

REVIEW ARTICLE

Health-related quality of life in narcolepsy: A systematic review and meta-analysis

Ragy Tadrous¹  | Deirdre O'Rourke² | David Mockler¹ | Julie Broderick¹

¹Trinity College Dublin, Ireland

²Department of Neurology, St James' Hospital, Dublin, Ireland

Correspondence

Ragy Tadrous, Physiotherapy Department, Trinity Centre for Health Sciences, St James' Hospital, James' Street, Dublin 8, D08W9RT, Ireland.
Email: rtadrous@tcd.ie

Summary

To date, there has been no systematic analysis of the literature regarding health-related quality of life in narcolepsy. This systematic review aimed to examine the impact of narcolepsy on health-related quality of life, measured through standardised health-related quality of life questionnaires such as the Short Form 36 and Functional Outcome of Sleep Questionnaire. The following databases: Medline, Embase, Cinahl, and Web of Science were searched for studies that investigated health-related quality of life in adults with narcolepsy. Studies were reviewed independently by two reviewers, and a random-effects meta-analysis was performed. A total of 30 studies were eligible for inclusion in the review. Additionally, meta-analyses were conducted for the Short Form 36 and the EQ5D. The Short Form 36 meta-analysis identified that the pooled mean scores for the Physical Component Summary (45.91) were less affected than the Mental Component Summary (42.98). People with narcolepsy experience substantially lower health-related quality of life when compared with the general population norms of the USA, UK, France and Norway, as well as compared with people with chronic diseases such as multiple sclerosis, diabetes, hypertension and epilepsy. Further research is warranted to identify the longitudinal effects of narcolepsy on health-related quality of life, and to develop a narcolepsy-specific health-related quality of life tool.

KEYWORDS

narcolepsy, quality of life, health-related quality of life

1 | INTRODUCTION

Narcolepsy is a rare, disabling chronic neurological disorder that is characterised by excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations and sleep paralysis. Narcolepsy can be classified into two subtypes: type 1 narcolepsy (NT1) and type

2 narcolepsy (NT2), both of which have similar clinical presentations. However, NT1 can be distinguished by the presence of cataplexy, which is defined as an episodic loss of muscle tone in full consciousness that typically arises following intense emotions such as laughter or anger and decreased cerebrospinal fluid levels of hypocretin (Sateia, 2014). The incidence of narcolepsy is estimated to be 25–50 per 100,000 in Western populations (Overeem, Black, & Lammers, 2008). Symptom onset typically occurs in adolescence; however, approximately one-third of

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people with narcolepsy experience initial symptoms in adulthood (Dauvilliers et al., 2001).

Health-related quality of life (HRQoL) can be described as a “multidimensional concept that includes subjective reports of symptoms, side effects, functioning in multiple life domains, and general perceptions of life satisfaction and quality” (Revicki, Kleinman, & Cella, 2014). Narcolepsy is a neurological condition that can predispose to the development of social and occupational dysfunction (Morse & Sanjeev, 2018). This condition has been associated with considerable detriment to daily life, including impaired quality of life, occupational and academic difficulties, and adversely affected social and personal relationships (Emsellem et al., 2020; Flores, Villa, Black, Chervin, & Witt, 2016; Kapella et al., 2015). With significant correlations identified between symptom severity and HRQoL (Dauvilliers et al., 2017), mitigating the deleterious effect of narcolepsy on HRQoL should be a critical therapeutic goal for people with narcolepsy.

Despite the frequent inclusion of HRQoL as an outcome measure in narcolepsy trials; to date, there has been no systematic review and meta-analysis to synthesise the literature and provide a summative assessment of the impact of narcolepsy on HRQoL. The aim of this review was to systematically review the literature assessing HRQoL in people with narcolepsy, provide pooled mean scores of the domains of the various HRQoL tools used in this population if possible, and to compare HRQoL in people with narcolepsy with general population norms and other chronic health conditions. Additional objectives of this review are to explore: (a) the heterogeneity of the published studies; (b) the tools used to assess HRQoL in this population; and (c) the influence of study characteristics on HRQoL.

2 | METHODS

This systematic review sought to identify the HRQoL of people with narcolepsy. This review followed the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)” statement guidelines. A study protocol that included the proposed search strategy and methodology was registered with PROSPERO, the international prospective registry of systematic reviews (PROSPERO) database (www.crd.york.ac.uk/prospero/) in April 2020 (Identification number: CRD42020156036).

2.1 | Eligibility criteria

The target population for this review was people with narcolepsy recruited from the general population, primary care or secondary care settings. Observational studies (case-control, cohort and cross-sectional) and experimental studies (randomised control trials, pre-post design, quasi-experimental) were deemed eligible if they assessed HRQoL in people with narcolepsy using a validated HRQoL questionnaire. HRQoL has been defined as “a term referring to the health aspects of quality of life, generally considered to reflect the impact of disease and treatment on disability and daily functioning; it has also been considered to

reflect the impact of perceived health on an individual's ability to live a fulfilling life. However, more specifically HRQoL is a measure of the value assigned to duration of life as modified by impairments, functional states, perceptions and opportunities, as influenced by disease, injury, treatment and policy” (Ahmed & Andrich, 2015). Articles were deemed ineligible for inclusion if they were case-series, case reports, expert opinion or consensus statements, or deduplicate studies that utilised the same participant data. Studies were required to provide mean scores with standard deviations (SDs) or standard errors (SEs) for each domain of their chosen HRQoL tool to be eligible for inclusion for each respective meta-analysis. Articles were restricted to those published in English; however, no limitation was placed on the publication year of articles.

