts and completed suicide in all included studies with or without control groups. We performed a Shapiro–Wilk normality test to test whether the data fit a normal distribution. If we transformed the rate of suicidality in epilepsy *via* Freeman-Tukey double arcsine transformation, we performed a meta-analysis. The test level α of the effect was set to 0.05. Statistical heterogeneity was evaluated by the I² statistic. The fixed-effects model was used for comparisons with I² \geq 50%. Sensitivity analysis was used to evaluate the stability of the meta-analysis results by omitting every study.

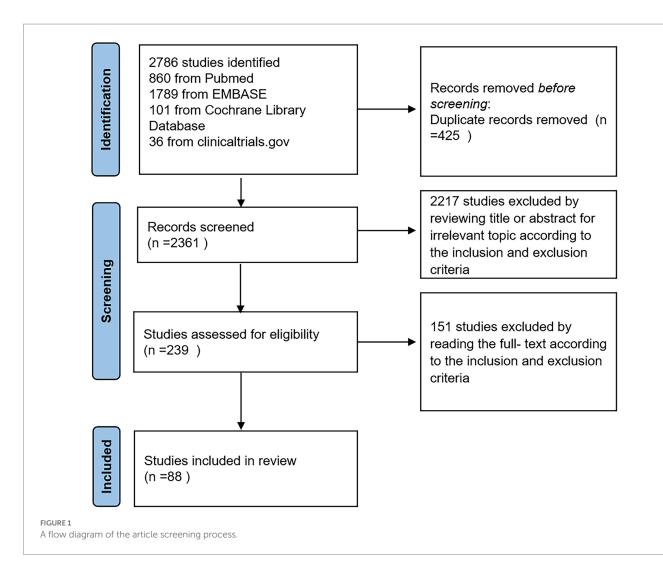
We also performed prespecified analyses to evaluate subgroup differences in the pooled OR and incidence rate by country, age of the population, and measurement of suicidality. We also performed the subgroup analysis to calculate the pooled rate by specific type of epilepsy. We classified the studies into three subgroups according to different types of measurements for suicidality, including diagnostic interviews (such as the Mini International Neuropsychiatric Interview), questionnaires (such as the Beck Depression Inventory and Patient Health Questionnaire-9), and medical records (such as the International Classification of Diseases code). Using meta-regression, we evaluated the effects of year of publication and proportion of women in the study population on the observed associations.

3. Results

We screened 2,786 studies and selected 239 studies for full-text review. Following screening, we included 88 articles in our metaanalysis. A flow diagram of the article screening process according to

¹ https://clinicaltrials.gov/

² http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp



PRISMA is shown in Figure 1 and the PRISMA checklist is shown in Supplementary Table S1. Among a total of 8,079,058 participants, 1,178,401 were PWE, and 6,900,657 participants were controls. There were 35 cohort studies, 42 cross-sectional studies, 10 case-control studies and 1 randomized controlled experiment (RCT) (16). Among studies with a control group, 11 articles reported suicidal ideation, 14 articles reported suicide attempts, and 11 articles reported completed suicide. Sixty-eight articles studied only adults, 10 articles studied only children (<18 years old), and 4 articles studied both adults and children. Other 6 articles did not report the age of population. Six articles addressed newly diagnosed with epilepsy (NDE), 5 articles addressed temporal lobe epilepsy (TLE), and 5 articles addressed drug-resistant epilepsy (DRE). Others did not specify the type of epilepsy. The population in the study of Mula (17) was from Italy Germany and France. We classified this study into a subgroup of developed countries in subgroup analysis because of the larger population in Germany. NOS scores ranged from 5 to 9. The characteristics of the included studies are shown in Supplementary Table S2. PWE were at a higher total risk of suicidality than the general population (pooled OR, 2.60; 95%: 2.13-3.18, *p* < 0.0001, Figure 2).

