The Burden of Caring for Individuals with Tuberous Sclerosis Complex (TSC) Who Experience Epileptic Seizures: A Descriptive UK Survey

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Abstract

Introduction Tuberous sclerosis complex (TSC) is a rare multisystem genetic condition characterised by benign tumours; prevalent manifestations include epilepsy and neuropsychiatric disorders. This study examined the burden of TSC for primary caregivers and families, exploring the impact of characteristics such as seizures.

Methods Primary caregivers of individuals with TSC in the United Kingdom participated in an online survey, comprising the Pediatric Quality of Life Inventory™ Family Impact Module, Hospital Anxiety and Depression Scale (HADS), and TSC-specific items. Responses were analysed using descriptive and regression analysis statistics (closed-ended) or qualitative content analysis (open-ended).

Results Seventy-three participants partially completed and 59 fully completed the survey; 95% were female, and 90% were parents of an individual with TSC. A median (range) of 2 (1–11) household members were carers. Primary caregivers spent a mean (standard deviation [SD]) of 104.3 (51.7) hours caring in the previous week, reporting high mean (SD) HADS scores of 11.2 (4.8) (anxiety) and 7.9 (4.4) (depression) and considerable family burden. Increased seizure frequency increased hours spent caring by primary caregivers ($p = 0.01$) and was associated with a decreased mean (SD) family functioning score of 46.2 (23.0) and parent health-related quality of life (HRQL) score of 45.4 (20.3) (both $p = 0.03$). Multivariable models predicted intellectual disability increased hours spent caring by primary caregivers ($p = 0.01$–0.04), and neuropsychiatric comorbidities decreased family functioning ($p = 0.02$) and caregiver HRQL ($p < 0.01$).

Conclusion These findings highlight the role of epileptic seizures and neuropsychiatric disorders in the considerable burden of TSC on primary caregivers and families.

Key Points for Decision Makers

This United Kingdom survey found that caregivers and other household members spend a substantial amount of time on tuberous sclerosis complex (TSC) care each week, with seizure frequency identified as a significant predictor of time spent caring.

Caregivers also highlighted the need for continuous care with little respite, reporting high rates of anxiety and depression and a considerable family burden.

This study adds to the existing evidence suggesting that TSC not only negatively affects the individual, but also has a substantial impact on their primary caregivers and families.

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1 Introduction

Tuberous sclerosis complex (TSC) is a rare multisystem genetic disorder with prevalence estimates ranging from ~1/11,000 to 1/26,000 individuals [1–5]. TSC is characterised by benign tumours in multiple organs, most commonly the skin, brain, kidneys, lungs, eyes, and heart [6]. Clinical manifestations of TSC can vary between individuals and occur at different life stages [6]. TSC is also associated with neurodevelopmental and neuropsychiatric disorders, e.g. learning difficulties, autism, challenging behaviour, anxiety, and depression, known as 'TSC-associated neuropsychiatric disorders' (TAND) [6–8]. Approximately half of individuals with TSC who have epilepsy also have intellectual disabilities, ranging in severity from mild to profound, with higher prevalence observed in those not controlled by treatment [9]. As such, individuals with TSC require medical evaluation, surveillance, and management throughout their life [10].

Epilepsy is a highly prevalent TSC manifestation, estimated to affect 84% of individuals [9]. Epilepsy is one of the most common causes of TSC-related mortality, particularly due to status epilepticus and sudden unexpected death in epilepsy (SUDEP) [6]. Early onset of epilepsy has been associated with a higher frequency and severity of intellectual disability [11] and a slower gain in intellectual ability, which has also been linked to seizure severity [12]. Individuals with TSC who have epilepsy have been shown to have lower health-related quality of life (HRQL) compared with those without epilepsy [13]. HRQL has also been shown to worsen with increasing seizure frequency and severity [14–16] and to improve following medical intervention for seizure control [17–22].

Evidence describing how the burden of TSC extends to caregivers and parents has also emerged. Caregivers of individuals with TSC have significantly lower HRQL and more depressive symptoms compared with healthy populations [23, 24]. Caregivers have reported anxiety regarding the unknown future and possibility of medical emergencies, new symptoms, repeated surgeries, and treatment side effects [25, 26]. The need for supervision and monitoring of individuals with TSC due to seizures can also have a negative impact on caregivers and family members [25], with parental stress being linked to seizure occurrence [27]. Moreover, TSC is associated with substantial direct and indirect costs for patients and caregivers, as well as an impairment to work productivity in adults [28, 29]. TSC can impact the whole family, with activities centred around the needs of the affected individual and siblings consequently missing out on family time [25, 26].