2.2 | Data sources and search strategy

In collaboration with a senior medical librarian with specialist skills in systematic review searching (DM), a comprehensive search strategy was developed. The search encompassed four electronic databases: CINAHL, EMBASE, Medline (OVID) and Web of Science. The terms searched consisted of keywords and subject headings that were adapted for each database, and can be divided into three categories: (a) the condition (e.g. “narcolepsy”, “narcolepsy type 1”, “narcolepsy type 2”, “narcolepsy with cataplexy”); (b) HRQoL (“quality of life”, “quality of life assessment”, “HRQoL”); and (c) HRQoL tools (e.g. “Short Form 36”, “European Quality of Life 5 Dimensions Visual Analogue Scale”, “functional outcome of sleep questionnaire”). The reference lists of articles identified in the initial search were scanned to identify any studies potentially missed.

2.3 | Selection of eligible studies

Articles were retrieved and deduplicated. Titles and abstracts were screened to determine their eligibility for inclusion by two researchers (RT and JB). Inter-rater disagreements were resolved through careful re-examination and discussion of the article between reviewers until a consensus was reached. The full texts of the potentially eligible studies were retrieved and independently assessed by both reviewers (RT and JB) to determine eligibility for inclusion in the final analyses. A similar method of addressing disagreements between researchers was applied for the full-text screening phase.

2.4 | Data extraction and quality assessment

Primary data extraction was conducted by RT, with JB examining the articles independently to reduce bias. Two researchers (RT and JB) independently appraised the risk of bias of included studies, with disagreements resolved through discussion between researchers until a conclusion was reached. A modified version of the Joanna Briggs Institute Checklist for Analytical Cross-Sectional Studies (Moola et al., 2017) was utilised to assess the risk of bias of included

studies. This modified tool utilised the following five domains to assess bias: (a) sample; (b) subjects and setting; (c) objective measures of disease; (d) outcome measured; and (e) statistical analysis. Any discrepancies were resolved through discussion and review of the original article. If included articles were longitudinal or follow-up studies, baseline HRQoL data were selected for analysis.

2.5 | Statistical analysis

Statistical heterogeneity was determined using I^2 -values, with values nearing 25%, 50% and 75% representing low, moderate and high heterogeneity, respectively (Higgins, Thompson, Deeks, & Altman, 2003). As high levels of heterogeneity were identified between studies, random-effects meta-analyses with 95% confidence intervals (CIs) using Comprehensive Meta-Analysis were employed. Meta-analyses were conducted for each domain of the Short Form 36 (SF36), and the utility and visual analogue scale (VAS) scores of the EQ5D. Two separate meta-analyses were conducted for the physical (PCS) and mental (MCS) component summaries for the SF36, respectively. The first meta-analyses included only studies that provided calculated PCS and MCS values and their SDs. The second meta-analysis utilised the formula outlined by Taft, Karlsson, and Sullivan (2001) to calculate the PCS and MCS values from the domain scores when summary scores were not provided. SDs for these PCS and MCS scores were imputed according to the process outlined by Furukawa, Barbui, Cipriani, Brambilla, and Watanabe (2006). HRQoL questionnaires that were unable to be meta-analysed were discussed in a narrative summary. The impact of study variables and characteristics on HRQoL was assessed using Spearman's correlation analyses with adjusted r^2 . The HRQoL of people with narcolepsy was compared against normative

SF36 values obtained from the USA (Ware, Snow, Kosinski, & Gandek, 1993), UK (Jenkinson, Coulter, & Wright, 1993), France (Audureau, Rican, & Coste, 2013) and Norway (Ribu, Hanestad, Moum, Birkeland, & Rustoen, 2007). Data from people with narcolepsy were also plotted alongside data from people with epilepsy (Hermann et al., 1996), multiple sclerosis (Hermann et al., 1996), diabetes (Ribu et al., 2007) and hypertension (Kusek et al., 2002).

3 | RESULTS

3.1 | Study screening

The search strategy yielded 5,706 articles and, following deduplication, 3,399 unique articles had their titles and abstracts assessed for eligibility. From these articles, 3,338 articles were deemed ineligible and excluded. The full texts of the remaining 61 articles were screened to determine eligibility for inclusion, and 31 were excluded; with 24 being published abstracts, three duplicate data sets, three utilising ineligible outcome measures, and one study that assessed people without a formal diagnosis of narcolepsy. The remaining 30 articles were included in a descriptive synthesis, of which 17 articles were included in the SF36 meta-analysis, and five in the EQ5D meta-analysis. Figure 1 shows the study selection process.

3.2 | Characteristics of included studies

The characteristics of the included studies are outlined in Table 1. The 30 reviewed studies represent a total sample of 4,600 people with narcolepsy, of which 54.31% were female ($n = 2,498$). The number of

