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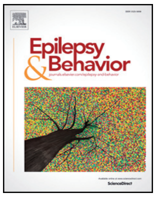

Health utilities and quality of life in individuals with tuberous sclerosis complex (TSC) who experience epileptic seizures: A web-based survey

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ABSTRACT

Objectives: Individuals with tuberous sclerosis complex (TSC) experience a wide range of health impacts, including epileptic seizures, negatively impacting their health-related quality of life (HRQoL). Health state utility values (HSUVs) are index values representing HRQoL and are used as key inputs for health economic analyses. Such data are currently very limited in the TSC population. The objective of this study was to generate HSUVs for TSC health states, defined by the number and type of seizures experienced in the previous week, and to compare with UK normative values.

Methods: This cross-sectional study involved 186 participants (individuals with TSC = 61, caregivers reporting for individuals with TSC = 125) from Europe and North America who completed a web-based survey. Participants completed the [EuroQol - 5 dimensions - 3 levels] (self-report version for individuals with TSC or proxy version 1 for caregivers).

Results: The mean age of individuals with TSC was 27.3 years (self-reported: 41.3 years, caregiver-reported: 20.5 years); 56% were males. Most individuals with TSC (71%) reported experiencing between one and ten seizures in the week prior to participating in the study. The most frequently reported type of seizure was *focal: simple partial* (50%). Across all participants (combined self-report and caregiver-report), the mean HSUV was 0.474 (95% confidence interval [CI]: 0.424–0.524), significantly lower than the UK norm (0.856, 95%CI: 0.848–0.864) [1]. Mean HSUV and HRQoL scores were consistently lower when reported by caregivers than when self-reported by individuals with TSC (HSUV = 0.351 vs. 0.727). This is in part because caregivers reported for individuals with TSC who experienced more frequent and severe seizures than those who were able to self-report. HSUVs incrementally decreased with the experience of more frequent (1–5 per week: HSUV = 0.666 vs. >20: HSUV = 0.290) and more severe seizures (focal: simple partial: HSUV = 0.450 vs. generalized: convulsive: HSUV = 0.194).

Conclusions: The HRQoL and HSUV index scores indicate substantial impairment among individuals with TSC; HSUVs were shown to decrease considerably with increases in seizure frequency or seizure severity, indicating that more burdensome seizure health states are associated with poorer HRQoL.

1. Introduction

Tuberous Sclerosis Complex (TSC) is a rare genetic condition characterized by the growth of benign tumors in various organs of the body [1]; TSC occurs in between 1 in 5000 and 1 in 10,000 live births [2–6]. No single feature of TSC is considered definitively diagnostic [7], indeed individuals with TSC experience a wide range of health impacts that include epileptic seizures, learning difficulties, and behavioral problems [8]. The majority of TSC cases are diagnosed during childhood [9].

Epileptic seizures occur in 85% of patients with TSC [10] and are considered one of the most impactful symptoms on the health-related quality of life (HRQoL) of individuals with TSC [11]. Furthermore, incidents of epileptic seizures are likely to contribute to developmental delay among individuals with TSC [12]. A higher burden of TSC-associated epilepsy is

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associated with refractory seizures and a subsequent impairment in HRQoL for these individuals with TSC [13].

Given the negative impact on HRQoL in this patient population, it is important to quantify the impact of seizures in individuals with TSC to demonstrate the potential benefit of treatment, especially if there is a reduction in seizure intensity and frequency. HRQoL can be represented through the measurement of health state utility values (HSUVs). A HSUV is a single score that is generated as an estimate of the preference for a given health state where a value of 1.0 represents full health, 0.0 represents death, and negative values represent states worse than death [14,15]. HSUVs represent key inputs for health economic models to support pharmaceutical product launch and reimbursement [16].

The HRQoL among individuals with TSC is substantially lower than that of the general population [17]. Similarly, in general populations with epilepsy, seizures of moderate severity and treatment-related side effects of moderate severity are associated with low utility values (range: 0.48 to 0.96), and reflect the factors associated with impairment in HRQoL for these individuals with TSC [13].

There is however a paucity of literature detailing the HSUVs for individuals with TSC. The primary objective of this study was to establish HSUVs for individuals with TSC, using health states defined by the frequency and severity of seizures experienced.

2. Material and methods

2.1. Study design and participant recruitment

The study design was noninterventional and cross-sectional, involving completion of a web-based survey by individuals with TSC who had experienced at least one seizure in the previous six months and/or caregivers of individuals with TSC who had experienced at least one seizure in the previous six months.

Participants were recruited from the United Kingdom, Canada, and mainland Europe through patient advocacy and support groups. Given the geographical spread of participants, ethical approval was sought and obtained from two centralized Independent Review Boards (Copernicus Group IRB: ADE1-17-328 and Freiburger Ethik-Kommission International [FEKI]: 017/1959).

The web-based survey was shared with members of advocacy groups operating in each of the three regions (UK: Tuberous Sclerosis Association [TSA], Canada: Tuberous Sclerosis Canada Sclérose Tubéreuse [TSCST], Europe: European Tuberous Sclerosis Association [ETSC]). All advocacy groups shared an electronic link to the survey with its members through social media and, in some cases, via mailshot or on the group webpage. The survey was also shared with members of the UK TSA via leaflets distributed at an event organized by the advocacy group.

