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REVIEW ARTICLE



Determinants of health-related quality of life of patients with focal epilepsy: A systematic literature review

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Abstract

Objective: Focal epilepsy can have significant negative impacts on a person's health-related quality of life (HRQoL). Although studies have been published on HRQoL in persons with focal epilepsy (PWFE), determinants of HRQoL have not been comprehensively examined. This systematic literature review (SLR) queried existing literature to identify aspects associated with HRQoL in PWFE without focus on resective epilepsy surgery, with an interest in identifying modifiable determinants for medical/nonmedical interventions.

Methods: This SLR was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Searches were conducted in PubMed and Google Scholar for articles published from January 1, 1900, to February 19, 2023, reporting on the association between HRQoL or employability and a range of demographic, psychosocial, or epilepsy-related factors and comorbidities in PWFE.

Results: A total of 879 abstracts were identified, with 126 manuscripts reviewed and 37 studies selected for inclusion that quantified the relationship between HRQoL and the variable of interest by multivariate (N=21) or univariate only (N=15) methods; 10 multivariate models also included univariate data. In adjusted models, the most commonly examined determinants of HRQoL included depression (n=15/21), number of antiseizure medications (ASMs; n=13/21), seizure frequency (continuous seizure count, n=11/21; seizure freedom, n=5/21), anxiety (n=10/21), duration of disease (n=9/21), and cognition (n=9/21). Depression, anxiety, and cognition were frequently seen as significant contributors to HRQoL when studied (14/15 [93%], 9/10 [90%], and 7/9 [78%], respectively). Among concepts studied less frequently, ASM severity/adverse event burden was significant each time examined (in 5/19 studies). Attainment of seizure freedom and employability was significant 75% (n=3/4) and 72% (n=5/7) of the time, respectively.

Pamela Engelhart and Caleb Marcin contributed equally to this work.

A preliminary version of this study was presented at the American Epilepsy Society Annual Meeting, December 1–5, 2023, in Orlando, Florida, and will be presented at the American Academy of Neurology 2024 Annual Meeting, April 13–18, 2024, Denver, Colorado.

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Significance: Poor HRQoL in PWFE can be attributed to a multitude of factors, including depression, anxiety, factors in disease management, and employability. An unmet need remains in addressing elements associated with poor HRQoL in this population.

KEYWORDS

determinants of health, focal epilepsy, seizure outcomes

1 | INTRODUCTION

According to the World Health Organization, epilepsy affects approximately 50 million people worldwide, with focal epilepsy representing an estimated 60% of these cases.^{1,2} Focal epilepsy is characterized by recurring seizures originating in one area of the brain, with or without spread to adjacent areas or the opposite hemisphere.³ Focal seizures typically last between 30s and 2 min during the ictal phase, with the main symptoms occurring for the duration of this period.^{3,4} Symptoms experienced in the ictal phase can include auras that refer to signs and symptoms that occur at the onset of a seizure, visual hallucinations, paralysis-like states, and jerking movements.^{4,5} Further, patients can undergo physical harm, primarily due to injuries incurred during seizures, such as falls, fractures, bruises, and burns.⁶ In addition, seizures can be the source of mental distress in the form of feelings of confusion, anxiety, and depression. This distress may also be present during pre- and post-ictal phases, with confusion occurring within a few minutes of this phase and anxiety and depression more often being chronic.⁷ More severe cases of epilepsy are at risk of status epilepticus, defined as a prolonged seizure lasting more than 5 min, and sudden unexpected death in epilepsy.⁸

Focal epilepsy can have significant negative impacts on a person's health-related quality of life (HRQoL), with reports indicating HRQoL is worse among persons with focal epilepsy (PWFE) than the general healthy population and worse than persons with generalized epilepsy.^{9–11} Further, patients with uncontrolled disease have worse HRQoL than those whose condition is controlled. PWFE experience job-related impacts such as absenteeism, presenteeism, or inability to work due to debilitating symptoms and/or unpredictability of seizure occurrence.¹² Many studies of HRQoL in PWFE have focused on the impact of epilepsy surgery. However, by limiting to the postsurgical population, these studies reflect only a fraction of the PWFE population as between 32% and 60% of patients evaluated do not proceed to surgery.^{13–16}

There is a need to study HRQoL in PWFE with the goal to improve the drivers of this important aspect of patient experience. While there have been several studies examining the HRQoL in PWFE, the literature examining

Key points

- Focal epilepsy can have significant negative impacts on a person's health-related quality of life (HRQoL).
- Determinants of HRQoL in persons with focal epilepsy (PWFE) have not been extensively studied.
- In this review, 37 studies were included that examined the relationship between HRQoL and the patient or clinical variable(s) of interest.
- A multitude of factors are attributed to poor HRQoL, including depression, anxiety, factors in disease management, and employability.
- Addressing poor HRQoL in PWFE remains an unmet need and a focus area for further research.

determinants of HRQoL in this population has not been comprehensively examined. This systematic literature review (SLR) aims to evaluate the existing literature on this topic to identify aspects associated with poorer HRQoL and impacts to employment in this population, with the goal of identifying modifiable determinants to inform potential focus areas for medical and non-medical interventions.

2 MATERIALS AND METHODS

As a general consideration, recent pathologic research accentuates the importance of distinguishing between focal and generalized epilepsy,¹⁷ as they operate differently in the brain and consequently have the potential to express different symptoms and impacts. While some seizure experiences may be common across patients, understanding the distinct experiences of focal epilepsy is paramount. As such, the search strategy targeted the focal epilepsy population, including patients and their families.

A priority of this search was to identify studies that assessed HRQoL and examined its association in PWFE with employability; demographic, psychosocial, and condition-related factors; and comorbidities. The methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Population, Intervention, Comparison, Outcomes and Study (PICOS) framework for reporting of eligibility criteria.¹⁸

Articles were gathered and assessed from two databases: PubMed and Google Scholar. The following search terms were applied in the PubMed search, with the time of publication ranging from January 1, 1900 to February 19, 2023: ("focal epilepsy" [Title/Abstract] OR "focal seizure"[Title/Abstract] OR "focal onset seizure"[Title/ Abstract] OR "FOS" [Title/Abstract] OR "temporal lobe epilepsy"[Title/Abstract]) AND (("quality of life"[Title/ Abstract] OR "HRQoL" [Title/Abstract]) OR ("productivity"[Title/Abstract] OR "work productivity"[Title/ Abstract] OR "work loss" [Title/Abstract] OR "lost productivity"[Title/Abstract] OR "income"[Title/Abstract] OR "employment" [Title/Abstract] OR "absenteeism" [Title/Abstract] OR "WPAI" [Title/Abstract] OR "work burden"[Title/Abstract] OR "career burden"[Title/Abstract]) OR ("burden" [Title/Abstract] OR "burden of illness" [Title/Abstract] OR "BOI" [Title/Abstract] OR "burden of disease"[Title/Abstract]) OR ("caregiver"[Title/Abstract] OR "caregiver burden" [Title/Abstract] OR "family burden"[Title/Abstract] OR "caretaker"[Title/Abstract])). We subsequently amended the search strategy to include (OR _Epileptic____¹

"extratemporal epilep*"[Title/Abstract]) to specifically identify any additional articles discussing extratemporal epilepsies; however, no new articles were identified beyond our original search.

In addition, a backwards citation search was performed on included references to identify other potentially related papers that met our research objectives but may not have been captured by the original searches.