Previous studies assessing the burden of TSC have failed to capture the multifaceted nature of TSC and how it evolves with age, the subsequent impact on the whole family, and how different manifestations affect this [21, 23, 30–32]. This study examined the impact of TSC on primary caregivers and other household members, and how this varies by disease severity, focusing on seizure frequency, and age in individuals with TSC. Care and psychosocial aspects of caregiver and family burden were assessed, and the effects of seizure frequency and other demographic/clinical characteristics on this burden were explored. The study also aimed to understand the wider household involvement in TSC care, and the non-healthcare-related costs and impacts on productivity for caregivers and their families.

2 Methods

2.1 Study Design and Population

A cross-sectional online survey of caregivers of individuals with TSC in the United Kingdom (UK) was conducted. Eligible participants were aged ≥ 18 years and were primary, unpaid caregivers living with an individual with TSC in the UK.

2.2 Recruitment and Data Collection

Participants were recruited between May–July 2021 via the Tuberous Sclerosis Association (TSA), a UK-based charity supporting individuals and families affected by TSC. A study advert was shared on TSA social media platforms and monthly newsletters, with a link to the survey (Electronic Supplementary Material 1 [ESM1]). The target sample size was 100 caregivers, based on an informal recruitment feasibility assessment by the TSA. Individuals who accessed the survey were asked to complete a screening survey to ensure they met the eligibility criteria. Eligible participants were given further detail regarding the study and their rights and asked to complete a consent form before proceeding to the main survey (ESM2). A donation of £20 was made by GW Pharmaceuticals, now part of Jazz Pharmaceuticals, Inc., to the TSA for every participant recruited.

Participants had to answer 'required' questions before progressing, and they were able to return to previous pages to review their answers. To ensure anonymity, no process was in place to prevent multiple entries from a single participant.

2.3 Survey

An online survey was designed to capture different impacts of caring for an individual with TSC, including time burden and psychosocial impact on the family, activities undertaken by different family members, the extent to which caring

limited their ability to do other things, and economic burden (ESM3). In this study, 'professional social care' describes any care paid for by the healthcare system or household. In the UK, professional social care is available to support families of patients requiring practical support because of illness or disability; it can be funded by the household privately or by the local council [33]. Non-healthcare-related costs included requirement for additional childcare, average yearly out-of-pocket costs related to caring responsibilities, hours of private funded care, money spent on private care, and state-funded care received. Survey development was guided by the study objectives and informed by a rapid literature review (ESM4) and feedback from the TSA. Closed- and open-ended questions specifically developed for this study were included, as well as existing standardised instruments. The bespoke, de-novo items included:

- Demographic and clinical characteristics of the individual with TSC.
- Demographic and clinical characteristics of the caregiver and other household members.
- Care activities undertaken and hours of care provided by the primary caregiver and other household members.
- Impacts on productivity and non-healthcare-related costs to the primary caregiver and other household members.

Two standardised measures were used to assess the psychosocial and physical burden of TSC on caregivers and other household members: Pediatric Quality of Life Inventory (PedsQL)™ Family Impact Module (FIM) and Hospital Anxiety and Depression Scale (HADS).

2.3.1 PedsQL FIM

The PedsQL FIM measures the impact of paediatric chronic health conditions on parents and families (link provided in ESM3) [34]. It includes 36 items answered on a five-point scale, with 0 indicating the issue is *never* a problem and 4 indicating it is *always* a problem. Items are reverse scored and linearly transformed to a 0–100 scale, with higher values indicating better functioning [34]. The PedsQL FIM Total Scale score was computed, as well as two summary scores: the Family Functioning Summary score and the Parent HRQL score.

2.3.2 HADS

The HADS measures anxiety and depression and can be used as a screening tool to assess symptom severity or to define 'caseness' of anxiety disorders and depression (link provided in ESM3) [35]. It includes 14 items, with seven items each for anxiety and depression. The responses are scored on a scale from 0 to 3: higher scores indicate higher symptom

frequency. 'Caseness' is defined as a score from 8 to 10: scores ≥ 11 are considered 'probable clinical caseness'.

2.4 Analysis

A detailed statistical analysis plan was developed prior to the start of analysis. All survey respondents were analysed, irrespective of survey completion, and no missing data were imputed. Respondents' data were only included in individual analyses where they were complete for all included outcomes.

Descriptive statistics were summarised for closed-ended responses: count and percentage data for categorical variables; mean and standard deviation (SD), and median (interquartile range [IQR] or range) for continuous variables. Scoring guidelines published by developers of the standardised measures were followed to compute scores. Open-ended responses were qualitatively analysed by grouping into response categories; example quotes for each response category were selected.