The survey was made available in English, French, and German. Participants were required to provide an answer to all items to submit the survey; missing data were therefore not possible.

Although the aim of the study was to generate HSUVs for individuals with TSC, it was recognized that around 45–75% of individuals with TSC typically have cognitive impairments [8]. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Practices Task Force (2013) recommends that for the assessment of children and adolescents “informant-reported outcome measures may be necessary when children are not able to complete patient-reported outcome (PRO) measures reliably on their own because of their developmental stage, illness severity, language ability, or cognitive functioning” [18]. Caregivers were therefore given the opportunity to complete the survey either alongside, or instead of, self-reporting by individuals with TSC.

The web-based survey encompassed three separate surveys, designed to be completed by each of the following types of participant or participants:

- Caregiver or parent of an individual with TSC who is aged 2 to 65 years old (caregiver-reported);
- Individual with TSC who is 18 to 65 years old self-completing the survey (self-reported);
- Individual with TSC aged 12 to 65 years old alongside their caregiver or parent (demographic and clinical information of individual with TSC reported by both participants in combination, health status questionnaire completed separately by each participant).

The seizure experience of individuals with TSC was reported by survey participants. Participants were provided with descriptions of each seizure type. Next to each description participants were asked to report whether the individual with TSC had experienced that seizure type in the previous week. Participants were also asked to report the number of times the individual with TSC had experienced a seizure of any type in the previous week.

2.2. Health status questionnaire

An electronic version of the EQ-5D-3L was completed at one timepoint. Although a five level version of the EQ-5D has been developed (EQ-5D-5L), the National Institute of Health and Care Excellence (NICE) recommends that the EQ-5D-3L should be used for reference–case analyses [19]. The EQ-5D-3L is a widely used generic measure of health status with two components: the EQ-5D descriptive system and the EQ-5D Visual Analog Scale (VAS). The descriptive system includes five questions relating to five dimensions of health status (Mobility, Self-care, Usual activities, Pain/discomfort, Anxiety/depression) [20,21]. For each dimension, respondents are asked to indicate which of the three health state levels best describes their current health state. For all dimensions, Level 1 represents the least impairment (or no problems), Level 2 refers to some problems, and Level 3 represents most impairment (or extreme problems). HSUVs are derived by applying weights (defined by country-specific value sets) to the levels endorsed for each of the five dimensions. These scores are then combined to produce a single summary score. The HSUVs presented as part of this study were derived using the UK value set developed using the time trade-off (TTO) technique [21].

The EQ-5D-3L also includes a VAS that asks respondents to rate their self-perceived general health on a scale from 0 (Worst imaginable health state) to 100 (Best imaginable health state) [20].

Caregivers completed the EQ-5D-3L proxy version 1 on behalf of the individual they cared for; individuals with TSC who could self-report completed the EQ-5D-3L themselves.

2.3. Procedures

The link for the web-based survey remained active for 21 weeks from August 2017 to January 2018. Until December 2017 the survey was shared only via the UK-based patient advocacy group. Because of the lower-than-expected recruitment from the UK advocacy group, recruitment was expanded to other geographical regions. From December 2017 to January 2018, the survey was also shared via the Canada-based TSC advocacy group (TS Canada ST) and the Europe-based ETSC.

2.4. Data analysis

Descriptive and summary statistics were calculated for the demographic and clinical characteristics of the participant sample, and the index and dimension scores for each version of the EQ-5D-3L (proxy and self-report). The Minimal Clinically Important Difference (MCID) refers to “*the difference in change scores between two treatment groups, or the change score within one treatment group, that can be considered clinically important*” [22]. Currently, no TSC-specific MCID scores are available to allow interpretation of differences in mean EQ-5D-3L utility and VAS scores. However, there are values for populations with chronic epilepsy that have been used to allow comparison between the current study sample and published values: a difference of 0.06 in utility values or 10 points for VAS scores is considered to be clinically meaningful [23]. The MCID scores for a population with epilepsy were considered suitable for comparisons in this population with TSC because the epileptic seizures experienced by many individuals with TSC were the main focus of this study. Scores were also compared to EQ-5D-3L UK normative scores.

Where estimates of mean HSUVs and VAS scores are reported, 95% confidence intervals [CIs] are presented; *t*-tests ($p < 0.05$) are used to compare the significance of mean differences between groups.

3. Results

3.1. Survey completion

The web-based survey was completed by 186 participants, of which, 61 responses were self-reported (32.8%), and 125 were caregiver-reported for individuals with TSC (67.2%). No participants completed the survey as a dyad (i.e., individual with TSC aged 12 to 65 years old alongside their caregiver or parent). The survey was completed in 10 minutes or less by 126 participants (67.7%).

3.2. Participant information

The sample included a slightly higher number of males (n = 104, 55.9%) than females (n = 82, 44.1%) (Table 1). The mean age of the total sample was 27.3 years, with a higher mean age reported by self-reported participants (41.3 years, standard deviation [SD] = 7.5) than among caregiver-reported participants (20.5 years, SD = 18.3). Participants in the sample represented a wide range of levels of educational attainment and work status.