The abstracts of all the results were screened for inclusion by two reviewers. If the abstract lacked inclusion details, then the entire paper was reviewed. The PICOS criteria were applied as follows (Table 1): (1) inclusion criteria were studies that included patients (all ages) diagnosed with focal epilepsy and assessed the HRQoL or disease burden of these patients or their caregivers; (2) the types of study designs included for review reflected cross-sectional, cohort, observational, interventional/comparative, and prospective and retrospective studies; and (3) study design parameters were pre-specified as needing to include quantified measures of association between the outcome of interest and the parameter under evaluation. Studies conducting multivariate or univariate analysis were included. Exclusion criteria were studies that (1) were not in English, and (2) grouped focal epilepsy data with data from patients with generalized epilepsy (without distinction of the data in PWFE). In addition, studies that examined changes in

TABLE 1	Details of systematic literature review methodo	ology.
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Research question	What are the determinants of HRQoL in patients with focal epilepsy?
Databases	PubMed and Google Scholar
Timeframe	• Full text articles and reviews: January 1, 1900 to February 19, 2023
Inclusion criteria (PICOS criteria followed)	 (P) Patients diagnosed with focal epilepsy, all ages (I) Both interventional and non-interventional studies were considered (C) Not applicable (O) Study assessed the HRQoL or disease burden in this population or in their caregivers; study examined univariate and/or multivariate association between HRQoL and employability; demographic, psychosocial, and condition-related factors; and comorbidities (S) All study designs were evaluated; however, only studies that quantified findings via multivariate models (e.g., reporting β-values, adjusted R², magnitude of variance) or univariate analyses (e.g., reporting Pearson or Spearman's correlations, Kendall's tau statistic) were included
Exclusion criteria	 Studies that only included comparative descriptive data (<i>t</i>-test, Mann–Whitney <i>U</i> test) Not available in English language Grouped focal epilepsy data with generalized epilepsy data (without distinction) Studies evaluating changes in HRQoL or employment after resective surgery, as comprehensive systematic literature reviews on these topics were recently published^{19,20}
Data extraction	 Data were extracted from studies with measures of HRQoL for PWFE that also included any variable examined as potentially impacting the outcome (e.g., determinants) We accepted all significance levels as determined by study authors, noting there was variability in thresholds chosen and whether multiplicity was accounted for; when the threshold was not specified, <i>p</i> < .05 was considered significant
Publication date	• No limit
Country	No restriction

Abbreviations: HRQoL, health-related quality of life; PICOS, Population, Intervention, Comparison, Outcomes and Study; PWFE, persons with focal epilepsy.

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HRQoL or employment after resective surgery were excluded once we identified that comprehensive SLRs had been published addressing these topics.^{19,20} There were no restrictions by location or type of setting.

Data were extracted from studies with measures of HRQoL for PWFE that also included any variable examined as potentially impacting the HRQoL of PWFE (e.g., determinants). As such, while some included studies with data on HRQoL as part of a larger research scope, this review summarizes only the findings relevant to factors associated with HRQoL in PWFE, and the demographic and clinical characterization of the cohorts studied.

Considering the range of methodologic and statistical approaches researchers have applied to inform this question, a priority for the interpretation of findings was established where studies that evaluated determinants of HRQoL through linear or logistic multivariate analysis were prioritized (e.g., standardized coefficients $[\beta]$; multiple regression, hierarchical regression, linear mixed effects, stepwise regression [backward or forward], and mediated serial analysis) as these approaches are designed to reduce confounding from other factors in a comprehensive manner. Thus, data examining univariate relationships (e.g., Pearson's or Spearman's correlations [r, rho], and Kendall's tau $[\tau]$) are included but considered supplemental. Data presenting differences in HRQoL between group means using a p value statistic (such as implementing t-tests, chisquared, or analysis of variance [including use of the F-test to explain variance in dependent variables]) but lacking assessment to the degree of the relationship were considered out of scope, as the strength and directionality of the relationship is not specified. We accepted all significance levels as determined by study authors, noting there was variability in thresholds chosen and whether multiplicity was accounted for. When the threshold was not specified, p values <.05 were considered significant.

Potential factors of interest measured through questionnaires and assessments included, but were not limited to, seizure frequency or severity, use of drug therapy, mood disorders, psychiatric disorders, level of independence and mobility, social supports, motivation, and selfesteem. Employability was examined as both a potential determinant and an outcome of interest.

Figure 1 shows the study selection process (PRISMA diagram) for the literature identified. An overview of the studies is described in Table 2, with details further extracted in Table S1. While the focus of the review was to identify predictors of overall or total HRQoL or employability, domains or subscore data were also extracted where available. To aid in the interpretation of findings from the identified studies, tabular and graphical summaries of the study findings were prepared. When a whole population and subgroup(s) were studied, only the findings for the whole population were included. The resulting data synthesis was qualitative in nature due to the heterogeneity of the methods and populations employed in the identified studies.

3 | RESULTS

A total of 879 abstracts were identified from the initial search and screened, with 126 manuscripts reviewed and 37 studies selected for inclusion (Figure 1).

3.1 | Study characteristics

Of the 37 studies identified for inclusion in this review (Table 1; Tables S1 and S2), N=36 studies examined HRQoL outcomes and N=1 examined the relationship between employability and seizure type (focal vs. generalized). Of the N=36 HRQoL studies, approximately half (N=21, 58%) leveraged multivariate analysis, of which 10 also included univariate data, whereas N=15 studies employed a univariate approach only.

Both cross-sectional (N=29) and longitudinal (N=7)study designs were employed. Cohorts examined in the studies included PWFE (overall) and comparative studies within PWFE (e.g., examining academic/employment impacts, medical, or surgical treatments, left or right temporal lobe epilepsy [TLE]) and between PWFE and others (e.g., healthy controls). TLE represented the most common subset of focal epilepsy studied. Studies reflected research conducted across N=17 countries, with N=18/36 studies coming from Europe, N = 7/36 studies from North America and N=6/36 studies from South America. A majority of the studies (N=26, 72%) specified adults exclusively in the inclusion criteria, where adult was defined as age ≥ 16 or \geq 17 years in N=8/26 of the studies. Two studies included both adults and pediatric patients and N=6 studies did not specify age in the inclusion criteria. No studies were identified as recruiting pediatric patients alone. The one study examining determinants of employability was conducted among Malaysian patients aged ≥16 years using a cross-sectional design in PWFE and generalized epilepsy and implemented multivariate modeling.

The included HRQoL studies used a variety of assessments in the form of surveys and questionnaires to evaluate HRQoL. Epilepsy-specific patient-reported outcome HRQoL measures were used most often, as compared to generic HRQoL measures, with the Quality of Life in Epilepsy Inventory 31-item (QOLIE-31) the most frequently used (included in N=13 multivariate models [62%] and N=9 univariate models [60%]). Other epilepsy-specific measures include versions of the QOLIE (QOLIE-89, QOLIE-36, QOLIE-31-P, QOLIE-10), Epilepsy



FIGURE 1 PRISMA diagram for study selection. HRQoL, health-related quality of life; SLR, systematic literature review.

Surgery Inventory (ESI-55), Quality of Life in Childhood Epilepsy 82 item (QOLCE-82), Subjective Handicap of Epilepsy (SHE), and Bonner Skalen für Epilepsie (BPSE). The generic measures used included the World Health Organization Quality of Life instrument (WHOQOL-100), Short-Form Health Survey-36 (SF-36), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Totality of HRQoL measures and other clinical measures (e.g., assessments of depression, anxiety, cognition) are detailed by study in Table S1.

3.2 | Determinants of poor HRQoL

Overall, the studies examined a broad range of determinants of HRQoL (N= 53); details on all variables examined in both multivariate and univariate models are provided in Table S2.