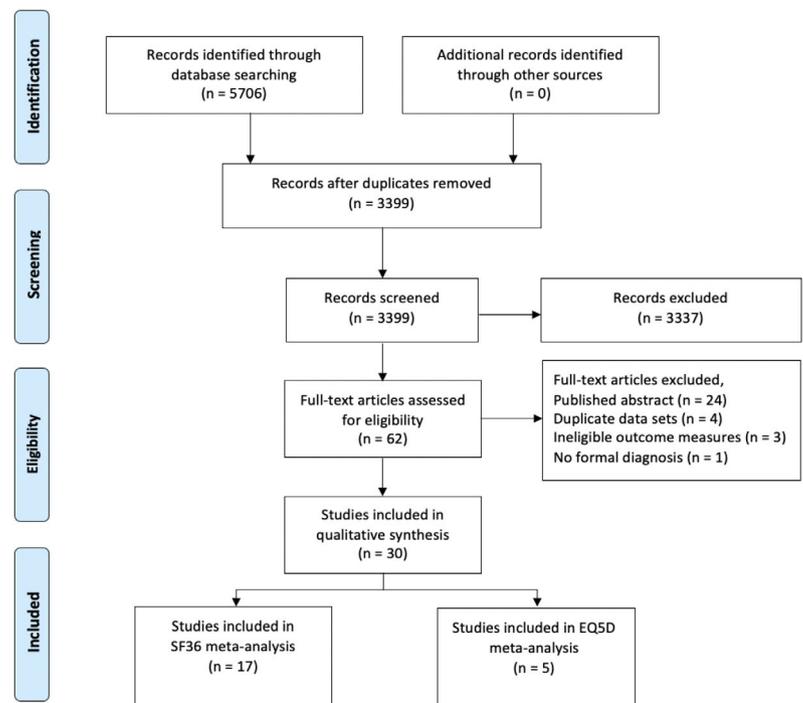


FIGURE 1 Flow diagram of studies screened for eligibility

TABLE 1 Study characteristics

Author	Year	Country	Study type	Industry funding	Sample size	M/F	Age (years)	Instrument	Quality Score	Comparison Groups/Control
Becker	2004	America	Cohort study	Yes	151	70/81	39.00 (18–68)	SF36	4/5	No control group
Beusterien	1999	America	RCT	NR	481	251/307	42	SF36 with additional scales	3/5	Placebo control
Bogan	2017	America	Post hoc analysis	Yes	228	79/149	40.50 (± 15.30)	SF-36	4/5	Placebo control
Campell	2011	New Zealand	Cross-sectional	No	54	20/34	54.70 (± 18.30)	SF36	3/5	No control group
Daniels	2001	UK	Cross-sectional	No	305	120/185	56.00 (18–89)	SF36	3/5	No control group
Dauvilliers	2009	France	Cross-sectional	Yes	492	238/254	41.64 (± 16.53)	SF36	5/5	No Control Group: Compared NT1, NT2 and IH
Dauvilliers	2011	France	Cross-sectional	Yes	67	31/36	44.8% < 40; 55.2% > 40	SF36, FOSQ	5/5	Compared with matched controls
Dauvilliers	2017	France	Cross-sectional	NR	175	104/71	41.50 (± 17.36)	EQ5D	4/5	Compared drug-free and treated patients
Dauvilliers	2019	France	Cross-sectional	NR	39	22/17	39.45 (± 18.20)	EQ5D	4/5	No control group: compared IH with NT1
David	2012	Portugal	Cross-sectional	NR	51	26/25	43.40 (± 15.30)	SF36	4/5	Compared with population norms
Dodel	2007	Germany	Cross-sectional	NR	75	46/29	48.90 (± 15.20)	SF36, EQ5D	4/5	Compared with population norms
Droogleeveer Fortuyn	2012	Netherlands	Cross-sectional	NR	80	46/34	48.3 (± 14.70)	SF36	3/5	No Control Group Compared fatigued versus non-fatigued
Ensellem	2020	America	RCT	Yes	231	82/154	36.23 (± 13.20)	SF36, EQ5D, FOSQ	4/5	Placebo control
Ervik	2006	Norway	Cross-sectional	NR	77	16/54	53.0 (± 17.40)	SF36	5/5	No control group
Flores	2016	America	Cross-sectional	Yes	437	219/218	46.70 (± 16.40)	SF36 PCS and MCS	3/5	Compared with population norms
Ingravallo	2008	Italy	Cross-sectional	No	15	9/6	48.70 (± 18.80)	SF36 PCS and MCS	5/5	No control group
Ingravallo	2012	Italy	Cross-sectional	NR	100	51/49	37.10 (18–65)	EQ5D	3/5	Compared with population norms
Kapella	2015	America	Cross-sectional	No	122	27/95	27.10 (± 5.00)	SF36, FOSQ	3/5	Acquaintance Approach for control group
Kayaba	2018	Japan	Cross-sectional	No	39	20/119	24.60 (± 8.30)	SF36 PCS and MCS	4/5	Compared with BIIS and DSPD
Kovalska	2016	Czech Republic	Case-control	No	42	18/24	71.86 (± 7.45)	VAS EQ5D	5/5	Age- and gender-matched controls
Mitler	2000	America	Cross-sectional	No	478	220/258	42.00 (± 13.0)	SF36	4/5	No control group
Ozaki	2008	Japan	Cross-sectional	No	55	20/35	30.29 (± 10.59)	SF36	5/5	Treated versus drug-naïve

(Continues)

TABLE 1 (Continued)

Author	Year	Country	Study type	Industry funding	Sample size	M/F	Age (years)	Instrument	Quality Score	Comparison Groups/Control
Ozaki	2012	Japan	Cross-sectional	No	131	71/63	32.21 (\pm 8.68)	SF36	5/5	Treated versus drug-naïve
Rovere	2008	Brazil	Cross-sectional	No	40	12/28	41.85 (\pm 14.5)	WHOQOL-BREF	3/5	Control group present
Sarkanen	2016	Finland	Cross-sectional	NR	51	25/26	NR	WHO-5 Well-Being Index	4/5	Compared with NT1
Song	2019	South Korea	Cross-sectional	No	63	43/20	27.03 (\pm 9.29)	K-SF36	5/5	No control group
Teixeira	2004	Scotland	Cross-sectional	No	49	30/19	47.00 (\pm 18.00)	SF36, FOSQ	5/5	Untreated OSAHS and CPAP-treated OSAHS
Vignatelli	2004	Italy	Cross-sectional	No	108	62/46	43.20 (\pm 16.40)	SF36	5/5	Compared with population norms
Vignatelli	2011	Italy	5-year prospective cohort	No	54	42/12	48.00 (\pm 18.40)	SF36	5/5	5-year follow-up
Weaver	2006	America	RCT	Yes	228	79/149	40.50 (\pm 15.30)	FOSQ	5/5	Placebo control

BISS, behaviourally induced insufficient sleep syndrome; CPAP, continuous positive airway pressure; DSPD, delayed sleep phase disorder; FOSQ, Functional Outcome of Sleep Questionnaire; IH, idiopathic hypersomnia; K-SF36, Korean Short Form 36; MCS, mental component summary; NR, not reported; NT1, type 1 narcolepsy; NT2, type 2 narcolepsy; OSAHS, obstructive sleep apnea hypopnea syndrome; PCS, physical component summary; RCT, randomised controlled trial; SF36, Short Form 36; VAS, visual analogue scale.