The clinical characteristics of individuals with TSC are presented in Table 2. Twenty-one individuals with TSC (n = 21, 11.3%) reported that they had not experienced a seizure in the past week and were reported as seizure-free. The largest proportion of individuals with TSC (n = 81, 43.5%) experienced between one and five seizures in the previous week. The most commonly experienced type of seizure was “focal: simple partial” (n = 92, 49.5%), followed by “focal: simple complex” (n = 83, 44.6%) and “secondary generalized: convulsive” (n = 43, 23.1%). Over half of the individuals with TSC who could self-report (n = 36, 59.0%) took no antiepileptic drugs (AEDs) in the past week, whereas all but one individual with TSC in the caregiver-reported group had taken at least one AED in the past week.

Table 1
Demographic characteristics of individuals with TSC (n = 186).

Characteristic	Self-reported individuals with TSC (N = 61) n (%)	Individuals with TSC reported by caregivers (N = 125) n (%)	All individuals with TSC (N = 186) n (%)
Gender			
Female	12 (19.7%)	70 (56.0%)	**82 (44.1%)**
Male	49 (80.3%)	55 (44.0%)	**104 (55.9%)**
Age group			
2–5	–	33 (26.4%)	**33 (17.7%)**
6–11	–	27 (21.6%)	**27 (14.5%)**
12–17	–	10 (8.0%)	**10 (5.4%)**
18–29	2 (3.3%)	20 (16.0%)	**22 (11.8%)**
30–39	26 (42.6%)	8 (6.4%)	**34 (18.3%)**
40–49	24 (39.3%)	12 (9.6%)	**36 (19.4%)**
50–65	9 (14.8%)	15 (12.0%)	**24 (12.9%)**
Age			
Mean (SD)	41.3 (7.5)	20.5 (18.3)	**27.3 (18.4)**
Minimum–Maximum	23–55	2–58	**2–58**
Highest level of education attained			
Too young for school	0	27 (21.6%)	**27 (14.5%)**
Primary education	1 (1.6%)	34 (27.2%)	**35 (18.8%)**
Some years of secondary school/high school	11 (18.0%)	13 (10.4%)	**24 (12.9%)**
Some years of university/college	18 (29.5%)	11 (8.8%)	**29 (15.6%)**
Certificate program	2 (3.3%)	5 (4.0%)	**7 (3.8%)**
University/college degree	13 (21.3%)	3 (2.4%)	**16 (8.6%)**
Graduate or professional degree	15 (24.6%)	5 (4.0%)	**20 (10.8%)**
Other	1 (1.6%)	27 (21.6%)	**28 (15.1%)**
Work status			
Working full time	8 (13.1%)	3 (2.4%)	**11 (5.9%)**
Working part time	20 (32.8%)	2 (1.6%)	**22 (11.8%)**
Looking for work/not working	22 (36.1%)	0	**22 (11.8%)**
Full-time homemaker	3 (4.9%)	4 (3.2%)	**7 (3.8%)**
Student	2 (3.3%)	22 (17.6%)	**24 (12.9%)**
Not working due to medical reasons	6 (9.8%)	37 (29.6%)	**43 (23.1%)**
Too young to work	0	51 (40.8%)	**51 (27.4%)**
Retired	0	1 (0.8%)	**1 (0.5%)**
Other	0	5 (4.0%)	**5 (2.7%)**
Country			
England	30 (49.2%)	66 (52.8%)	**96 (51.6%)**
Germany	2 (3.3%)	22 (17.6%)	**24 (12.9%)**
United States	9 (14.8%)	3 (2.4%)	**12 (6.5%)**
Scotland	4 (6.6%)	7 (5.6%)	**11 (5.9%)**
Netherlands	4 (6.6%)	5 (4.0%)	**9 (4.8%)**
Sweden	3 (4.9%)	5 (4.0%)	**8 (4.3%)**
Wales	3 (4.9%)	3 (2.4%)	**6 (3.2%)**
Canada	1 (1.6%)	5 (4.0%)	**6 (3.2%)**
Belgium	1 (1.6%)	2 (1.6%)	**3 (1.6%)**
Northern Ireland	1 (1.6%)	2 (1.6%)	**3 (1.6%)**
Spain	2 (3.3%)	0	**2 (1.1%)**
Other European countries	1 (1.6%)	5 (4.0%)	**6 (3.2%)**

Table 2
Clinical characteristics of individuals with TSC (n = 186).

Characteristic	Self-reported individuals with TSC (N = 61) n (%)	Individuals with TSC reported by caregivers (N = 125) n (%)	All individuals with TSC (N = 186) n (%)
Seizure frequency in the previous week			
Seizure-free in the previous week	1 (1.6%)	20 (16.0%)	**21 (11.3%)**
1–5 per week	58 (95.1%)	23 (18.4%)	**81 (43.5%)**
5–10 per week	2 (3.3%)	49 (39.2%)	**51 (27.4%)**
11–20 per week	0	15 (12.0%)	**15 (8.1%)**
More than 20 per week	0	18 (14.4%)	**18 (9.7%)**
Seizure types experienced in the previous week			
Focal: simple partial	39 (63.9%)	53 (42.4%)	**92 (49.5%)**
Generalized: absence	1 (1.6%)	35 (28.0%)	**36 (19.4%)**
Focal: complex partial	30 (49.2%)	53 (42.4%)	**83 (44.6%)**
Secondarily generalized: convulsive	5 (8.2%)	38 (30.4%)	**43 (23.1%)**
Generalized: convulsive	4 (6.6%)	36 (28.8%)	**40 (21.5%)**
Other (including infantile spasms)	1 (1.6%)	17 (13.6%)	**18 (9.7%)**
Number of antiepileptic drugs (AEDs) taken in the previous week			
None	36 (59.0%)	1 (0.8%)	**37 (19.9%)**
One	11 (18.0%)	30 (24.0%)	**41 (22.0%)**
Two	12 (19.7%)	53 (42.4%)	**65 (34.9%)**
Three	1 (1.6%)	32 (25.6%)	**33 (17.7%)**
Four	1 (1.6%)	7 (5.6%)	**8 (4.3%)**
Five	0	1 (0.8%)	**1 (0.5%)**
Six	0	1 (0.8%)	**1 (0.5%)**