3.3 | Multivariate analyses

In considering the adjusted models, the most commonly examined variables within the multivariate analyses included depression (n=15, 71% of studies),^{9,11,21,24,26,28–36,38} number of antiseizure medications (ASMs; n=13, 62% of studies),^{9,21,25–29,31,33,34,37–39} seizure frequency (as

continuous number in n=11, 52%),^{9,11,26,28-33,35,37} anxiety (n=10, 48% of studies),^{9,22-24,28-31,33,35} duration of disease (n=9, 43% of studies),^{9,24,29-33,35,37} and cognition (n=9, 43% of studies).^{22,24-26,29,30,34,36,38} Depression, anxiety, and cognition were significant contributors to HRQoL the majority of times studied (n=14/15 [93%], n=9/10 [90%], and n=7/9 [78%] respectively).^{9,11,21-36,38} The strength of the relationship between depression and HRQoL was strongest in a majority of the studies (n=13) where data were presented (Figure 2).^{9,11,21,24-26,28-32,35,36} Interestingly, anxiety was often examined alongside depression, as 80% of the models probing anxiety also included depression (n=8/10).^{9,24,28-31,33,35} However, only 53% of models probing depression (n=8/15) included anxiety.^{9,24,28-31,35,38}

In addition, several aspects were studied less frequently but found to be significant every time or a majority of the time studied, including ASM severity/adverse event (AE) burden (n=5, 100%),^{21,24,25,27,28} whether seizure freedom was achieved (dichotomized by Engel class I [absence] vs. II, III and IV [presence]) (n=3, 75%),^{25,27,39} and employment (n=4, 67%).^{21,23,27,28} While only studied once, each of the following were significant: driving ability, impairment during seizures, seizure severity, efficacy of ASM, family stress, family history of psychiatric disorder, and spirituality. Among the large number of potential determinants identified across studies, the findings for depression, anxiety, seizure burden (seizure frequency and seizure

		so	r	ders					
	Variables assessed			Employment, seizure frequency (impairment), number of ASM (AEDs), ASM severity/burden (SEALS), depression	Variables assessed: age at disease onset, disease duration, number of ASMs, anxiety, depression, affective temperaments	Anxiety, delayed memory	Academic insertion, employment insertion, anxiety	Occupational status, duration of seizures, adverse effects of ASMs, anxiety, depression, cognitive function, sleep quality	Multivariate: Education, employment, Liverpool adverse events profile, seizure outcome, AEDs (y/n), surgical group (y/n), depression, memory Univariate: Medication adherence surgical group (y/n), current employment, <9 years of education, sex, having a partner, children, religion, driving, age at first seizure, age of onset, duration of epilepsy, age at surgery, duration of epilepsy until surgery, age at interview, side of pathology, presence of aura, HRQoL
	HRQoL outcome measures and mean score at baseline (mean (SD))	(1)		QOLIE-31-P 68.2 (18.3)	SF-36 (general health subscale) 48.52 (24.52)	QOLJE-31 (converted from raw numeric values to percentile scores) 36.91 (27.22)	QOLJE-31 (overall) 64.22 (14.89); QOLJE-31 (composite) 55.32 (15.52)	QOLIE-31 50.20 (15.32)	QOLJE-31 75.44 (surgical); 60.08 (clinical)
	Patient age (years), mean (SD)			45.8 (15.7)	39.02 (10.53) (TLE); 40.05 (16.35) (ETLE); 36.91 (9.88) (control)	39.13 (12.18)	39.49 (12.39)	28 (SD not given)	43.90 (9.03)
cluded studies.	Seizure frequency mean (SD) (unless otherwise stated)	(N/A	2.35 (2.84) (TLE; past 3 months)	12.81 (24.21) (per month)	N/A	≥1 seizure daily=13 (27.7%)	N/A
ulations among inc	Number of patients	and the second sec		102	50	119	59	47	71
nd patient pop	Country	(Japan	Turkey	Spain	Spain	China	Brazil
w of study designs a	Study design		ultivariate models	Cross-sectional/ prospective	Cross-sectional/ prospective	Cross-sectional/ prospective	Cross-sectional/ prospective	Cross-sectional/ prospective	Cross-sectional/ prospective
TABLE 2 Overvie	Study		Studies employing m	Azuma ^a (2014) ²¹	Basaran (2021) (ETLE and TLE) ⁹	Cano-Lopez (2023á) ²²	Catalan- Aguilar (2022) ²³	Chen ^a (2018) ²⁴	Dias ^a (2017) ²⁵

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	-	y of TLE, MTS status, age zure frequency, number n, memory, executive 'seizure onset	ag, employment, driving f aura, AED (y/n), AEDS ED severity, duration of izure free since surgery, nt, tumor (y/n) a partner (y/n), age at y, comorbidity (y/n), nt (y/n), HS (y/n), side (t), driving, employment, freedom, seizure free, EDS (y/n), AED side r AED side effects, tumor	mployment, seizure freedom, number of a efficacy of AEDs, tolerability, degree of y, depression, patient 1 their seizures, disability ther (y/n), driving a ent, age at onset, age at ent, age at onset, age at
	Variables assessed	Education, laterality of seizure onset, sei of ASMs, depression functioning, side of	Multivariate: Drivir partner, presence of side effects (y/n), A seizure freedom, sei psychiatric treatmei Univariate: Having surgery, age at reply psychiatric treatmei of surgery (left/righ duration of seizure presence of aura, A effect (y/n), severity,	Multivariate: Sex, ei frequency, seizure f AEDs, patient-ratec patient-rated AED t comorbidity, anxiet perceived change ir status Univariate: Sex, par car (y/n), employm- monitoring, age at r
	HRQoL outcome measures and mean score at baseline (mean (SD))	QOLIE-31 Not reported	QOLIE-31 Not reported	QOLIE-31 Not reported
	Patient age (years), mean (SD)	35.02 (11.92)	43.6 (11.1)	36.0 (13.8)
	Seizure frequency mean (SD) (unless otherwise stated)	6.98 (7.65) per month	N/A	≥1 seizure per month= 33 (27.0%)
	Number of patients	52	222	125
	Country	USA	Germany	Germany
lued)	Study design	Cross-sectional/ prospective	Cross-sectional/ prospective	Longitudinal/ retrospective
TABLE 2 (Contir	Study	Ehrlich (2019) ²⁶	Elsharkawy ^a (2009) ²⁷	Elsharkawy ^a (2012) ²⁸

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of comorbidity, certificate of disability (y/n), side effects (y/n), comorbidity (y/n), degree

surgery denied (y/n), patient perceived change in seizures since presurgical evaluation, depression, anxiety

patient-rated efficacy of AEDs, number of AEDs, patient-rated tolerability of AEDs,

Jun Dise	orders						
Variables assessed	Age, education, side of TLE, age of onset, disease duration, mental speed, seizure frequency, anxiety, depression, memory, praxis, sorting, perception, mood, QME score	Multivariate: Age, schooling, disease duration, age at disease onset, monthly seizure frequency, personal meaning, mood, inner energy, awe and transcendence, openness anxiety, depression, cognition Univariate: Age, schooling, disease duration, age at disease onset, monthly seizure frequency, spirituality, HRQoL	Sex, age, education, duration of epilepsy, frequency of seizures, AED monotherapy versus polytherapy, seizure severity, depression, anxiety	Sex, chronologic age, laterality of TLE, presence/absence of HA and/or HS, age at onset, duration of disease, seizure frequency, ADL scores, depression	Laterality of HS, presence of GTCS, age of onset, disease duration, seizure frequency, number of ASMs, anxiety, depression	Number of ASMs or DDD (daily drug dosage), cognitive performance	Sex, age, education, side of TLE, duration of epilepsy, seizure frequency, anxiety, depression
HRQoL outcome measures and mean score at baseline (mean (SD))	QOLIE-89 Left TLE=70.27 (14.37) Right TLE=58.07 (14.19)	WHOQOL-100 Not reported	QOLIE-89 Not reported	BPSE Not reported (only percentage of high- scoring patients in each subscore)	QOLIE-31 52.97 (17.91)	QOLIE-31 52.80 (13.77)	QOLIE-31 58.4 (16.5)
Patient age (years), mean (SD)	40.38 (14.62) left TLE; 55.31 (10.10) right TLE	39.94 (16.83)	38.2 (10.8)	33.1 (9.4) left TLE; 36.6 (10.3) right TLE	39.830 (9.054) TLE-HS; 29.640 (10.055) control	39.76 (11.66)	35.4 (9.7)
Seizure frequency mean (SD) (unless otherwise stated)	Left TLE= 7.05 ± 9.41 (per month) Right TLE 6.65 ± 9.43 (per month)	6.44 (3.78)	N/A	Left-sided TLE mean (SD) = 9.8 (14.7) per month; Right-sided TLE mean (SD) = 14.1 (20.7) per month	N/A	8.19 (11.46) per month	N/A
Number of patients	65	32	87	56	35	75	106
Country	Italy	Portugal/ Italy	NSA	Austria	Brazil	Spain	Italy
Study design	Cross-sectional/ prospective	Cross-sectional/ prospective	Cross-sectional/ prospective	Cross-sectional/ prospective	Cross-sectional/ prospective	Cross-sectional/ prospective	Cross-sectional/ prospective
Study	Giovagnoli (2000) ²⁹	Giovagnoli ^a (2006) ³⁰	Johnson (2004) ³¹	Lehrner (1999) ³²	Lima (2021) ³³	Lozano-Garcia (2021) ³⁴	Meldolesi ^a (2006) ³⁵