There were 47 articles reporting suicidal ideation in PWE. Based on the pooled data from 11 of 47 articles with a control group, we found that PWE were significantly more likely to experience suicidal ideation than those without epilepsy (pooled OR, 2.70; 95% CI, 2.21–3.30, p < 0.0001). The funnel plot was symmetrical, and Egger's regression test suggested limited publication bias among these studies (p=0.08). We also found that the pooled prevalence rate of suicidal ideation in PWE in 47 studies was 19.73% (95% CI: 17.00–22.62%, Figure 3).

Thirty-three articles reported suicide attempts in PWE. Based on the pooled data from 14 of 33 articles with a control group, we found that PWE were significantly more likely to experience suicide attempts than those without epilepsy (pooled OR, 2.74; 95% CI, 2.08–3.61, p < 0.0001). The funnel plot was symmetrical, and Egger's regression test suggested limited publication bias among these studies (p = 0.25). Because the study designs of two articles (18, 19) were case–control studies, we excluded them to calculate the pooled prevalence rate of suicide attempts in PWE in 31 studies, and the result was 5.96% (95% CI: 4.82–7.20%, Figure 4).

Twenty-nine articles reported complete suicide in PWE. Based on the pooled data from 11 of 29 articles with a control group, we found that there was significant difference in the risk of completed suicide between the PWE and those without epilepsy (pooled OR, 2.36; 95% CI, 1.45–3.83, p=0.0006). The funnel plot was symmetrical, and Egger's regression test suggested limited publication bias among these

	2.5.67	erimental		Control				
Study	Events	Total	Events	Total	Odds Ratio	OR	95%-CI	Weigh
uicide attempt					1 3			
Mekonen, 2020	53	292	47	481		2.0477	[1.3411; 3.1267]	3.19
in C. 2019	216	54520	74	109040		5.8571	[4.4972; 7.6282]	3.49
liasen, 2018	553	8974	1292	89740		4.4956	[4.0593; 4.9787]	3.69
Virrell, 2020	9	339	15	678		1.2055	[0.5220; 2.7836]	2.29
larnod, 2018 (child)	8	9801	12	39204		2.6680	[1.0903; 6.5287]	2.19
arnod, 2018 (adult)	351	68543	185	137086	1 270	3,8090	[3.1869; 4.5525]	3.69
(won, 2011	42	10240	39	40960		4.3213	[2.7932; 6.6855]	3.19
lesdorffer.2016	278	14059	434	56184		2.5913	[2.2265; 3.0158]	3.69
Stefanello,2010	17	153	8	154		2.2812	[0.9536; 5.4571]	2.29
Baldin 2015	13	257	3	134		2.3265	[0.6513; 8.3109]	1.59
Christiansen 2012	111	3465	1211	72765	page.	1.9555	[1.6051; 2.3823]	3.5%
anCott 2010	64	7445	768	104651		1.1729	[0.9079; 1.5152]	3.59
vana 2010	33	16120	4239	4514366		2.1826	[1.5490; 3.0752]	3.39
lesdorffer 2006	21	324	9	647		4.9131	[2.2237; 10.8553]	2.39
landom effects model	21	194532	3	5166090		2.7402	[2.0786; 3.6124]	41.19
leterogeneity: $l^2 = 93\%$, τ^2	= 0.2125, p					2.1402	Terror on the real	- 1. 17
uicide ideation								
	5840	84400	0405	00000	100	0 4770	10 0440, 0 05001	0.70
Selassie, 2014	5649	64188	2425	89808		3.4773	[3.3119; 3.6509]	3.79
Seo, 2015	208	684	20	229		4.5664	[2.8064; 7.4301]	3.09
lamed, 2012	47	200	9	100		3.1060	[1.4542; 6.6340]	2.49
Virrell, 2020	20	339	24	678		1.7085	[0.9299; 3.1390]	2.79
Stefanello,2010	51	153	36	154		1.6389	[0.9918; 2.7081]	3.09
Vagner 2015	460	6730	306	15305		3.5961	[3.1028; 4.1679]	3.69
Baldin 2015	41	257	18	134		1.2233	[0.6725; 2.2252]	2.89
(won 2013	107	568	7	125		3.9126	[1.7741; 8.6291]	2.39
Fellez-Zenteno 2007	63	253	4885	38727		2.1613	[1.6229; 2.8785]	3.4%
Hesdorffer 2006	37	324	35	647		2.2543	[1.3908; 3.6538]	3.0%
Jacob 2002	10	50	1	30		7.2500	[0.8786; 59.8282]	0.79
Random effects model Heterogeneity: $l^2 = 75\%$, τ^2	= 0 0552 p	73746		143937		2.6996	[2.2113; 3.2957]	30.6%
	are seen in							
ompleted suicide		50705	202	4470704			14 5000 0 00755	
Sorton, 2018	63	58738	808	1170794		2.0733	[1.5993; 2.6879]	3.5%
Frlangsen, 2020	1048	181686	34435	7118709		1.1936	[1.1222; 1.2694]	3.7%
Vebb, 2012	10	873	156	17480		1.2853	[0.6757; 2.4449]	2.79
Christensen, 2007	492	21169	3140	423128		3.1826	[2.8911; 3.5035]	3.69
(won, 2011	1	10240	5	40960		0.8000	[0.0935; 6.8481]	0.7%
levalainen, 2013	3	1296	24	5792		0.5576	[0.1677; 1.8546]	1.69
Virrell, 2020	3	339	1	678		6.0448	[0.6264; 58.3302]	0.6%
ontanella 2020	26	910	44	6346		4.2128	[2.5810; 6.8756]	3.0%
la 2019	51	2838	312	56758		3.3106	[2.4563; 4.4620]	3.49
azel 2013	510	69995	1058	660869		4.5773	[4.1172; 5.0889]	3.69
vana 2010	4	16120	262	4514366		4.2763	[1.5929; 11.4806]	1.99
tandom effects model leterogeneity: $I^2 = 98\%$, τ^2	-0.5710 -	364204		14015860		2.3561	[1.4485; 3.8322]	28.3%
	- u.uz.ia, p							
andom effects model	0.0047	632482		19325887	· · · · · · · · · · · · · · · · · · ·	2.6047	[2.1322; 3.1820]	100.09
Heterogeneity: $I^2 = 97\%$, τ^2	= 0.2847, p	< 0.01			0.1 0.5 1 2 10			