3.3. EQ-5D-3L dimension response distribution

Fig. 1 presents the response distribution for each EQ-5D-3L dimension for all participants.

3.4. EQ-5D-3L dimension and HSUVs

3.4.1. Overview of EQ-5D-3L dimension and HSUVs

Mean dimension scores of the EQ-5D-3L are presented in Fig. 2. The Pain/discomfort dimension was the only domain for which mean caregiver-reported scores were lower than mean self-reported scores. Caregiver-reported scores on the Self-care and Usual activities domains were significantly higher ($p < 0.0001$) than the equivalent self-reported scores for these dimensions.

EQ-5D-3L HSUVs are presented in Table 3 for caregiver participants, self-reported participants, and across all participants. The mean HSUV was significantly higher (indicating better health) in the group of individuals who self-reported than in the group with caregiver-reported scores (0.727 vs. 0.351, $p < 0.0001$).

3.4.2. HSUVs compared across groups defined by the frequency and type of seizures experienced

Mean EQ-5D-3L HSUVs were significantly lower ($p < 0.0001$) (indicating poorer health status) among those who experienced 5–10 seizures in the previous week (0.250) in comparison with those who experienced 1–4 seizures per week (0.666, $p < 0.0001$) and those who were seizure-free (0.582, $p = 0.0010$) (Fig. 3). Participants who experienced either 11–20 or more than 20 seizures in the previous week did not report lower HRQoL than those who experienced 5–10 seizures per week.

The seizure type considered least severe ("focal: simple partial") was associated with a higher HSUV (0.450) than the seizure type considered the most severe ("generalized: convulsive": 0.194) (indicating worse health status) (Fig. 4). The HSUVs among those who experienced generalized seizures ("generalized: absence": 0.297, "secondarily generalized: convulsive": 0.225, and "generalized: convulsive": 0.194) were observed to be consistently lower than among those who experienced focal seizures ("focal: simple partial": 0.450 and "focal: complex partial": 0.454). Of note, the seizure type categories were not mutually exclusive and individuals with TSC who experienced more than one seizure type in the past week were included in more than one category. (See Figs. 3 and 4.)

Each participant was asked to report which types of seizure they had experienced in the previous week and how many times they had experienced each type in that week.

Fig. 5 presents individual reports of seizure types, plotted against the frequency with which the seizure type was experienced by the

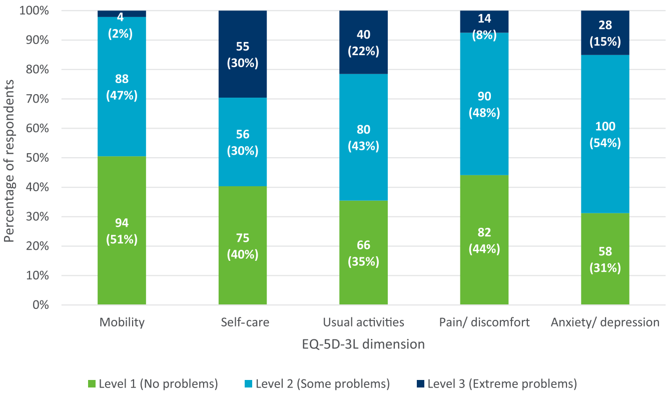


Fig. 1. EQ-5D-3L response distribution (all participants N = 186).

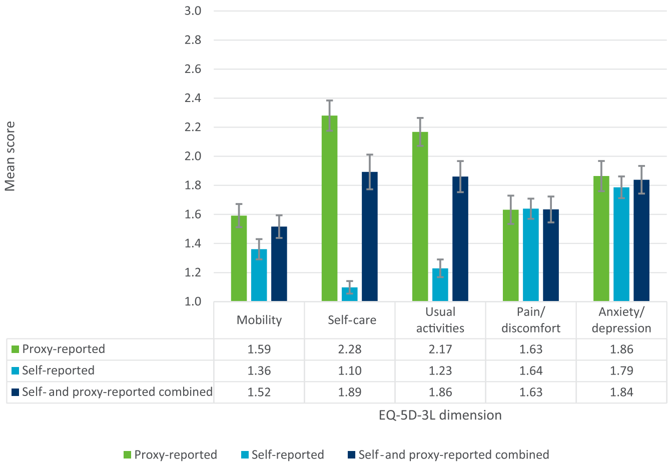


Fig. 2. Mean EQ-5D-3L dimension scores (N = 186).

Table 3
Summary of HSUVs generated using EQ-5D-3L.