TABLE 2 (Continued)

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	Variables assessed	Depressive symptoms, objective memory change	Sex, age, education, age at onset, duration of epilepsy, number of secondary generalized seizures, seizure frequency, days since last seizure, number of AEDs, total number of comorbid medical conditions, total number of comorbid psychiatric conditions	Maternal education, having HS, family stress, depressive features, parental psychiatric history, family stress, current AEDs, global executive composite, depression	Sex, seizure frequency, mood	Surgery, seizure status, AED use, intelligence level		Age, age at onset, duration of disease, duration of DRE, seizure frequency, days with seizure, number of AEDs, number of therapeutic trials, memory	Seizure frequency, number of AEDs	Depression, anxiety	Emotion recognition, emotional well-being, social function	(Continues)
	HRQoL outcome measures and mean score at baseline (mean (SD))	QOLIE-31 72.26 (20.27) (postoperative)	QOLIE-89 Not reported	QOLCE-82 52.98 (12.57)	QOLIE-31 54.73 (16.30)	QOLIE-36 UK Not reported		QOLIE-31 55.6 (17.1)	SF-36 Not reported	QOLIE-31 Not reported	QOLIE-31 57.63 (14.31)	
	Patient age (years), mean (SD)	39.4 (13.97)	37.02 (11.55)	11.99 (3.80)	38.83(12.01)	13.3 (3.1) Surgical group; age at surgery of patients who were assessed at follow-up		34.4 (9.5) overall; 36.3 (9.8) MTLE; 30.7 (8.1) lesional TLE	24.8 (4.35) pre- SAH; 27.0 (8.5) post-SAH	27.6 (9.05)	48.05 (11.50) MTLE	
	Seizure frequency mean (SD) (unless otherwise stated)	N/A	N/A	≥1 seizure per month=32 (39.0%)	8.43 (20.45) per month	N/A		8.9 (9.7) per month overall; 8.7 (8.9) per month MTLE; 9.2 (11.5) per month lesional TLE	>4 per month=12 (pre-SAH); 12 (post-SAH)	N/A	N/A	
	Number of patients	78	93	82	40	42		60	41	40	41	
	Country	Germany	USA	NSA	Portugal	UK	thods only	Mexico	Turkey	Indonesia	Italy	
	Study design	Cross-sectional/ prospective	Cross-sectional/ prospective	Cross-sectional/ prospective	Cross-sectional/ prospective	Longitudinal/ prospective	nivariate analysis me	Cross-sectional/ retrospective	Cross-sectional/ retrospective	Cross-sectional/ retrospective	Observational	
	Study	Mucke (2022) ³⁶	Pulsipher (2006) ³⁷	Schraegle (2021) ³⁸	Silva ^a (2019) ¹¹	Skirrow (2011) ³⁹	Studies employing ur	Alonso-Vanegas (2013) ⁴⁰	Aydemir (2004) ⁴¹	Bakhtiar (2021) ⁴²	Bonora (2011) ⁴³	

TABLE 2 (Continued)

TABLE 2 (Contin	(pən						
Study	Study design	Country	Number of patients	Seizure frequency mean (SD) (unless otherwise stated)	Patient age (years), mean (SD)	HRQoL outcome measures and mean score at baseline (mean (SD))	Variables assessed
Brandalise (2019) ⁴⁴	Cross-sectional/ prospective	Brazil	50	N/A	40.9 (10.4)	QOLJE-31 (overall QOL scores) 181.29 (36.21), before intervention; 191.12 (25.40), after intervention	Depression, resilience levels
Flint (2023) ⁴⁵	Cross-sectional/ prospective	UK/ Germany/ France/ Spain/Italy	361	3.47 (5.15)	Age range: 18–70 years; most between 26 and 45	QOLIE-31-P/SF-6D QOLIE-31-P=45.72 (14.29) SF-6D=.584 (.111)	Seizure frequency, seizure freedom achieved, seizure severity
Gois (2011) ⁴⁶	Cross-sectional/ prospective	Brazil	35	≥1 seizure per month=19 (54.3%)	39.82 (9.05)	QOLIE-31 51.57 (2.99)	Cognitive performance, social adjustment
Hermann (2000) ⁴⁷	Cross-sectional/ prospective	NSA	54	N/A	37.9 (11.6) years TLE	QOLIE-89 Not reported	Emotional-behavioral distress
Hopker (2017) ⁴⁸	Cross-sectional/ prospective	Brazil	30	4.4 per month	44.8 (SD not reported)	SHE Not reported	Sex, disease duration, seizure frequency, education attainment, stigma about epilepsy
Lowe (2004) ⁴⁹	Cross-sectional/ prospective	Australia	42	N/A	42.7 (9.2)	QOLIE-89 Not reported	Seizure outcome postsurgery
Meldolesi (2007) ⁵⁰	Longitudinal/ prospective	Italy	52	N/A	33.0 (9.4)	QOLIE-31 62.8 (18.3), before surgery; 68.4 (21.0) after surgery +2years	State anxiety, trait anxiety, depression, state anger, trait anger, outside-directed anger, inside-directed anger
Rose (1996) ⁵¹	Longitudinal/ prospective	Canada	77	1-20 per month (SPS)= 21; 1-20 per month (CPS)= 59; 1-20 per month (GS)= 8	31.7 (10.3)	ESI-55 Preoperative: 52.2 (14.9), physical health; 62.8 (14.3), mental health; 64.8 (19.9), role function Postoperative: 61.9 (16.8), physical health; 70.0 (14.6), mental health; 71.4 (24.8), role function	Neuroticism

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Study	Study design	Country	Number of patients	Seizure frequency mean (SD) (unless otherwise stated)	Patient age (years), mean (SD)	HRQoL outcome measures and mean score at baseline (mean (SD))	Variables assessed
Sajobi (2014) ⁵²	Longitudinal/ prospective	Canada	80	N/A	35.5 (9.9) surgical; 34.4 (9.9) medical	QOLIE-31 overall HRQoL domain 52.63 (9.25), surgical; 50.00 (17.53), medical	HRQoL domains Overall HRQoL, social function, energy, emotional well-being, seizure worry, memory, medication effect
Scevola (2017) ⁵³	Cross-sectional/ prospective	Argentina	77	7.73 (9.94) (with depression); 10.50 (10.98) (without depression)	32.1 (9.63) with depression 32.81 (13.33) without depression	QlesQ 64.99 (15.29), with depression; 77.56 (11.70), without depression	Depression, seizure frequency, overall HRQoL
Taskiran (2019) ⁵⁴	Cross-sectional / retrospective	Turkey	105	Number of patients with >4 seizures per month = 27 (26%)	35.9 (9.7)	QOLIE-31 57.2 (27.2)	Employment, epilepsy surgery, AED use, presence of depression, presence of anxiety, seizure freedom
Employment							
Wo (2016) ⁵⁵	Cross-sectional/ prospective	Malaysia	146	14.90 (45.82) per year	34.40(10.89)	N/A Not reported	Type of seizure, employability
Abbreviations: AED, anti Scale: ESI, Epilepsy Surge MTLE, mesial temporal lo PSQ1, Pittsburgh Sleep Qt QOLIE-89, Quality of Lifé seizure recurrence; STA1, WHO-Mood, World Healt	epileptic drug; ASM, ar iry Inventory; ETLE, ext obe epilepsy; NDDI-E, n aality Index; QiesQ, Que in Epilepsy-89; SAH, se State-Trait Anxiety Inv ih Organization Mood; V nivariate analyses.	ntiseizure medica: tra temporal lobe neurological disori ality of Life Enjoy elective amygdalo /entory; TEMPS, J /entory; TEMPS, J WHOQOL 100, W	tion; BAI, Beck Anx epilepsy; GTCS, gen ders depression inve ment and Satisfactic hippocampectomy; remperament Evalu 'orld Health Organi;	iety Inventory; BDI-II, Be eralized tonic-clonic seizi mtory for epilepsy; Post-Si on Questionnaire; QOLCE on Questionnaire; QOLCE sAS, Self-Rating Anxiety ation of Memphis, Pisa, au zation QOL.	ck Depression Inventor ure; HA, hippocampal i AH, postsurgery tempoi 2-82, Quality of Life in C Scale; SD, standard dev nd San Diego; TLE, tem	y-JI; BPSE, Bonner Skalen fu atrophy; HRQoL, health-relat ral lobe epilepsy patients; Pre Zhildhood Epilepsy Questionn viation; SDS, self-rating depre nporal lobe epilepsy; TLE-HS,	Epilepsie; CD-RISC-10, Connor–Davidson Resilience ed quality of life; HS, hippocampal sclerosis; SAH, pre-surgery temporal lobe epilepsy patients; naire 82; QOLIE-31, Quality of Life in Epilepsy-31; ssion scale; SF-36, short form health survey-36; SR, temporal lobe epilepsy with hippocampal sclerosis;