studies (p = 0.50). Because the study designs of 5 articles (20–24) were case–control studies, we excluded them to calculate the pooled prevalence rate of completed suicide in PWE in 24 studies, and the result was 0.24% (95% CI: 0.11–0.42%, Figure 5).

The results of prespecified subgroup analyses and meta-regression are shown in Supplementary Table S3. We performed subgroup analyses of the total risk of suicidality, including suicidal ideation, suicide attempts and completed suicide. Subgroup analyses of population about adult and child found no significant difference in suicidality. The rate of suicide attempts in developing countries was significantly higher than that in developed countries. There was no significant difference between different measurements of suicidality in the risk of suicidality. However, the rate of suicidal ideation diagnosed using interviews was higher than that diagnosed using other measurements of suicidality (Interview vs. Questionnaire vs. Medical record: pooled rate 0.22 vs. 0.18 vs. 0.08, p < 0.0001). The rate of suicide attempts diagnosed using interviews was similarly higher to those of other measurements of suicidality (Interview vs. Questionnaire vs. Medical record: pooled rate 0.12 vs. 0.09 vs. 0.01, p < 0.0001). The diagnosis of completed suicide was identified by medical records. The pooled prevalence rate of suicidal ideation in NDE, TLE and DRE were, respectively, 0.12, 0.27, and 0.29. And the pooled prevalence rate of suicidal attempts in NDE, TLE and DRE were, respectively, 0.16.