EQ-5D-3L version	N	HSUV				
		Mean	SD	Median	Min, Max	95%CI
Combined self-reported and caregiver-reported results (N = 186)	186	0.474	0.348	0.603	−0.429, 1.000	0.424–0.524
EQ-5D-3L self-report (N = 61)	61	0.727	0.13	0.727	0.291, 1.000	0.695–0.759
EQ-5D-3L proxy (version 1) (N = 125)	125	0.351	0.35	0.274	−0.429, 1.000	0.289–0.413

participant in the past week, and the HSUV reported for that participant. Data points on the figure represent each participant report of each seizure type; therefore, participants reported to have experienced *x* seizure types are represented by *x* data points. Individual participants may be represented by more than one data point, depending on the number of types of seizure experienced in the previous week. For each seizure type data points have been spread arbitrarily along the *x* axis in order to reduce overlap.

The figure makes clear that seizures experienced at a greater frequency are associated with lower HSUVs. Furthermore, more severe seizures — particularly "generalized: convulsive" — were associated with lower HSUVs.

3.5. EQ-5D-3L quality-of-life (VAS) scores

As shown in Table 4, mean VAS score was lower when reported by caregivers than when self-reported (63.40 versus 78.54, $p < 0.0001$) (again, indicating worse health when caregiver-reported). The mean VAS score was 68.37 when caregiver and self-reported participants were combined.

The VAS scores were compared across groups defined by seizure frequency (Fig. 6) and seizure severity (Fig. 7) experienced in the previous week. With the exception of the "11–20 per week" category, the mean VAS score was shown to decrease gradually, indicating poorer quality of life with increasing seizure frequency. The mean VAS score was higher among those who experienced both types of focal seizure than among those who experienced all three types of generalized seizure.

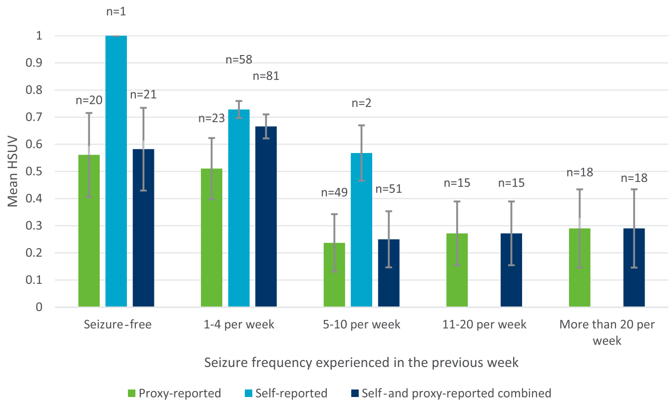
4. Discussion

This study strengthens limited existing evidence relating to the profound effect of TSC on HRQoL [19], in particular, the HSUVs of individuals with TSC associated with seizures, where currently no published data are available. The HSUVs and VAS scores were observed to follow largely similar trends: that as seizure frequency and/or severity increase, quality of life decreases. This demonstrates the potential benefit to individuals with TSC of a reduction in seizure intensity and frequency that may be associated with treatment.

The HSUVs for individuals with TSC (self-reported and caregiver-reported combined) who had experienced a seizure in the previous six months (HSUV = 0.474, 95%CI: 0.424–0.524) were significantly lower ($p < 0.0001$) than the general population reference value for the UK value set of the EQ-5D-3L (HSUV = 0.856, 95%CI: 0.848–0.864) [24]. This is indicative of severe impairment in individuals with TSC. The HSUVs obtained as part of this survey are comparable to EQ-5D utility scores obtained by face-to-face interviews in a Korean population with epilepsy, who reported mean scores of 0.303 for those showing <50% reduction in seizures, 0.493 for those showing >50% reduction in seizures, and 0.899 for those in a seizure-free state [25]. However, comparisons with this population should be treated with caution because utility scores in the Korean study were derived using a Korean value set; the reference EQ-5D-3L utility score for Korea is higher than the UK, at 0.915 versus 0.856 in UK [24]. It should also be noted that seizure-free participants in the Korean study cannot be directly compared with participants categorized as "seizure-free" in the web-based survey because those in the web-based survey must have experienced at least one seizure in the previous six months.

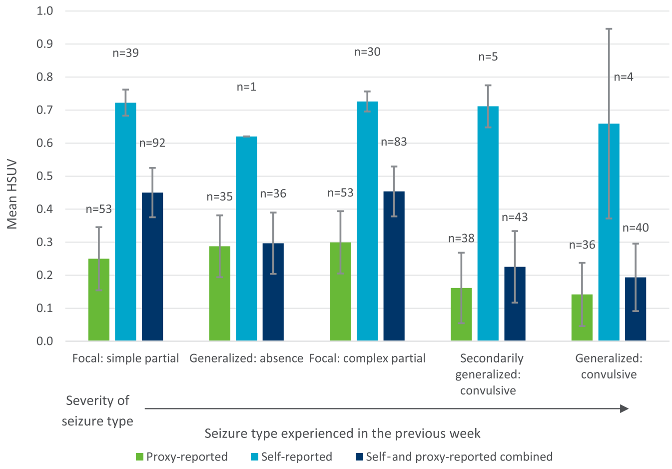
The mean VAS score for all individuals with TSC in the sample was also substantially lower than the UK population reference scores (68.3 versus 82.8) [26]. The VAS score among those who were seizure-free in the previous week (77.9) was similar to the UK population reference values with no clinically meaningful difference between the two mean scores.