TABLE 2 (Continued)

^aStudies also conducted univariate analyses.





FIGURE 2 Impactful determinants often studied and/or determinants less often studied but commonly associated with poor HRQoL in persons with focal epilepsy. AE, adverse event; ASM, antiseizure medication; HRQoL, health-related quality of life. ^aCognition includes cognitive function/measures, memory, and executive function.

freedom), ASM AE burden, cognition, and employment represent the most frequently studied topics and/or those that have the most consistent impacts on HRQoL. Further details of the results for each multivariate analysis can be found in Table 3.

examined), 25,27,45,49,54 seizure frequency (*n*=4, 57% of studies examined), 11,28,31,45,46 and employment (n=6, 75% of studies examined).^{21,24,25,27,28,54} Further details on the results of the univariate analyses can be found in Table 3.

3.4 **Univariate analyses**

The most commonly examined variables in studies employing univariate models (n=25) included sex (n=8), 32% of studies), 21,24,25,27,28,31,44,48,54 age (n = 10, 40% of studies),^{11,21,24,25,27,28,30,31,40,45,54} marital status or equivalent 28% of studies), 11,21,24,25,30,31,48,54 employment (*n*=8, 32%) of studies), 11, 21, 24, 25, 27, 28, 35, 54 age of onset (n = 8, 32% of studies), 11,21,25,27,28,30,40,54 disease duration (n=8, 32%) of studies), 11, 21, 24, 25, 28, 31, 40, 54 seizure frequency (n = 7, 28% of studies), 11,24,28,30,31,40,45,46 seizure freedom (n=6, 24% of studies), 25,27,28,45,49,54 number of ASM (n=9, 36%) of studies), 21,25,27,28,31,35,38,40,41,54 anxiety (n=7, 28% of studies),^{11,24,28,30,31,50,54} and depression (n = 14, 56% of studies).^{11,21,24,25,28,30,31,38,42,44,47,50,53,54}

Similar to the multivariate findings, depression was a significant contributor to HRQoL (n=13, 93% of studies examined).^{11,21,24,27,28,30,31,38,44,47,50,53,54} This was followed by anxiety (n=6, 88%) of studies examined), 24,28,30,31,50,54 seizure freedom (n = 5, 83% of studies

DISCUSSION 4

This SLR aimed to identify determinants of HRQoL for PWFE from the current literature. The results from studies in this review support that HRQoL in this disease population is quite complex, primarily involving a combination of disease-related factors (level of seizure control), disease management factors (ASM AE burden), comorbidities (anxiety, depression), and life-related factors (employment). Cognition as a determinant can be considered multifactorial as it can be a component with each of these areas. In addition to these main findings, several other factors were significantly associated with HRQoL when examined in one or two studies.

This study brings understanding to a diverse body of work, which contributes to a wide range of covariates examined for HRQoL in PWFE. In addition, the range of analytic approaches employed introduced challenges in synthesizing the results, even in the targeted qualitative fashion. As a result, a semiquantitative approach was used to produce a qualitative overview of the findings, as

TABLE 3 Summary of study results.



Study	Research question(s)	Main outcome(s)
Findings from multivaria	te models	
Azuma (2014)	Investigate the HRQoL in patients with epilepsy and its correlation with psychosocial impact, depression, seizure- related aspects, and living circumstances	Life satisfaction ($\beta =605$, $p < .0001$), depression ($\beta =260$, $p < .0001$), frequency of focal seizure with impairment of consciousness or awareness ($\beta =219$, $p < .0001$), and employment status ($\beta = .187$, $p = .0001$) were each associated with HRQoL. Variables had a relatively high prediction capacity ($R^2_{adj} = .74$). Life satisfaction was the strongest predictor of HRQoL
Basaran (2021) (ETLE and TLE)	Investigate the relationship between affective temperaments, depression, anxiety, disease characteristics, and HRQoL and explore predictors of HRQoL in patients with TLE and ETLE	HRQoL subscales were affected by several temperament aspects sporadically. Depression and anxiety (measured as a symptom or temperament) were typically the strongest determinants and the most frequently significant (e.g., each were independently associated with worse HRQoL for more than half of SF-36 subscales)
Cano-Lopez (2023)	Examine whether trait anxiety mediates the relationship between memory and HRQoL in this population	Trait anxiety had a significant direct effect on HRQoL ($\beta =47$, SE = .08, $p < .0001$), while delayed memory has an indirect effect on HRQoL when trait anxiety was used as a mediator ($\beta = .13$, SE = .06, $p = .04$). Delayed memory did not have a direct effect
Catalan-Aguilar (2022)	Analyze the effects of the academic and employment insertion on quality of life, anxiety, depression, social support, and executive functions as well as the relationships among these variables in patients with drug-resistant epilepsy	Anxiety had a significant direct effect on HRQoL (β =85, SE = .1, <i>p</i> < .00001) while employment/academic insertion had a significant indirect effect on HRQoL (β = -3.25, SE = 1.94), 95% CI [-7.85,28]
Chen (2018)	Analyze the independent associations between the QOLIE-31 and the demographic, clinical, psychiatric, and cognitive variables in PWTLE	Anxiety (β =847, <i>p</i> =.000), durations of seizures (β =552, <i>p</i> =.005), adverse effects of ASMs (β =-9.080, <i>p</i> =.018), and depression (β =365, <i>p</i> =.042) were significant predictors of HRQoL. Variables had a relatively high prediction capacity (R^2_{adj} =.60)
Dias (2017)	Evaluate long-term surgical outcomes in patients treated for mesial temporal lobe epilepsy	Seizure outcomes (seizure freedom), depression, and ASM adverse event burden were each significant predictors of HRQoL; model explains 73% of variability
Ehrlich (2019)	Evaluate the impact of VM and EF on HRQoL in patients with TLE	Depression (β =682, <i>p</i> < .001), number of AEDs (β =252, <i>p</i> = .017), and executive functioning abilities (β = .226, <i>p</i> = .19) were each associated with HRQoL. Severity of depressive symptoms was the strongest predictor of HRQoL
Elsharkawy (2009)	Identify determinants of HRQoL in long- term follow-up after TLE surgery in adults	Severity of AED side effects ($\beta =29$, $p < .001$), duration of seizure freedom (time from last seizure) ($\beta = .46$, $p < .001$), and employment ($\beta = .19$, $p < .01$) were important predictors in total HRQoL in the model with all patients. Time from last seizure and severity of side effects were significant predictors in a majority of the HRQoL domains (all patients)
Elsharkawy (2012)	Assess the determinants of HRQoL in adults with refractory FE who were not eligible for surgery or who rejected surgery after presurgical evaluation	Employment (β = 4.6, p = .05), AED efficacy (-4.6, p = .001), AED tolerability (-3.7, p = 0.01), depression (-15.8, p = .001), and anxiety (-12.3, p = .001) were significant predictors of total HRQoL in multivariate regression
Giovagnoli (2000)	Determine the contribution of memory performance on HRQoL in patients with left/right TLE	Mood (F =3.482, p < .0001), QME score (F =20.86, p < .0001), side of seizure (F =11.70, p =.0011), and disease duration variables (F =9.14, p =.0003) were significant predictors of overall QOLIE-89 score