The meta-regression showed that average age of population (slope 0.03 [0.0022–0.0565], p=0.0342) was a significant moderator that contributed to heterogeneity between the studies in the risk of suicidality. The year of publication and the percentage of females may not contribute to the heterogeneity between studies (p>0.05). The sensitivity analyses showed that the results of the meta-analysis were

Study	Events	Total	Proportion	95%-CI	Weigh
Oguz 2002	6	35	0.1714	[0.0656; 0.3365]	1.5%
Jacob 2002	10	50	0.2000	[0.1003; 0.3372]	1.7%
Hesdorffer 2006	37	324	0.1142	[0.0817; 0.1540]	2.29
Pompili, 2007	27	103	0.2621	[0.1804; 0.3580]	2.09
Tellez-Zenteno 2007	63	253	0.2490	[0.1970; 0.3070]	2.29
Stefanello,2010	51	153	0.3333	[0.2593; 0.4140]	2.19
De Oliveira, 2011	19	66	0.2879	[0.1830; 0.4125]	1.89
Gandy, 2012	49	147	0.3333	[0.2578; 0.4157]	2.19
Hecimovic, 2012	23	193		[0.0771; 0.1734]	2.19
Hamed, 2012	47	200		[0.1781; 0.3000]	2.29
Nuhu, 2013	34	170		[0.1427; 0.2681]	2.19
Hesdorffer, 2013	95	206		[0.3917; 0.5318]	2.29
Jones, 2013	36	177		[0.1487; 0.2703]	2.19
Kwon 2013	107	568		[0.1570; 0.2230]	2.39
Selassie, 2014	5649	64188	and the second se	[0.0858; 0.0902]	2.49
Wigg, 2014	13	98		[0.0726; 0.2162]	2.09
De Oliveira, 2014	42	126		[0.2519; 0.4228]	2.19
Andrijic, 2014	19	50		[0.2465; 0.5283]	1.79
Rathore 2014	17	237		[0.0423; 0.1124]	2.29
Meador, 2015	16	162		[0.0575; 0.1554]	2.19
Andrade-Machado, 2015	33	82		[0.2956; 0.5166]	1.99
Seo. 2015	208	684			2.39
Micoulaud-Franchi, 2015	37	116		[0.2355; 0.4119]	2.09
Didstein, 2015	387	2763		[0.1273; 0.1536]	2.39
Guilfoyle, 2015	21	156		[0.0853; 0.1984]	2.19
Wagner 2015	460	6730			2.39
Baldin 2015	41	257		[0.1170; 0.2101]	2.29
Bosak, 2016	30	301	-	[0.0683; 0.1392]	2.29
Mula, 2016	49	380		[0.0969; 0.1669]	2.29
Altura 2016	24	188		[0.0835; 0.1840]	2.19
Tsigebrhan, 2017	90	298		[0.2504; 0.3576]	2.2%
Friedman, 2018	155	770		[0.1735; 0.2314]	2.3%
Haile, 2018	122	410		[0.2537; 0.3444]	2.3%
Li X, 2019	59	269		[0.1714; 0.2738]	2.2%
Кмол, 2019	36	144		[0.1816; 0.3289]	2.19
Li Q, 2019	73	461		[0.1262; 0.1949]	2.3%
Stauder, 2020	14	80		[0.0991; 0.2762]	1.99
Dagar, 2020	13	119	-	[0.0595; 0.1796]	2.09
Dabla, 2020	42	100		[0.3220; 0.5229]	2.0%
Wirrell, 2020	20	339	and a second	[0.0364; 0.0896]	2.29
Sylla, 2020	25	140		[0.1190; 0.2522]	2.19
Kim, 2020	67	212		[0.2541; 0.3832]	2.29
Batchelor, 2021	51	144		[0.2763; 0.4381]	2.19
Schommer, 2021	578	2450		[0.2192; 0.2532]	2.39
Lin M, 2021	42	1879	0.0224	[0.0162; 0.0301]	2.39
Nigussie, 2021	149	563	0.2647	[0.2286; 0.3032]	2.39
Rashid, 2021	20	449	0.0445	[0.0274; 0.0680]	2.39
Random effects model		87990	0.1973	[0.1700; 0.2262]	100.0%
Heterogeneity: / ² = 98%, τ ² =	0.0135, p =	• 0	0.1 0.2 0.3 0.4 0.5		
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stable (Supplementary Figures S1–S4). The publication bias of the risk of suicidality were not significant and the funnel plots were shown in Supplementary Figures S5–S7.