Results from the study revealed that individuals with TSC who were seizure-free in the previous week had significantly higher HRQoL (n = 21, HSUV = 0.582, VAS = 77.86) than those who experienced more than 20 seizures per week (n = 18, HSUV =



Error bars represent 95% confidence intervals
Data is presented in supplementary data tables (Table 5)

Fig. 3. HSUVs by groups defined by seizure frequency experienced in the previous week.



Error bars represent 95% confidence intervals
Participants could select any number of seizure types
Data is presented in supplementary data tables (Table 5)

Fig. 4. HSUVs by groups defined by seizure types experienced in the previous week

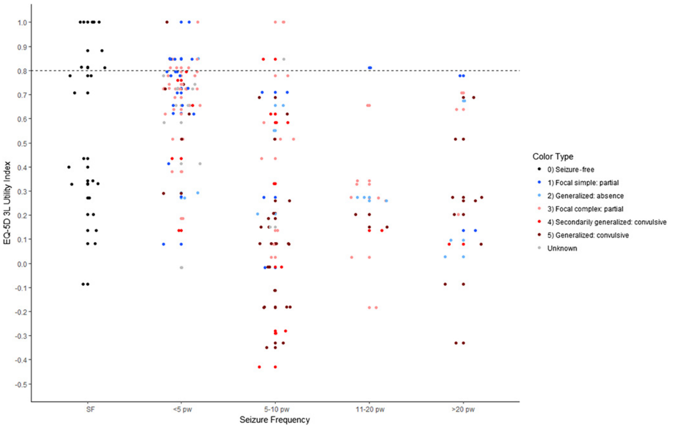
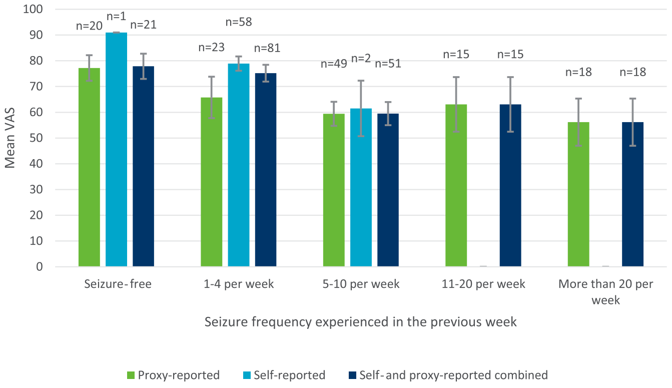


Fig. 5. Seizure type events plotted by the frequency with which they were experienced in the previous week, and by the HSUV reported for that participant.



Error bars represent 95% confidence intervals
Data is presented in supplementary data tables (Table 6)

Fig. 6. Mean VAS scores by seizure frequency in the previous week.

0.290, VAS = 56.17) ($p < 0.01$). The association between seizure frequency and HRQoL observed in this study reflects results published in populations with epilepsy where the majority of articles describe lower HRQoL with increasing seizure frequency [27–30]. Of note, HRQoL among those who experienced 1–4 seizures per week (n = 81, HSUV = 0.666, VAS = 75.19) was shown to be comparable with that of those who were seizure-free (n = 21, HSUV = 0.582, VAS = 77.86), and significantly higher than that of those who experienced 5–10 seizures ($p < 0.0001$). In consideration of this finding, achieving fewer than five seizures in a week may represent a treatment goal for individuals with TSC with seizures.

The HRQoL of individuals with TSC was also compared across groups defined by the experience of different seizure types. For the sake of interpreting these data, seizure types were ordered by the severity of symptoms experienced: Focal: simple partial, Generalized: absence, Focal: complex partial, Secondarily generalized: convulsive, Generalized: convulsive. However, it should be considered that the experience of seizure severity varies between individuals and that experiencing seizure types considered to be less severe can often be associated with severe impacts. It should also be noted that seizure type was self-reported by individuals with TSC/caregivers based on descriptions provided to participants, so these categorizations may not necessarily be reflective of the categorizations that would have been selected by a clinician.

Individuals with TSC who reported experiencing the least severe type of seizures ("focal: simple partial") had higher quality of life (n = 92, HSUV = 0.450, VAS = 68.9) than individuals with TSC who reported experiencing the most severe type of seizures ("generalized: convulsive": n = 40, HSUV = 0.194, VAS = 58.28) ($p < 0.0002$). A notable result was that "generalized absence" seizures were associated with similar HRQoL to other more severe types of generalized seizure ("secondarily generalized: convulsive" and "generalized convulsive"). This is contrary to expectations that "generalized: absence" seizures — a form of seizure most prominently experienced by children, characterized by comparatively mild symptoms, rapid recovery, and little postictal change [31,32] — would have a limited impact on HRQoL. This result can in part be explained because participants who experienced "generalized: absence" seizures were more likely to report having experienced a high frequency of seizures (33.3% "More than 20 per week" and 16.7% "11–20 seizures per week") than participants who had not experienced a "generalized: convulsive" seizure (4.0% "More than 20 per week" and 4.7% "11–20 seizures per week").