²² Epileptic **Disorders** TABLE 3 (Continued)

Study	Research question(s)	Main outcome(s)
Giovagnoli (2006)	Explore the possible role of spirituality in HRQoL	Significant predictors of WHOQOL-100 total score were mood (F =9.65, p =.004) and awe and transcendence (F =11.04, p <.001). Mood was also a significant predictor of 3 domains of the WHOQOL-100: Overall HRQoL (F =9.23, p =.005), physical (F =5.76, p =.008), and psychological (F =14.34, p =.001)
Johnson (2004)	Determine the independent effects of depression and anxiety on HRQoL in epilepsy as well as the relative explanatory power of psychiatric comorbidity compared with demographic and clinical epilepsy variables	Anxiety (R^2 =.65, p <.001) and depression (BDI R^2 =.62, p =.0001, and SCL-90-R R^2 =.67, p <.0001) were found to be independent determinants of poor HRQoL and each exerted the strongest negative effects on HRQoL, as compared to seizure-related variables (noting depression and anxiety were studied in separate models)
Lehrner (1999)	Determine the interrelations between clinical characteristics, cognitive function, ADL, depressive mood and HRQoL; evaluate with neurologic findings (laterality of seizure, hippocampal atrophy, sclerosis)	Depression alone was a predictor of HRQoL on each of the 6 domains of the BPSE (physical well-being, activity/capability, relations and family, emotion/mood, independence, coping/ control); in addition, seizure frequency was also a predictor on coping/control domain while ADL-cultural was also significant in the emotional/mood domain
Lima (2021)	Determine the interrelations between clinical characteristics, cognitive function, ADL, depressive mood, and HRQoL; evaluate with neurologic findings (laterality of seizure, hippocampal atrophy, sclerosis)	Anxiety trait symptoms were the most critical individual determinant of the HRQoL on both overall and domain scores for disease-specific and general HRQoL measures. Total QOLIE-31 (β = -1.757, <i>p</i> < .001) and overall ESI (β = -1.483, <i>p</i> = .011). Majority of the variance on HRQoL scores stemmed from depression and anxiety variables rather than epilepsyrelated variables
Lozano-Gracia (2021)	Assess whether cognitive performance predicts quality of life in patients with drug- resistant TLE using ASM as a mediator	Cognitive performance had a direct effect on HRQoL total score, $\beta = .23$ (95% CI: .15, 1.17; $p < .05$), and $R^2_{adj} = .47$. Cognitive performance had an effect on overall HRQoL through mediation of ASMs ($\beta = .21$, SE = .12, 95% CI: .02, .49; $R^2 = .56$). Cognitive performance had an effect on social function and seizure worry domains only when mediated through ASMs
Meldolesi (2006)	Elucidate the association between HRQoL and sociodemographic factors, clinical seizure factors, depression, and anxiety in DRTLE	Depression significantly impacted HRQoL when examined by both disease-specific or general HRQoL measures (QOLIE-31 $\beta =45$, $p < .0001$; WHOQOL-100 $\beta =33$, $p < .0001$). Anxiety was significant on QOLIE-31 total score ($\beta =21$, $p < .05$)
Mucke (2022)	Elucidate the association between HRQoL and sociodemographic factors, clinical seizure factors, depression, and anxiety in DRTLE	Objective memory change had a significant indirect effect on HRQoL when mediated by subjective memory change and depressive symptoms. Depressive symptoms were the only variables (out of objective memory change and subjective memory change) to have a direct effect on HRQoL
Pulsipher (2006)	1) Determine the relationship between comorbidity (medical and psychiatric) and HRQoL in a sample of adults with TLE. 2) determine if comorbid conditions (medical and/or psychiatric) are associated with HRQoL beyond what is attributable to basic demographic and clinical seizure characteristics	The number of comorbid conditions was the strongest predictor for three of five HRQoL factor scales and the overall HRQoL score (all $p < .01$). Both medical and psychiatric comorbid conditions contribute as predictors (total score). Education level ($p < .05$), duration of epilepsy, and days since last seizure ($\beta = .27$, $p = .02$) were all predictors of HRQoL
Schraegle (2021)	Exploring pathways by which executive functioning and depressive features impinge on HRQoL in context of psychosocial and seizure-specific factors	AEDs (β =071, 95% CI:171,001) and executive function (β =106, 95% CI:217,02) were each determinants of HRQoL when mediated by depressive features. Depressive features (β =30) and executive function (β =29) were independent significant predictors of HRQoL

TABLE 3 (Continued)



Study	Research question(s)	Main outcome(s)
Silva (2019)	Analyze the relationship between sociodemographic factors, epilepsy-related variables, psychiatric comorbidity, and HRQoL in a well-defined group of patients with focal DRE	Mood disorders ($\beta = -20.342$, $p = .002$) and sex ($\beta = -8.480$, $p = .071$) were significant predictors of HRQoL
Skirrow (2011)	Characterize intellectual and psychosocial functioning of children having undergone temporal lobe resection	Seizure freedom was the sole determinant of HRQoL (β = .44, p = .001)
Findings from univariate	e analyses	
Alonso-Vanegas (2013)	Explore the effects of clinical variables on self-reported HRQoL in DRTLE and correlate this information with results from the QOLIE-31 and selective memory tests	Older age at epilepsy onset, duration of epilepsy, and memory impairments were the variables correlated with the highest number of HRQoL domains in patients with TLE and MTLE-HS. However, only therapeutic trials were significant in total HRQoL
Aydemir (2004)	Evaluate changes in HRQoL for patient post-surgery, impacts of surgery	Number of antiepileptic medications was correlated with HRQoL-role limitations. No other domains of SF-36 were found to be significant
Bakhtiar (2021)	Analyze the effect between postoperative anxiety and depression on HRQoL levels	Anxiety and depression levels were each negatively correlated with HRQoL levels: depression correlated with medication effects, and social function; anxiety correlated with overall HRQoL, emotional well-being, energy/fatigue, and cognition; depression and anxiety correlated with adjustment
Bonora (2011)	Examine the relationship between recognizing emotions (facial emotions, gestures, body posture, or voices, e.g. prosody) and HRQoL (QOLIE-31) total and emotional well-being and social function subscales	No correlation was observed between ability to recognize facial emotion or emotional prosody recognition with HRQoL total score, or emotional well-being, or social function subscales scores
Brandalise (2019)	Relationship between HRQoL and depression and resilience was examined at two timepoints, pre- and post-intervention	A significant positive correlation was observed between resilience levels and HRQoL; a significant negative correlation was observed between depressive symptoms and HRQoL. Results were comparable at the pre-intervention and post- intervention timepoints
Flint (2023)	HRQoL (QOLIE 31-P and SF-6D) and its relationship with descriptors of seizure control (seizure freedom achieved, severity, frequency) were examined as well as the relationships between disease specific HRQoL measure (QOLIE 31-P) and generic measures of utility (SF-6D)	HRQoL was correlated with several seizure-related variables (seizure freedom, seizure severity, and seizure frequency) on both epilepsy-specific and general HRQoL measures. Uncontrolled FE (as measured by seizure freedom, seizure severity, seizure frequency) is associated with poor HRQoL on both epilepsy-specific and general HRQoL measures
Gois (2011)	Assess the social adjustment in patients with TLE using a self-reported questionnaire. Additionally, verify the influence of cognitive performance on HRQoL	Poor social adjustment was associated with lower cognitive function HRQoL subscores. No other significant association between social adjustment and other domains of HRQoL
Hermann (2000)	To examine the relationship between HRQoL (QOLIE-89) and emotional- behavioral distress (SLC-90-R: global severity index, symptom distress index or depression index)	Each emotional-behavioral distress index examined every domain, and total score (with some exception to the social support domain that was less impacted by emotional- behavioral distress indexes examined) was associated with poor HROoL