4. Discussion

This systematic review and meta-analysis found that PWE have a significantly greater risk of suicidality (2.60 times), including suicidal ideation (2.70 times), suicide attempts (2.74 times) and completed suicide (2.36 times). The rates of suicidal ideation, suicide attempts

and completed suicide in PWE were 19.73, 5.96, and 0.24%, respectively. This result is consistent with previous studies, which concluded that there was a clear relationship between epilepsy and suicide attempts and completed suicide (10, 25). Previous studies have focused more on suicide attempts and completed suicide. In this metaanalysis, we also found that the risk of suicidal ideation in epilepsy was significantly higher than that in the general population (2)⁻ which was not a consensus previously.

In the subgroup analysis, we found that the different diagnoses may not have influence on the relative risk of suicidality but affected the rate of suicidality, including suicidal ideation and attempts.

Study	Events	Total	Proportion 95%-CI	Weigh
Lin C, 2019	216	54520	0.0040 [0.0035; 0.0045]	3.9%
Haile, 2018	58	410	0.1415 [0.1092; 0.1790]	3.4%
Dabla, 2020	3	100	0.0300 [0.0062; 0.0852]	2.4%
Tsigebrhan, 2017	75	298	0.2517 [0.2034; 0.3050]	3.3%
Seo, 2015	108	684	0.1579 [0.1314; 0.1874]	3.6%
De Oliveira, 2014	30	126	0.2381 [0.1668; 0.3221]	2.6%
Hesdorffer, 2013	32	206	0.1553 [0.1087; 0.2122]	3.0%
De Oliveira, 2011	14	66	0.2121 [0.1211; 0.3302]	2.0%
Wirrell, 2020	9	339	0.0265 [0.0122; 0.0498]	3.3%
Kim, 2020	30	212	0.1415 [0.0976; 0.1958]	3.0%
Schommer, 2021	350	2450	0.1429 [0.1292; 0.1573]	3.8%
Lin M, 2021	21	1879	0.0112 [0.0069; 0.0170]	3.8%
Nigussie, 2021	71	563	0.1261 [0.0998; 0.1564]	3.5%
Doganavsargil-Baysal, 2017	12	89	0.1348 [0.0717; 0.2237]	2.3%
Jones, 2013	11	177	0.0621 [0.0314; 0.1085]	2.9%
Hara, 2009	7	145	0.0483 [0.0198; 0.0969]	2.8%
Harnod(child), 2018	8	9801	0.0008 [0.0004; 0.0016]	3.9%
Harnod(adult), 2018	351	68543	0.0051 [0.0048; 0.0057]	3.9%
Kwon, 2011	42	10240	0.0041 [0.0030; 0.0055]	3.9%
Hesdorffer, 2016	278	14059	0.0198 [0.0175; 0.0222]	3.9%
Stefanello,2010	17	153	0.1111 [0.0661; 0.1719]	2.8%
Kanemoto, 1999	4	57	0.0702 [0.0195; 0.1700]	1.9%
Mekonen, 2020	53	292	0.1815 [0.1390; 0.2306]	3.2%
Hamed, 2012	23	200	0.1150 [0.0743; 0.1875]	3.0%
Baldin 2015	13	257	0.0506 [0.0272; 0.0849]	3.2%
VanCott 2010	64	7445	0.0086 [0.0068; 0.0110]	3.9%
Arana 2010	33	16120	0.0020 [0.0014; 0.0029]	3.9%
Andersohn 2010	294	44300	0.0066 [0.0059; 0.0074]	3.9%
Hecimovic 2008	3	55	0.0545 [0.0114; 0.1512]	1.9%
Mohammadi 2006	37	454	0.0815 [0.0580; 0.1106]	3.5%
Hesdorffer 2006	21	324	0.0648 [0.0406; 0.0974]	3.39
Random effects model		234564	.0.0596 [0.0482; 0.0720]	100.0%
Heterogeneity: / ² = 99%, τ ² = 0.0	040, <i>p</i> = 0		0.05 0.1 0.15 0.2 0.25 0.3	
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We found that the rate of suicidality diagnosed by interviews was higher than that diagnosed by questionnaires and medical records. A lack of enough knowledge to seek medical attention in time, a lack of diagnosis from doctors or a lack of medical resources may cause the lower rate of suicidality identified by medical records. This result suggested that using medical records to diagnose suicide may underestimate suicidal rates. Analyses in different types of epilepsy found that there was a higher rate of suicide in DRE and TLE. The suicide rates reported for people with TLE were 6–25%, compared with 1.4–6.9% in the general population (20). Patients with TLE and DRE have a higher frequency of seizures, which is also associated with suicide (15).