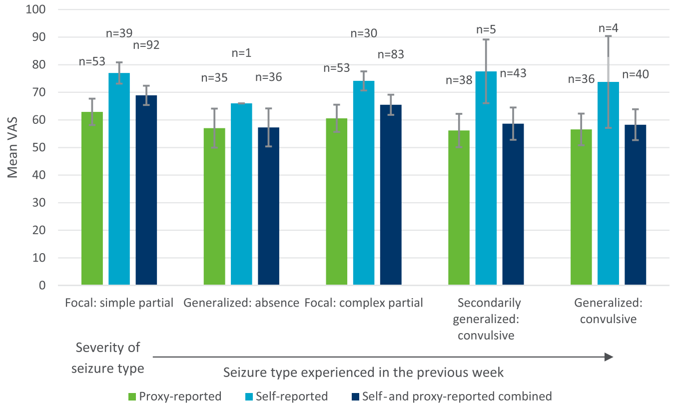
As with seizure frequency, evidence available in the literature regarding the effect of seizure type on HRQoL is not available in the population with TSC and limited in the population with epilepsy. Baker, Gagnon, and McNulty reported that seizure type was a significant predictor of HRQoL [29].

In this survey, self-reported values generated from the EQ-5D (HSUVs and VAS scores) from individuals with TSC were higher than caregiver-reported values. The difference in score between mean caregiver-reported scores and mean self-reported scores on both the utility index and VAS exceeded the threshold for being considered clinically meaningful [24]. The difference observed between self and caregiver-reported groups may be because those participants capable of completing the survey themselves were less likely to experience severe impairment compared with those who required a caregiver for the completion of the survey, though further evidence is necessary to support this. It should also be noted that there were differences in the seizure experience between self-reported and caregiver-reported groups (i.e., individuals who self-reported generally experienced less severe and fewer seizures in the past week). The vast majority of self-reported participants (96.7%) reported experiencing between one and five seizures in the previous week (including those who were seizure-free), while only 34.4% of caregiver-reported patients reported experiencing the same seizure frequency. Additionally, self-reported participants were four times less likely (n = 4, 6.6%) to have reported experiencing the most severe seizure type ("generalized: convulsive") than caregiver-reported participants (n = 36, 28.8%).

When interpreting the results of this study, certain limitations need to be taken into account including that TSC diagnosis was not made by a clinician. Instead, participants were asked to confirm that they had a diagnosis of TSC, and to confirm that they had experienced

Table 4
EQ-5D-3L VAS scores across groups defined by participant type and by seizure-related health states.

Seizure frequency	N	Mean	SD	Median	Min, Max	95%CI
Participant type						
Combined self-reported and caregiver-reported (N = 186)	186	68.37	17.95	72.50	10, 100	65.8–70.9
EQ-5D-3L self-reported (N = 61)	61	78.54	11.12	78.00	40, 98	75.7–81.3
EQ-5D-3L proxy (version 1) (N = 125)	125	63.40	18.58	63.00	10, 100	60.1–66.7



Error bars represent 95% confidence intervals
Data is provided in supplementary data tables (Table 6)
Participants could select any number of seizure types

Fig. 7. Mean VAS score by type of seizures experienced in the previous week.

a seizure in the previous six months; survey uptake by ineligible participants (i.e., without TSC diagnosis) was minimized by reducing survey visibility among individuals without an association to TSC. This was done by only sharing the survey among groups of individuals with TSC and caregivers (i.e., patient advocacy group social media pages and email mailing lists).

As part of the survey, participants were asked to report on their experience of different types of seizure in the previous week. In order to do this, participants were required to discriminate between different seizure types. Although the web-based survey provided definitions of each type of seizure that could be experienced by individuals with TSC, it is likely that some individuals with TSC and caregivers might have been unfamiliar with or not had a full understanding of the different types of epileptic seizures. If participants inaccurately reported on the types of seizures experienced, this would have introduced a level of measurement error.

Given the high level of cognitive impairment present in the patient population with TSC, it is likely that completion of the survey would have been challenging for a number of individuals with TSC [14]. This limitation was mitigated by allowing a caregiver to complete the proxy version of the EQ-5D-3L.

In addition, the survey was only shared in Europe and Canada, and was only made available in the following languages: English (UK), French (France and Canada), and German. Because of recruitment via a web-based survey, no quotas were used during recruitment. These factors may have affected the representativeness/generalizability of the sample population in comparison with that of the patient population with TSC of the participating countries.

5. Conclusions

This study provides estimates of HSUVs for health states defined by seizure frequency and seizure type among individuals with TSC. These are the first HSUVs to be published in this rare disease population. Participants had significantly lower HSUVs that the UK general population reflecting the considerable impairments experienced by individuals with TSC. Reported seizure type and frequency were shown to have an impact on both HRQoL and HSUVs. Features associated with lower quality of life include experiencing generalized rather than focal seizures and experiencing more than five seizures in the previous week versus fewer than five seizures. The results from this survey support the suggestion that besides aiming to abolish seizures, goals in treatment of TSC should include reducing the number of seizures to fewer than five per week and abolishing generalized forms of seizure.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2018.11.021.