24 Epileptic **Disorders** TABLE 3 (Continued)

Study	Research question(s)	Main outcome(s)
Hopker (2017)	Analyze the perceptions (quantitatively and qualitatively) of individuals with epilepsy and its impact on their HRQoL	Stigma about epilepsy was found to negatively impact HRQoL in the work and activity domain and social and personal life domains. Additional trends included how level of education may positively impact the "Work and Activity domain" and how sex can affect "Social and personal life" but were not significant)
Lowe (2004)	Examine long-term seizure outcomes post- lobectomy and HRQoL	Seizure-outcomes, both lower seizure frequency or being seizure-free (Engel class I), were associated with HRQoL (overall score and several subscales)
Meldolesi (2007)	The relationship was examined between HRQoL (QOLIE-31 or WHOQOL-100) and depression (BDI), along with state anxiety (STAI-S), trait anxiety (STAI-T), state anger (STAXI state anger), trait anger (STAXI trait anger), outside-directed anger (STAXI outside directed anger), and inside-directed anger (STAXI inside-directed anger)	Depression was associated with all facets of HRQoL examined in epilepsy-specific and generic HRQoL measures; state anxiety, state anger, and inside-directed anger associated with majority HRQoL aspects examined
Rose (1996)	Determine the association among neuroticism and HRQoL	Presence of neuroticism was negatively correlated with HRQoL
Sajobi (2014)	Relationship between HRQoL domains was examined at multiple timepoints, baseline, and 1 year later	The importance of social function increased over time, with a decrease in relative importance of seizure worry. After 1 year of treatment, seizure freedom and medication management were no longer associated with overall HRQoL in the medically treated group. In the surgically treated group, all domains achieved significance with overall HRQoL 1 year after surgery
Scevola (2017)	Determine the association between comorbid depression and HRQoL in patients with DRE	Depression was a significant predictor of poor HRQoL in patients with DRE
Taskiran (2019)	HRQoL and clinical/demographical variables were examined to elucidate their relationship	Employment, history of epilepsy surgery, AED use, presence of depression and anxiety, and achieving seizure freedom were all associated with HRQoL
Findings from univariate	analyses—that also examined multivariate mod	lels
Azuma (2014)	See above	Correlations between HRQoL and life satisfaction, depression, frequency of focal seizure with impairment, number of AEDs, sheltered work, and employment were found to be significant
Chen (2018)	See above	There were significant correlations of HRQoL with occupation, duration of epilepsy, adverse effects of ASMs, SAS, SDS, sleep quality, and cognition
Dias (2017)	See above	Correlation was observed between HRQoL and ASM AE burden, depression, seizure freedom achieved, non-adherence to medication, surgical group, current employment, and <9 years of education
Elsharkawy (2009)	See above	Severity of AED side effects, duration of seizure freedom, and employment were important predictors in total QOL in the model with all patients. Time from last seizure and severity of side effects were significant predictors in a majority of the HRQoL domains (all-patient model)
Elsharkawy (2012)	See above	Significant correlation between overall HRQoL and sex, employment, seizure frequency, patient-rated efficacy of AEDs, patient rated tolerability of AEDs, side effects (y/n), patient perceived change in seizures, depression, and anxiety

TABLE 3 (Continued)



Study	Research question(s)	Main outcome(s)
Johnson (2004)	See above	Variables with significant correlation to HRQoL included depression and anxiety
Schraegle (2021)	See above	All variables besides HS had significant correlations with HRQoL in univariate analysis
Silva (2019)	See above	A significant predictor of low HRQoL was mood disorders (depression)
Giovagnoli (2006)	See above	Age and schooling were predictors of a higher HRQoL total score along with many different spiritual, affect, and cognitive factors (meaning and purpose, wholeness and integration, spiritual strength, inner peace, hope and optimism, faith, and acceptance)
Meldolesi (2006)	See above	Depression followed by anxiety (in that order) each have the most negative impacts on HRQoL, as compared with clinical seizure factors

Abbreviations: ADL, activity of daily living; AED, anti-epileptic drug; AEP, adverse events profile; ASM, antiseizure medication; BDI-II, Beck Depression Inventory-II; BPSE, Bonner Skalen fur Epilepsie; CAH, corticoamygdalohippocampectomy; CD-RISC-10, Connor–Davidson Resilience Scale; CI, confidence interval; DRE, drug-resistant epilepsy; DRTLE, drug-resistant temporal lobe epilepsy; EF, executive functioning; ESI, epilepsy surgery inventory; ETLE, extra temporal lobe epilepsy; FE, focal epilepsy; HRQoL, health-related quality of life; MTLE, mesial temporal lobe epilepsy; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy; NS, not stated; PWTLE, patients with temporal lobe epilepsy; QOLIE-31, Quality of Life in Epilepsy-31; QOLIE-89, Quality of Life in Epilepsy-89; SAS, self-rating anxiety scale; SDS, self-rating depression scale; SEALS, Side Effects and Life Satisfaction Inventory; SF-36, short form health survey-36; SF-6D, short-form-six-dimension; SR, seizure recurrence; TLE, temporal lobe epilepsy, VM, verbal memory; WHOQOL-100, World Health Organization QOL; WPSI, Washington Psychosocial Seizure Inventory.

a meta-analysis was deemed inappropriate. Using this approach identified a number of trends for further exploration, harmonized from the range of studies.

Depression was the most prominent determinant of poorer HRQoL in PWFE regardless of the initial combination of factors with which it was studied. In addition, it was the strongest determinant in the majority of studies. This is meaningful due to the high prevalence of depression in PWFE, reported as 18%-40% in the cohorts included in this review (from N=3 studies). Depression and HRQoL can also have a bidirectional relationship, where changes in one can have a negative effect on the other.^{10,21} Therefore, research and clinical care should examine improvements in depression when improving patient HRQoL is the goal.

Anxiety also has an important role in patient HRQoL. Anxiety may result from the lack of seizure control and the challenges in planning daily activities when seizures occur spontaneously, such as social interaction, sports, or driving.⁵⁶ PWFE may also exhibit more avoidance behavior through fear of social rejection and unsafe feelings during seizures.^{9,11} Incidentally, research has found that anxiety is more prevalent in patients with a shorter duration of epilepsy.^{56,57} This is likely because PWFE are more likely to develop sufficient coping strategies with time.

Seizure frequency and severity lie at the center of this disease; therefore, it seems intuitive that these factors would be the main predictors of HRQoL, as more seizures not only cause disruption to life, but also require more care and treatment and lower the ability to carry out daily tasks, all while incurring additional medical costs. However, a number of studies in this review found the relationship between seizure burden and HRQoL to be more complex. Seizure burden was frequently examined; however, when examined as a continuous variable (e.g., seizure frequency), it was rarely significant.9,11,26,28-33,35,37 Only when dichotomized into seizure freedom versus still experiencing seizures, did it reach significance.^{25,27,31,45,54} Interestingly, the findings for ASM AE burden, which was studied less often, were consistently associated with HRQoL (e.g., a significant finding each time studied). Combining this with the findings for seizure frequency introduces the question of whether ASM AE burden or reduction in seizure frequency, if seizure freedom cannot be achieved, is the priority. This further speaks to the unmet needs for treatments, or procedures such as resective surgery, that have a lower AE burden and/or offer higher likelihood of seizure freedom. One explanation that could attest to this is the very complex nature of the patients enrolled in the studies, who may experience a number of other features and comorbidities. While in isolation (as simulated with the control introduced in multivariate models), seizure frequency was not a determinant of HRQoL; however, it may have impacted other aspects that were significant such as depression, anxiety, cognition, and ASM burden. Further studies can help to elucidate these findings.