participants in each study ranged from 15 to 558, with a mean of 153 participants in the included studies. The mean age of all participants was 40.8 years, with a 95% CI ranging from 37.12 to 44.46 years. The 30 included studies originated from 13 different countries (Table 1). Studies were predominantly based in North America and Europe (80.00%), and approximately one-third of studies ($n = 8$) were published in the USA (Becker, Schwartz, Feldman, & Hughes, 2004; Beusterien et al., 1999; Bogan et al., 2017; Emsellem et al., 2020; Flores et al., 2016; Kapella et al., 2015; Mitler, Harsh, Hirshkowitz, & Guilleminault, 2000; Weaver & Cuellar, 2006). Four studies were published in France (Dauvilliers et al., 2009, 2011, 2017, 2019) and Italy (Ingravallo et al., 2008, 2012; Vignatelli et al., 2004; Vignatelli, Plazzi, Peschechera, Delaj, & D'Alessandro, 2011), respectively. Additionally, three studies were published in Japan (Kayaba, Sasai-Sakuma, & Inoue, 2018; Ozaki et al., 2008, 2012). One study was published from each of the remaining countries (Table 1).

3.3 | HRQoL measurement tools

A total of seven different questionnaires (SF8, SF12, SF36, EQ5D, WHOQOL-BREF, WHO-5, Functional Outcomes of Sleep Questionnaire [FOSQ]) were utilised in the 30 included studies to assess HRQoL in this population. Of these questionnaires, six of these were generic, and one was a sleep-specific HRQoL questionnaire (Table 2). The most frequently used questionnaire was the SF36, which was utilised in 22 of the 30 studies (Table 1). The EQ5D was used to assess HRQoL in six studies (Dauvilliers et al., 2017, 2019; Dodel et al., 2007; Emsellem et al., 2020; Ingravallo et al., 2012; Kovalska et al., 2016), and the FOSQ was used in five studies (Dauvilliers et al., 2011; Emsellem et al., 2020; Kapella et al., 2015; Teixeira, Faccenda, & Douglas, 2004; Weaver & Cuellar, 2006). The remaining questionnaires were used in singular studies (Table 1).

3.4 | Study designs

A total of 22 studies utilised a cross-sectional design to assess HRQoL (Table 1), making it the most commonly used method to assess HRQoL in this population. Studies by Weaver and Cuellar (2006), Beusterien et al. (1999) and Emsellem et al. (2020) utilised multicentre, randomised, placebo-controlled designs for their studies. Cohort studies were conducted by Becker et al. (2004), and Vignatelli, Plazzi, Peschechera, Delaj, and D'Alessandro (2011). The latter study was the only study that incorporated a longitudinal design in this population, as it followed up with participants 5 years after the initial study conducted by Vignatelli et al. (2004). The remaining study designs were only used in individual studies, and are shown in Table 1.

3.5 | Employment status

Nine of the included studies, representing a sample of 643 participants, reported the employment status of respondents (David et al.,

TABLE 2 Meta-analysed SF36 results and associated study variables

	PF	RP	BP	GH	PCS	PCSI	V	SF	RE	MH	MCS	MCSI
Pooled mean	67.84	45.99	64.19	53.59	48.32	45.91	42.01	55.66	55.22	58.71	45.47	42.98
95% CI	59.26–76.42	40.80–51.17	56.87–71.50	48.12–59.05	44.45–52.20	43.01–48.81	37.22–46.79	46.56–64.75	48.79–61.66	52.14–65.27	39.97–50.97	39.02–46.95
Heterogeneity I^2 %	99.58	95.76	98.87	98.19	99.10	98.89	98.15	99.15	97.41	98.83	99.43	99.11
Correlators												
Sample size	-0.217	-0.566	-0.154	0.091	-0.310	0.132	-0.434	-0.273	-0.119	1.000**	-0.600	-0.288
Mean age	0.608*	0.643*	0.671*	0.245	-0.168	0.195	0.392	0.811**	0.706*	-0.497	-0.119	0.436
% Female	-0.448	0.021	-0.203	-0.503	-0.466	-0.327	-0.238	-0.203	-0.385	0.028	-0.285	-0.395
Publication year	-0.748**	0.035	-0.638*	-0.0723**	0.000	-0.210	0.007	-0.603*	-0.473	-0.063	-0.142	0.330

BP, Bodily Pain; CI, confidence interval; GH, general health; MCS, mental component summary (imputed standard deviations); MH, mental health; PCS, physical component summary; PCSI, physical component summary (imputed standard deviations); PF, physical functioning; RE, emotional role limitations; RP, physical role limitations; SF, social functioning; V, vitality.

*Correlation is significant at $p = .05$; **Correlation is significant at $p = .01$.

2012); Dodel et al., 2007; Ingravallo et al., 2008, 2012; Kapella et al., 2015; Ozaki et al., 2008, 2012; Rovere, Rossini, & Reimão, 2008; Vignatelli et al., 2004). Of those surveyed, 69.92% ($n = 450$) reported being employed.

Five studies reported employment-related difficulties experienced by respondents (Flores et al., 2016; Ingravallo et al., 2012; Kapella et al., 2015; Kovalska et al., 2016; Teixeira et al., 2004). Changes of employment were reported by the working population of the sample recruited by Ingravallo et al. (2012) ($n = 84$), with 31% ($n = 26$) reporting changes to work due to narcolepsy, 58% ($n = 15$) changing job types, 31% ($n = 8$) losing or leaving their jobs without finding other employment, and 11% ($n = 3$) changing their working schedule.