References

[1] Inoki K, Guan K-L. Tuberous sclerosis complex, implication from a rare genetic disease to common cancer treatment. Hum Mol Genet 2009;18(R1):R94-100.
[2] Curatolo P, Bonbardieri R, Jozwiak S. Tuberous sclerosis. Lancet 2008;23(372(9639)):657–68.
[3] Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. Ann N Y Acad Sci 1991;615(1):125–7.
[4] Hallett L, Foster T, Liu Z, Blieden M, Valentim J. Burden of disease and unmet needs in tuberous sclerosis complex with neurological manifestations: systematic review. Curr Med Res Opin 2011;27(8):1571–83.
[5] O'Callaghan FJ, Shiell AW, Osborne JP, Martyn CN. Prevalence of tuberous sclerosis estimated by capture–recapture analysis. Lancet 1998;351(9114):1490.
[6] Hong CH, Tu HP, Lin JR, Lee CH. An estimation of the incidence of tuberous sclerosis complex in a nationwide retrospective cohort study (1997–2010). Br J Dermatol 2016;174(6):1282–9.
[7] Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med 2006;355(13):1345–56.
[8] Prather P, de Vries PJ. Behavioral and cognitive aspects of tuberous sclerosis complex. J Child Neurol 2004;19(9):666–74.
[9] Staley BA, Vail EA, Thiele EA. Tuberous sclerosis complex: diagnostic challenges, presenting symptoms, and commonly missed signs. Pediatrics 2010;127(1):e117–25.
[10] Chu-Shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia 2010;51(7):1236–41.
[11] Roth J, Olasunkanmi A, MacAllister WS, Weil E, Uy CC, Devinsky O, et al. Quality of life following epilepsy surgery for children with tuberous sclerosis complex. Epilepsy Behav 2011;20(3):561–5.
[12] Weiner HL, Carlson C, Ridgway EB, Zaroff CM, Miles D, LaJoie J, et al. Epilepsy surgery in young children with tuberous sclerosis: results of a novel approach. Pediatrics 2006;117(5):1494–502.
[13] Patel A, Watchko S, Nellesen D, Herbst F, Neary M. The natural history and burden of illness of epilepsy in tuberous sclerosis complex (TSC): a systematic literature review. Eur J Paediatr Neurol 2017;21:e186–7.
[14] Torrance GW. Measurement of health state utilities for economic appraisal: a review. J Health Econ 1986;5(1):1–30.
[15] Bansback N, Harrison M, Brazier J, Davies L, Kopec J, Marra C, et al. Health state utility values: a description of their development and application for rheumatic diseases. Arthritis Care Res 2008;59(7):1018–26.
[16] Brazier J, Deverill M, Green C. A review of the use of health status measures in economic evaluation. J Health Serv Res Policy 1999;4(3):174–84.
[17] Amin S, Mallick AA, Lux A, O'Callaghan F. Quality of life in patients with Tuberous Sclerosis Complex (TSC). Eur J Paediatr Neurol 2017;21:E4–6.
[18] Matza LS, Patrick DL, Riley AW, Alexander JJ, Rajmil L, Pleil AM, et al. Pediatric patient-reported outcome instruments for research to support medical product labeling: report of the ISPOR PRO good research practices for the assessment of children and adolescents task force. Value Health 2013;16(4):461–79.

[19] National Institute for Health and Care Excellence. Position statement on use of the EQ-5D-5L valuation set; 2017.
[20] van Reenen M, Oppe M. EQ-5D-3L user guide: basic information on how to use the EQ-5D-3L instrument version 5.1 [Internet]. Rotterdam: EuroQol Research Foundation; 2015 [cited 2016 January 16].
[21] Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35(11): 1095–108.
[22] Zou KH, Cappelleri JC, Bushmakin AG, Alvir JMJ, Alemayehu D, Symonds T. Patient-reported outcomes: measurement, implementation and interpretation. Chapman and Hall/CRC; 2013.
[23] Langfitt J, Vickrey B, McDermott M, Messing S, Berg AT, Spencer SS, et al. Validity and responsiveness of generic preference-based HRQOL instruments in chronic epilepsy. Qual Life Res 2006;15(5):899–914.
[24] Szende A, Janssen B, Cabases J. Self-reported population health: an international perspective based on EQ-5D. Springer; 2014.
[25] Kang H-J, Kang E, Jo M-W, Park E-J, Yoon S, Lee E-K. The utility score of epilepsy with partial seizure measured by TTO, VAS, and EQ-5D in the general Korean population. Epilepsy Res 2014;108(5):963–71.
[26] Janssen B, Szende A. Population norms for the EQ-5D. Self-reported population health: an international perspective based on EQ-5D. Springer; 2014. p. 19–30.
[27] Jacoby A, Baker G, Buck D. Quality of life of people with epilepsy: a European study. Epilepsia 1996;37:9.
[28] Leidy NK, Elixhauser A, Vickrey B, Means E, Willian M. Seizure frequency and the health-related quality of life of adults with epilepsy. Neurology 1999;53(1):162.
[29] Baker GA, Gagnon D, McNulty P. The relationship between seizure frequency, seizure type and quality of life: findings from three European countries. Epilepsy Res 1998;30(3):231–40.
[30] Guekht AB, Mitrokhina TV, Lebedeva AV, Dzugaeva FK, Milchakova LE, Lokshina OB, et al. Factors influencing on quality of life in people with epilepsy. Seizure 2007;16(2):128–33.
[31] Lynn DJ, Newton HB, Rae-Grant AD. The 5-minute neurology consult. Lippincott Williams & Wilkins; 2012.
[32] Johnson RT, Griffin JW, McArthur JC. Current therapy in neurologic disease. Elsevier Health Sciences, vol. 1; 2006.