Subgroup analyses found that the rate of suicidal ideation in developing countries was significantly higher than that in developed countries, consistent with the findings of the WHO World Mental Health Surveys (26). The WHO reported that 78% of deaths from suicide worldwide occurred in low-income countries (3). At the same time, we found no significant differences in the risk of suicide between adults and children with epilepsy. However, meta- regression showed that the increased average age of the population may be associated with a higher risk of suicidality. The global suicide rate was lowest in patients younger than 15 years old and steadily increased thereafter until the age of 70 (3). Meta-regression showed that the percentage of females may not affect the results of the meta-analysis. On the

contrary, other meta-analysis showed that the percentage of females contributed to heterogeneity between the studies (10). The researcher considered male PWE may attempt suicide by more lethal methods (27). However, the prevalence of major depressive disorder in epilepsy is higher in females than that in males (28). It still need more studies to explore the relationship between gender and suicide.

The relationship between epilepsy and suicidality is complex, and epilepsy is a frequently misunderstood and highly stigmatized condition. Epilepsy affects relationships with family and friends, employment, school, and leisure activities and results in social and economic consequences (2, 29). It was reported that psychiatric risk factors, type of epilepsy syndrome and exposure to certain antiseizure medications (ASMs) have been associated with an increased risk of suicide in PWE (30, 31). However, the results about the increased risk of suicide in patients taking ASMs are contradictory (32), with some studies observing an increased suicidality risk (33, 34) and others reporting no increased risk (35, 36). PWE may have a high magnitude of comorbid psychiatric illness (37). Many previous studies have proven that the presence of depression is highly associated with suicidal ideation (21). The possible reason for suicide in PWE might be the direct effect of depression, which can make people feel hopeless and worthless. In addition to psychiatric comorbidity, other common comorbidity in PWE such as traumatic brain injury (38), neurodevelopmental disorders (Autism-spectrum disorder) (39),