Termination from employment was frequently reported, with 33% ($n = 40$) of those surveyed by Kapella et al. (2015) reporting being previously discharged from employment, and 52% ($n = 25$) of respondents recruited by Teixeira et al. (2004) reporting losing or leaving a job. As reported by Kovalska et al. (2016), participants with narcolepsy changed employment more frequently than age-and-gender-matched controls (2.67 ± 2.45 times versus 2.42 ± 1.83 times, respectively).

Participants surveyed by Teixeira et al. (2004) reported work-related difficulties such as falling asleep at work (67%, $n = 39$), low productivity (37%, $n = 18$) and accidents at work (15%, $n = 7$). The economic consequences of narcolepsy on employment were quantified by Flores et al. (2016), and compared with matched controls, people with narcolepsy had significantly higher costs associated with absenteeism (\$12,839 versus \$7,631) and presenteeism (\$7,013 versus \$4,987).

3.6 | Impact on HRQoL as measured by the SF36

The pooled mean results of the SF36 domains are reported with 95% CIs in Table 2. From the obtained results, the mental domains of the quality of life in people with narcolepsy are more affected than the physical domains. Both the imputed (42.98) and non-imputed (45.87) MCS were lower than the imputed (45.91) and non-imputed (49.32) PCS (Table 2). The most affected SF36 domains were Vitality (42.01) and Physical Role Limitations (45.99), and the least affected domains were Physical Functioning (67.84) and Bodily Pain (64.19; Table 2).

3.6.1 | Associated study variables

Spearman's correlation analyses with adjusted r^2 -values were used to assess the factors associated with HRQoL, and included study quality, sample size, publication year, the proportion of female participants, and mean participant age (Table 2). Participant age was shown to significantly positively correlate with physical functioning ($r^2 = .608$, $p = .05$), physical role limitations ($r^2 = .643$, $p = .05$), bodily pain ($r^2 = .651$, $p = .05$), emotional role limitations ($r^2 = .706$, $p = .05$) and social functioning ($r^2 = .811$, $p = .01$). Similarly, publication year demonstrated significant negative correlations with physical functioning ($r^2 = -.748$, $p = .01$), general health ($r^2 = .0723$, $p = .01$) and

social functioning ($r^2 = -.603, p = .05$). This finding implies that reported HRQoL has improved throughout the years. Sample size was shown to have a strong positive correlation on the mental health domain ($r^2 = 1.000, p = .01$; Table 2).

3.6.2 | Comparison of HRQoL with general population norms and other chronic health conditions

The mean HRQoL for each domain of the SF36 was plotted against the general population norms for the USA (Ware et al., 1993), UK

(Jenkinson et al., 1993), France (Audureau et al., 2013) and Norway (Ribu et al., 2007) in Figure 2. This comparison indicates that the HRQoL of people with narcolepsy is considerably impaired when compared with the general population, particularly the physical role limitations, social functioning, and emotional role limitations domains. Figure 3 compares the SF36 scores of people with narcolepsy with other chronic health conditions, including epilepsy (Hermann et al., 1996), multiple sclerosis (Hermann et al., 1996), diabetes (Ribu et al., 2007) and hypertension (Kusek et al., 2002). People with narcolepsy experience consistently lower levels of mental health, emotional role limitations, social functioning and

FIGURE 2 Short Form 36 (SF36) values compared with general population norms

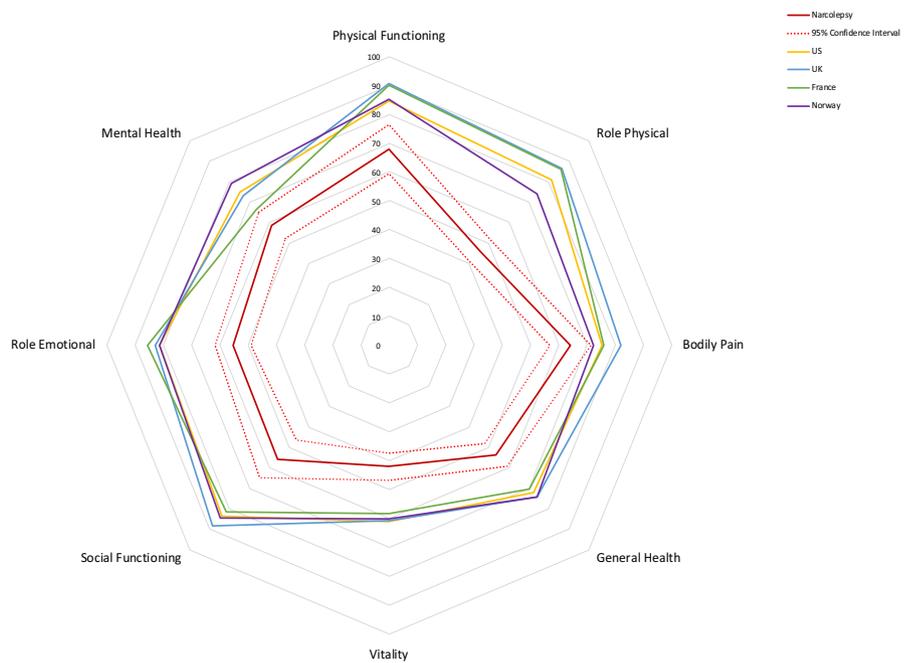
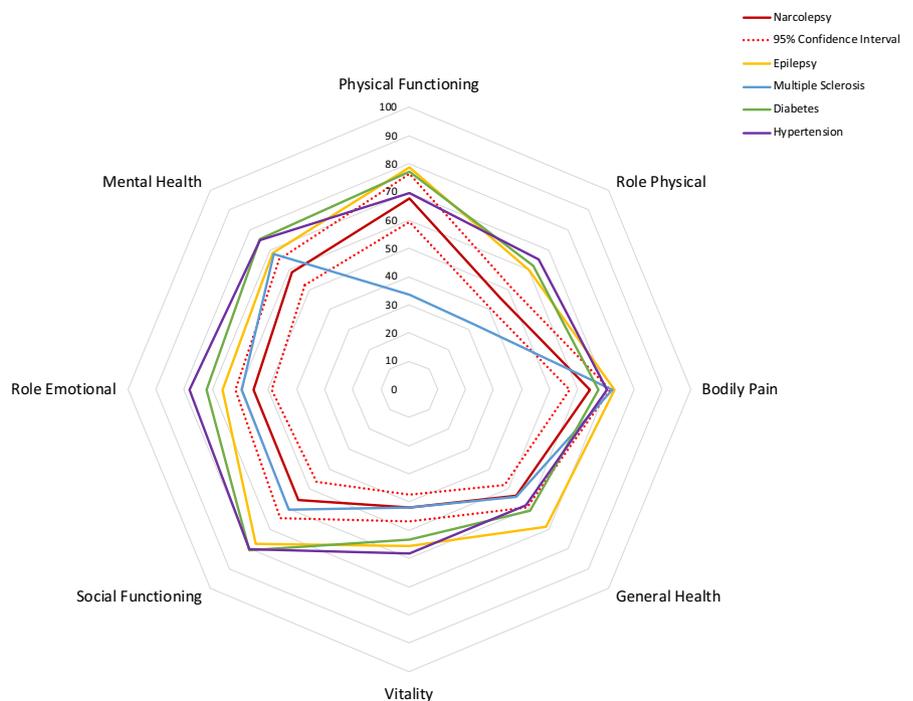