Findings from univariate models are primarily confirmative of the findings from the multivariate models. The

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attainment of seizure freedom was consistently associated with better HRQoL regardless of analytics employed in n=3 of 4 multivariate models. This is an important finding that warrants additional research, as it is frequently reported that seizure frequency is one of the most important considerations in HRQoL, whereas it should perhaps be considered dichotomously as to whether seizure freedom was attained.

The number of ASMs was associated with HRQoL in 23% of multivariate models (n=3 of 13 models). There is a question as to whether the role of ASMs in HROoL is about the number of ASMs taken or about the side effects associated with treatments. We examined models where both were studied and found that in every multivariate model where they were examined together (n=4), the number of ASMs was not significant whereas the ASM AE burden was significant.^{21,25,27,28} ASMs can have a range of AEs, the most prevalent being fatigue, dizziness, headache, drowsiness, nausea, and vomiting, as well as some more severe AEs on a case-by-case basis, such as cognitive deficits, idiosyncratic effects (such as skin rashes), chronic effects (such as weight gain), behavioral issues, and suicidal ideation. Separate from the level of seizure control achieved with ASMs, these AEs can still be present and have a negative impact on patient HRQoL.58

The findings herein have some similar themes as those identified by Shakhatreh et al. in their review examining determinants of improved HRQoL in PWFE following resective surgery.¹⁹ Specifically, preoperative absence of mood disorder, better preoperative cognition, postoperative improvement in depression, not being on antidepressants following surgery, and engagement in paid employment before and after surgery are consistent with our findings. Postoperative verbal memory decline was reported with worsened HRQoL, consistent with our findings. In contrast, they identified that the presence of mood disorders postoperatively to not be significantly associated with HRQoL. They also reported mixed results regarding whether attaining seizure freedom was associated with significant improvements in HRQoL, as when measured by QOLIE-31 improvements were seen but were not observed when measured by QOLIE-89. They discuss potential reasons for this as smaller sample size of the QOLIE-89 group and/or the reduced sensitivity of the QOLIE-89 to detect clinically meaningful changes. The authors also discuss how changes in HRQoL once seizure freedom is achieved may not be attainable for a range of reasons that include neurocognitive issues, and the time it takes for the seizure freedom to translate to daily impacts (on aspects like employment, relationships, driving). Based on these findings, the authors may have studied a different construct than that of our examination.

Although measured less often, employment was a determinant of HRQoL a majority of the time studied. People with better employability have less self-perceived stigma, more self-determined motivation, higher self-esteem, better perceived social support, and higher education levels.⁵⁵ In addition, Aguirre et al. (2017) reported that only half as many PWFE are employed compared with healthy controls (37% and 67%, respectively).⁵⁹ Gupta et al. (2017) showed in a US study that, for PWFE, as seizure frequency increases work impairment and presenteeism increase. In a study of European and Brazilian PWFE, work impairment, absenteeism, and presenteeism each increase as seizure frequency increases.¹²

This review is the first to synthesize predictors of HRQoL in PWFE. PWFE have widespread unmet needs that come in the form of physical, mental, and emotional stressors, as well as financial hardship, as outlined in this SLR. Many publications on this topic address all patients with epilepsy or drug-resistant epilepsy, consequently leaving room for interpretation of findings as it applies to PWFE. We identified 2 SLRs pertaining to HRQoL in PWFE published prior to this work.^{60,61} A review by Villanueva et al. (2021) focuses on unmet needs and value drivers in the treatment of focal epilepsy in Spain and draws conclusions that drug-resistant epilepsy is associated with reduced HRQoL and that there is a lack of availability of specific treatment protocols.⁶⁰ However, their review does not address the broader question of factors affecting HRQoL beyond disease severity and treatment, which limits the conclusions. An earlier review conducted by Schmitz et al. (2010) reports that HRQoL is influenced by mood status and AEs to a greater extent than seizure control.⁶¹ While this statement is consistent with our findings, Schmitz's review focuses more on the effects of each different medication rather than overall HRQoL-related factors. The current work takes a more comprehensive approach to the question and examined a range of factors and study designs. In addition, as there were two reviews on impacts of resective surgery on changes to HRQoL and employability,^{19,20} we chose to examine HRQoL (and employability) as a static outcome rather than including work that specifically evaluated changes due to an intervention.

These findings highlight the impacts that depression and anxiety comorbidities can have on HRQoL. In addition to seizure control as a goal of treatment, management of comorbidities is an important aspect of improving patient HRQoL. The challenges with this stem from the potential for different clinicians to manage these different aspects of the patient, where epileptologists/neurologists tend to manage seizure, and primary care physicians or psychiatrists tend to manage depression and anxiety. These

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findings speak to the importance of well-coordinated care in this complex population.

The main limitation of this review was that each study had its own research questions and analytic approaches, with considerable variability, prohibiting a meta-analysis approach. It is also important to note that the listing of possible determinants examined was different across the studies, as each took different perspectives and/or examined different data source. Therefore, care must be taken into account when interpreting results. Also, these studies did not account for multiplicity in the *p* value derivation, lending for the potential for false-positive findings. Additionally, some studies were not comprehensive in presentation of data, with gaps in information limiting clear interpretation of results (e.g., statements in the text lacking associated pvalues and graphs without correlation/p-values). However, our approach of looking for trends across studies can help to mitigate these limitations. Many of the included studies also had smaller cohorts drawn from specialty treatment centers of a given country, which limits the generalizability of findings. This is expected, as HRQoL is not frequently captured in routine day-to-day care. Nonetheless, it raises questions to the generalizability of the findings to a broader population. Most adult ages were represented in each included study, though many tended to have mean ages in the 30s and 40s, which is another factor to consider when extrapolating results to a wider population. Therefore, while there has been a recent increase in the body of research evaluating HRQoL in focal epilepsy, there is still an apparent gap in conclusions that can be drawn about this population due to limitations previously addressed. Future research should include a broader range of possible predictors of HRQoL in PWFE, such as those identified herein (e.g., ASM AE burden, seizure freedoms as opposed to number of seizures, employability).

It is essential to understand which aspects of focal epilepsy have the biggest effect(s) on HRQoL in order to improve patient HRQoL outcomes. The findings of this review prove helpful in addressing this need, as the previously existing literature surrounding this issue is quite disparate. This systematic review further raises awareness of the unmet need in this disease population and acts as a guide to help drive future research and drug development, which will be crucial in improving the HRQoL of these patients. Future research must continue to work to find solutions to each of these issues to improve the quality of patients' lives.

AUTHOR CONTRIBUTIONS

M.H.P., J.L., and J.M. contributed to study conception and design. Material preparation and data collection were performed by P.E., C.M., D.D., and M.H.P. All authors contributed to data analysis and interpretation. All authors

commented on the manuscript during development and approved the final version.

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CONFLICT OF INTEREST STATEMENT

PE, CM, and DD were employees of Biohaven at the time of study. JL, GI, VC, and MHP are employees of Biohaven. JM has nothing to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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³⁰ Epileptic **Disorders**

Test Yourself

- 1. What are examples of modifiable determinants of health?
 - A. Age and sex assigned at birth
 - B. Family history of disease, race, and ethnicity
 - C. Current ASM prescribed, depression severity, and occupation
 - D. Results of a genetic test
- 2. Which of these modifiable determinants were shown to be frequently associated with HRQoL?
 - A. Depression
 - B. Anxiety
 - C. Attainment of seizure freedom
 - D. All of the above
- 3. Why are findings from multivariate analyses more informative than findings from univariate analyses?
 - A. Multivariate allow for simultaneous control of multiple (potentially) confounding aspects
 - B. Multivariate analyses take a shorter amount of time to run than univariate analysis
 - C. Univariate analyses can only be conducted with continuous data
 - D. Univariate analyses can only be conducted with small data sets