Study	Events	Total							Proportion	95%-CI	Weight
Gorton, 2018	63	58738	•						0.0011	[0.0008; 0.0014]	5.0%
Erlangsen, 2020	1048	181686		*					0.0058	[0.0054; 0.0081]	5.0%
Hara, 2009	1	145	-	10					0.0069	[0.0002; 0.0378]	1.9%
Кwon, 2011	1	10240							0.0001	[0.0000; 0.0005]	4.9%
Chamorro-Munoz, 2017	2	2309	-						0.0009	[0.0001; 0.0031]	4.5%
Granbichler, 2015	9	4295	-						0.0021	[0.0010; 0.0040]	4.8%
Singhal, 2014	257	509117	1						0.0005	[0.0004; 0.0006]	5.0%
Nevalainen, 2013	3	1296	-	-					0.0023	[0.0005; 0.0087]	4.2%
Nilsson, 1997	53	9061		-					0.0058	[0.0044; 0.0076]	4.9%
Lip, 1992	3	1000	-	-					0.0030	[0.0006; 0.0087]	4.1%
Wirrell, 2020	3	339	-	-					0.0088	[0.0018; 0.0256]	3.0%
Fazel 2013	510	69995		-					0.0073	[0.0087; 0.0079]	5.0%
Arana 2010	4	16120	12						0.0002	[0.0001; 0.0006]	4.9%
Camfield 2002	2	692		12					0.0029	[0.0004; 0.0104]	3.7%
Nilsson 2002	9	6880	-						0.0013	[0.0006; 0.0025]	4.8%
Blumer 2002	5	10739							0.0005	[0.0002; 0.0011]	4.9%
Lhatoo 2001	1	792		-					0.0013	[0.0000; 0.0070]	3.9%
Shaddleton 1999	7	1355	-	-					0.0052	[0.0021; 0.0106]	4.3%
Cockerell 1994	1	564		-					0.0018	[0.0000; 0.0098]	3.5%
Mendez 1993	4	1611	10	-					0.0025	[0.0007; 0.0063]	4.4%
Hauser 1980	3	618		-					0.0049	[0.0010; 0.0141]	3.6%
White 1979	21	1980		-					0.0106	[0.0066; 0.0162]	4.5%
Currie 1971	3	666	-18	-					0.0045	[0.0009; 0.0131]	3.7%
Lindsay 1979	1	100		-90					0.0100	[0.0003; 0.0545]	1.5%
Random effects model		890338	-	_	-	-	- 1		0.0024	[0.0011; 0.0042]	100.0%
Heterogeneity: $l^2 = 99\%$, τ^2	= 0.0011, p	= 0		0.01	0.02	0.03	0.04	0.05			
URE 5			h epiler								

stroke (40), etc. may also be associated with the increased risk of suicidality.

The mechanism of suicidal behavior in PWE is still uncertain. That may suggest the possible common neurobiological pathogenic mechanisms in suicidality and epilepsy including disturbances of several neurotransmitters and the hypothalamic pituitary adrenal axis (41). Further exploration of depression in PWE will help us to better understand the neurobiology of suicidality and epilepsy (42). Based on the high rate of suicidality among PWE, we should focus on the prevention of suicidality. Countries and communities may lower suicide rates through primary and secondary prevention (43), such as improving seizure control and patient education (44).

The present study had several limitations. First, our included studies had obvious heterogeneity, even after subgroup analysis and meta-regression. This may be due to the different designs, sample sizes, age, sex, duration of epilepsy, comorbid substance use, comorbid depression and anxiety etc. Due to obvious heterogeneity, we cannot specify the pooled prevalence in the meta analysis as the lifetime prevalence or 1-year prevalence. Second, most of the included studies were retrospective, which might have limited the power of our analysis to measure significant differences in outcomes. Similarly, recall bias cannot be excluded. We only searched for articles in English with limited search terms, "epilepsy," and "suicide"; therefore, several studies may be ignored. Third, the diagnostic tools for assessing suicidality and populations differed among the studies, which may contribute to the heterogeneity. Fourth, there are few articles about specific types of epilepsy in children, which need to further explore in future studies.

This systematic review and meta-analysis found that PWE are at an increased risk of suicidality, including suicidal ideation, suicide attempts and completed suicide. The rate of suicidal ideation, suicide attempts and completed suicide in PWE were about 19.73, 5.96, and 0.24%. In view of the high risk of suicidality in PWE, it is important for clinicians to pay more attention and provide essential screening for early identification and prevention at the time of diagnosis. For especially TLE and DRE, it is necessary to screen by Mini International Neuropsychiatric Interview which can reduce the omission diagnostic rate.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

HW and YZ was responsible for the search, data acquisition and interpretation, and drafting the manuscript. HW performed the meta-analysis and generated the figures. YZ was responsible for the study conception and drafting the tables. GT, DC, and YF was responsible for study design and checking the data. LL revised the manuscript and provided the study funding. All coauthors reviewed the final version. All authors had full access to all the data in the study and final responsibility for the decision to submit for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1097516/ full#supplementary-material

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