FIGURE 3 Short Form 36 (SF36) values compared with chronic diseases



bodily pain when compared with the aforementioned chronic health conditions. When compared with epilepsy, diabetes and hypertension, people with narcolepsy scored lower in all eight domains of the SF36. With the exception of physical functioning, physical role limitations and vitality, people with narcolepsy scored lower than people with multiple sclerosis in the remaining five SF36 subscales (Figure 3).

3.7 | Other HRQoL questionnaires

3.7.1 | EQ5D

The EQ5D was utilised in six studies (Dauvilliers et al., 2017, 2019; Dodel et al., 2007; Emsellem et al., 2020; Ingravallo et al., 2012; Kovalska et al., 2016) to assess HRQoL in people with narcolepsy. The mean utility score obtained from the analysed studies was 0.85 (0.82–0.88, 95% CI). Additionally, the mean score obtained from the VAS of the EQ5D was 66.63, with the 95% CI ranging from 61.83 to 71.43. Figure 4 compares the VAS scores of the sample with narcolepsy with population norms of the USA, UK and France (Szende, Janssen, & Cabases, 2014).

3.8 | FOSQ

The FOSQ was utilised in five studies (Dauvilliers et al., 2011; Emsellem et al., 2020; Kapella et al., 2015; Teixeira et al., 2004; Weaver & Cuellar, 2006) to assess HRQoL in this population. Studies by Dauvilliers et al. (2011) and Weaver and Cuellar (2006) were excluded from the analysis as they failed to report their baseline values for the FOSQ domains. The results from Kapella et al. (2015) and Teixeira et al. (2004) identified that Activity Levels (2.27) and Vigilance (2.34) were the most affected quality of life domains, and Sexual Wellbeing (3.0) and Social Outcomes (2.71) were the least affected domains. The total score obtained from Kapella et al. (2015) (13.3) was considerably higher than that of Teixeira et al. (2004) (9.5). However, the study by Teixeira et al. (2004) did not assess Sexual

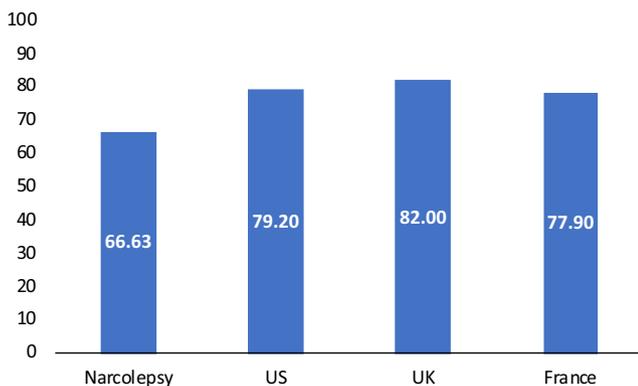


FIGURE 4 EQ5D visual analogue scale (VAS) scores compared with general population norms

Wellbeing. When the Sexual Wellbeing domain is excluded from the results obtained by Kapella et al. (2015), their adjusted total score becomes 10.3. The FOSQ-10, a concise version of the FOSQ, was utilised by Emsellem et al. (2020). The total scores for the FOSQ-10 ranged from 11.4 to 12.2, with a mean total score of 11.675 (3.21) reported.

3.8.1 | Concise short forms

The SF8 and SF12 were utilised by Kayaba et al. (2018) and Flores et al. (2016), respectively. The study by Flores et al. (2016) failed to report the SF12 results obtained by their study. The study by Kayaba et al. (2018) reported the component summaries obtained by their participants, and identified that physical wellbeing (50.7 ± 6.4) was less severely affected than mental wellbeing (44.8 ± 9.6), as measured by the PCS and MCS, respectively.

3.8.2 | WHO questionnaires

The WHOQOL-BREF and WHO-5 were used by Rovere et al. (2008) and Sarkanen, Alakuijala, and Partinen (2016) to assess HRQoL in their studies, respectively. The results obtained by Rovere et al. (2008) identified that Physical Wellbeing was the most affected HRQoL domain (48.93 ± 15.67), followed by Environmental factors (50.16 ± 15.32). Conversely, Social Wellbeing (60.83 ± 17.11) and Psychological Wellbeing (56.04 ± 14.74) were the least affected HRQoL domains in this population. The results obtained from Sarkanen et al. (2016) failed to report baseline values for the WHO-5, only reporting the total scores obtained upon the initial (45.5 ± 24.8) and follow-up visits (48.0 ± 19.3).

3.9 | Quality assessment

Quality assessment of the included studies can be found in Table 3. The appraisal scores for the included studies ranged from 3 to 5, with articles successfully providing sufficient information for a mean of $4 (\pm 0.82)$ of the five domains. Only 12 studies scored the maximal possible score of 5, and 10 scored 4/5. Inclusion criteria were the poorest performing section, with 13 of the 30 articles failing to clearly state the inclusion criteria for their study (Table 3).

4 | DISCUSSION

This was the first systematic review and meta-analyses to comprehensively assess the impact of narcolepsy on HRQoL. This review identified that narcolepsy negatively impacts HRQoL, and that people with narcolepsy report considerably lower quality of life than general populations as well as several other chronic disease populations. Furthermore, the majority of included studies were of

TABLE 3 Quality appraisal using the JBI checklist for analytical cross-sectional studies

Study ID	Inclusion criteria	Subjects and setting	Objective measures disease	Outcomes measures	Statistical analysis
Becker et al. (2004)	Yes	Unclear	Yes	Yes	Yes
Beusterien et al. (1999)	Unclear	Unclear	Yes	Yes	Yes
Bogan et al. (2017)	Yes	Unclear	Yes	Yes	Yes
Campbell et al. (2011)	Unclear	Yes	No	Yes	Yes
Daniels et al. (2001)	Unclear	Yes	Unclear	Yes	Yes
Dauvilliers et al. (2009)	Yes	Yes	Yes	Yes	Yes
Dauvilliers et al. (2011)	Unclear	Yes	Yes	Yes	Yes
Dauvilliers et al. (2017)	Unclear	Yes	Yes	Yes	Yes
Dauvilliers et al. (2019)	Yes	Yes	Yes	Yes	Yes
David et al. (2012)	Unclear	Yes	Yes	Yes	Yes
Dodel et al. (2007)	Unclear	Yes	Yes	Yes	Yes
Droogleever Fortuyn et al. (2012)	Unclear	Unclear	Yes	Yes	Yes
Emsellem et al. (2020)	Yes	Unclear	Yes	Yes	Yes
Ervik et al. (2006)	Yes	Yes	Yes	Yes	Yes
Flores et al. (2016)	Yes	Unclear	No	Yes	Yes
Ingravallo et al. (2008)	No	Unclear	Yes	Yes	Yes
Ingravallo et al. (2012)	Yes	Yes	Yes	Yes	Yes
Kapella et al. (2015)	Unclear	Yes	Unclear	Yes	Yes
Kayaba et al. (2018)	Unclear	Yes	Yes	Yes	Yes
Kovalska et al. (2016)	Yes	Yes	Yes	Yes	Yes
Mitler et al. (2000)	Yes	Unclear	Yes	Yes	Yes
Ozaki et al. (2008)	Yes	Yes	Yes	Yes	Yes
Ozaki et al. (2012)	Yes	Yes	Yes	Yes	Yes
Rovere et al. (2008)	Unclear	Unclear	Yes	Yes	Yes
Sarkanen et al. (2016)	Unclear	Yes	Yes	Yes	Yes
Song et al. (2019)	Yes	Yes	Yes	Yes	Yes
Teixera et al. (2004)	Yes	Yes	Yes	Yes	Yes
Vignatelli et al. (2004)	Yes	Yes	Yes	Yes	Yes
Vignatelli et al. (2011)	Yes	Yes	Yes	Yes	Yes
Weaver & Cuellar (2006)	Yes	Yes	Yes	Yes	Yes

high quality as measured by the JBI Checklist for Analytical Cross-Sectional Studies tool.

The most notably affected HRQoL domain compared with the general population was physical role limitations. However, mental domains were also considerably affected; in particular, social functioning and emotional role limitations. Furthermore, people with narcolepsy reported considerably lower HRQoL in all SF36 domains compared with people with diabetes, epilepsy and hypertension. When compared with multiple sclerosis, with the exception of physical functioning (+34.34), physical role limitations (+13.29) and vitality (+0.11), people with narcolepsy scored lower than in the remaining five SF36 subscales. These comparisons serve to highlight the high symptom burden associated with narcolepsy. The finding that people with narcolepsy report poorer quality of life than people with epilepsy is consistent with the findings of the study conducted by Broughton, Guberman, and Roberts (1984). The comparison

between narcolepsy and epilepsy is particularly notable as both neurological conditions cause individuals to experience episodic attacks and excessive daytime sleepiness to some extent. However, EDS in people with narcolepsy is a consistent feature as part of their underlying condition, whilst EDS in people with epilepsy may be as a result of medications, uncontrolled seizures or a comorbid sleep disorder (Broughton et al., 1984). More appropriate comparisons are limited until similar reviews are conducted in other disorders of hypersomnolence.

This review shows the burden that narcolepsy places on people experiencing this condition. In particular, the MCS scores (42.98) were lower than those of the PCS (45.91), suggesting that narcolepsy has a more significant impact on the mental wellbeing than the physical wellbeing of people with narcolepsy. However, the most affected HRQoL domains primarily related to physical wellbeing, as physical role limitations (45.99) and vitality (42.01), were the most

affected SF36 domains, and activity levels (2.27) were the most affected FOSQ domain. These results highlight that impairment with daily activities, fatigue and reduced energy levels are central to the lived experience associated with narcolepsy. A possible explanation for this finding is the interrelationship between physical performance and mental wellbeing in people with narcolepsy suggested by Morse and Sanjeev (2018), with less physical activity in people with narcolepsy being linked to poorer mood (Bruck, Kennedy, Cooper, & Apel, 2005). This population generally has reduced opportunities to exercise due to time constraints related to sleepiness and social isolation (Kapella et al., 2015), and considerably lower physical activity has been reported in people with narcolepsy compared with the general population (Parmar et al., 2019). A vicious cycle can be established with sedentary behaviour promoting increased sleepiness severity (Golden & Lipford, 2018), and this increased symptom burden further reducing habitual levels of physical activity and HRQoL (Matoulek, Tuka, Fialova, Nevsimalova, & Sonka, 2017). The impact of physical activity levels on physical and mental wellbeing in this population warrants further exploration.

This review identified significant negative correlations between date of publication and the physical functioning ($p = .01$), general health ($p = .01$) and social functioning ($p = .05$) domains of the SF36. This finding may imply that improved treatment options and knowledge about narcolepsy by medical professionals can have positive effects on HRQoL in people with narcolepsy. Similarly, this review identified that older age of symptom onset was negatively associated with physical role limitations, physical functioning and vitality ($p = .01$). In a study by Ingravallo et al. (2012), people with the onset of narcolepsy occurring later in life viewed their health as worse, achieved lower educational levels and experienced more employment problems than those with onset earlier in life. Possible explanations for the relationship between later onset and poorer HRQoL may include reduced habituation to their condition. The effect of ageing on HRQoL, however, remains ambiguous. Increasing age was found to be positively associated with physical functioning, physical role limitations, bodily pain, emotional role limitations ($p = .05$) and social functioning ($p = .01$). However, the findings from studies by Vignatelli et al. (2004) and Vignatelli, Plazzi, Peschechera, Delaj, and D'Alessandro (2011) showed that there was no significant difference in SF36 domain scores, and only slight declines in the component summaries. A possible explanation for the positive correlation associated with age is that as this population ages, they become more accepting of their condition. Further longitudinal research is necessary to evaluate the long-term impact of ageing on HRQoL in this population.

This review highlighted that there was diversity in HRQoL tools utilised, with a total of six tools employed. However, there was some agreement on the tools used to measure HRQoL in people with narcolepsy as over two-thirds of the included studies utilised the SF36 ($n = 22$). Only five studies utilised the FOSQ, a sleep-disorder-specific tool and, of which, four utilised a combination of generic and sleep-disorder-specific tools. Although the SF36 is a comprehensive generic HRQoL tool, it may lack the specificity to assess the subtle aspects

of the HRQoL imposed by narcolepsy. Similarly, although the FOSQ may be a sleep-disorder-specific tool, it is not a narcolepsy-specific tool and similar issues to the SF36 may arise. The study by Beusterien et al. (1999) reported that they utilised supplemental scales in an attempt to assess common issues in narcolepsy, namely measures of overall health perceptions, driving limitations and social support. To the authors' knowledge, this was the only study to incorporate these additional scales to assess HRQoL in people with narcolepsy. This review has identified the considerable need for the development of a psychometrically robust narcolepsy-specific tool to assess HRQoL in this population. The combination of a generic and a condition-specific HRQoL tool is recommended to assess HRQoL in this population, as this would enable comparison with other health conditions, and detection of sleep-disorder-specific HRQoL impairments.

Several limitations pertained to this review. Firstly, this review excluded articles that were not published in English or grey literature due to time constraints. The decision to include the baseline values obtained from randomised control trials may have limited this review, as the obtained sample may not be wholly representative of people with narcolepsy due to the strict inclusion criteria that are often associated with such trials. Additionally, participants would likely have been on different medication regimens and, as a result, the heterogeneity of the overall sample must be considered when interpreting the results of this review. Furthermore, the certainty of participants' diagnosis of narcolepsy must be considered, particularly for earlier studies, as their large and heterogenous samples may have included individuals with similar conditions such as insufficient sleep syndrome or idiopathic hypersomnia. Another potential limitation of this review was the substantial number of included studies that failed to report the PCS and MCS scores for the SF36 ($n = 8$). Although these summary scores could be calculated from the domain scores provided, the standard deviation of these scores could not be calculated and, as a result, standard deviations had to be imputed according to the formula described by Furukawa et al. (2006). Comparable methods were adopted by similar systematic reviews, such as the reviews conducted by Matcham et al. (2014) and Gu et al. (2019). Additionally, both the imputed and non-imputed values of the component summaries were reported to address this limitation. Another possible limitation of this study included the relatively small sample sizes of the chronic conditions used to compare against the SF36 domain scores obtained by people with narcolepsy. Consequently, the results of this comparison must be cautiously interpreted. As the majority of studies ($n = 26$) did not provide subgroup results, the comparison between type 1 and type 2 narcolepsy was unable to be made. Similarly, the relationship between employment status and HRQoL could not be explored as the nine studies that reported employment status used different tools. Strengths of this review include that PRISMA guidelines were closely followed to ensure that our search strategy captured the complete and relevant published literature. Furthermore, studies were evaluated using a

standardised measure, and included studies were generally high quality as measured by the JBI tool.

5 | CONCLUSION

This is the first review that has attempted to systematically assess the impact of narcolepsy on HRQoL. HRQoL is an important endpoint in narcolepsy research. Given the reduced HRQoL in people with narcolepsy, its measurement can aid the assessment of treatment response, and can help guide the allocation of resources within the clinical setting. The results of this review demonstrated that people with narcolepsy experience substantial impairment of their mental and physical wellbeing compared with general populations as well as other chronic disease populations, but a more consistent approach is needed to explore the effect of narcolepsy on HRQoL. The possible usefulness of a validated, patient-reported measure specific for narcolepsy and its symptoms should be evaluated to measure the true impact of this disease. Future research should explore the effects of ageing on HRQoL in people with narcolepsy, HRQoL differences in NT1 and NT2, predictors of HRQoL, and the potential role of physical activity as well as other non-pharmacological strategies to improve mental and physical wellbeing in this population.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

Ragy Tadrous: Protocol development, screening, data extraction, risk of bias assessment, data analysis and write up. Deirdre O'Rourke: Reviewing and editing completed manuscript. David Mockler: Creation of search strategy for database searching. Julie Broderick: Protocol development, screening, risk of bias assessment, reviewing and editing the completed manuscript.

ORCID

Ragy Tadrous  <https://orcid.org/0000-0001-9976-8834>

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