To identify factors associated with the burden of TSC on primary caregivers and other household members, bivariate regression analyses were conducted to describe the relationship between several response and explanatory variables. Response variables included the following: hours of care by the primary caregiver and all household members; PedsQL FIM Total Scale, Family Functioning Summary, and Parent HRQL Summary scores; and HADS scores and 'probable clinical caseness'. Explanatory variables included demographic and clinical characteristics for individuals with TSC and primary caregivers, such as seizure frequency (in the previous week), age, and intellectual ability of the individual with TSC. Explanatory variables significantly associated with a response variable at the 0.10 level ($p \leq 0.10$) were initially included in multivariable models. Explanatory variables subsequently found to be nonsignificant in multivariable analyses were removed from the final models.

Exploratory analyses suggested relationships between seizure frequency and response variables were nonlinear: a change from zero to few seizures greatly affected response variables, but changes became smaller with increasing seizure frequency. Thus, models using different transformations of seizure frequency were assessed based on their statistical goodness of fit and interpretability. Although a logarithmic transformation fitted the data best, the final model included seizure frequency categorised into three levels using the 25th and 75th percentiles as cut-off points, as this model captured the general shape of the relationship and was easier to interpret (Supplementary Fig. 1 and Supplementary Table 1 in ESM5).

Multicollinearity between variables was assessed using correlation analyses (Pearson for continuous variables and Spearman for categorical variables) and, in the multivariable models, using the Variance Inflation Factor. Neither analysis identified any multicollinearity issues.

In models including PedsQL FIM and HADS scores as response variables, caregiver health conditions were excluded as explanatory variables due to conceptual overlap. Additionally, due to the strong correlation (Spearman's rho = − 0.8 [normal ability] to 0.3 [severe disability]) between intellectual ability and developmental delay, only intellectual ability was included in models where both variables were significant predictors in bivariate analyses for the corresponding response variable.

All analyses were conducted using R v4.1 [36]. Results were considered statistically significant if $p \leq 0.05$.

3 Results

Overall, 112 people entered the screening survey, and 100 completed one or more screening question. Of 93 eligible caregivers, 75 provided consent, 73 answered one or more question in the main survey, and 59 completed the main survey.

3.1 Demographic and Clinical Characteristics of the Individuals with TSC

There was a similar proportion of adults and children/adolescents with TSC, most of whom were cared for by their parent and received special needs support (if in education or training; Table 1). These individuals often had tumours in multiple organs, developmental delay (87%), and impaired intellectual ability (87%), with various neuropsychiatric comorbidities reported (Table 2). Most individuals (95%) had experienced an epileptic seizure during their lifetime, of whom 94% were receiving treatment for these seizures at the time of the survey (Table 2). Over 75% of these individuals had one or more epileptic seizure in the previous week, with a median (IQR) of 4 (1–15) seizures. Focal seizures *with* impaired awareness

Table 1 Demographic characteristics of individuals with TSC (caregiver proxy-reported)

Characteristic		n (%)[a]
Relationship of primary caregiver ($N = 73$)	Parent	66 (90)
	Partner	2 (3)
	Relative	4 (6)
	Other	1 (1)
Sex ($N = 73$)	Female	40 (55)
	Male	32 (44)
	Other	1 (1)
Age (years) ($N = 73$)	Mean (SD)	20.0 (13.5)
	Children (0–11 years)	25 (34)
	Adolescent (12–17 years)	9 (12)
	Adult (≥ 18 years)	39 (53)
School education ($N = 31$)[b]	Mainstream	8 (26)
	Mainstream with special needs support	11 (35)
	Special needs	14 (45)
Occupation ($N = 41$)[c]	Employed (part-time)	2 (5)
	In education or training	10 (24)
	Unable to work due to their health	26 (62)
	Unemployed or looking for work	1 (2)
	Other	3 (7)
Adult training or education ($N = 10$)[d]	Mainstream	1 (10)
	Mainstream with special needs support	4 (40)
	Education or training for people with special needs	5 (50)
Attending day care centre ($N = 27$)[e]	Yes	10 (37)

N number of individuals analysed, *n* number of individuals in each category, *SD* standard deviation, *TSC* tuberous sclerosis complex

[a]Value presented is the number (proportion) of individuals in each category, unless stated otherwise

[b]Only caregivers who cared for an individual aged ≤ 16 years

[c]Only caregivers who cared for an individual aged ≥ 16 years

[d]Only caregivers who cared for an individual aged ≥ 16 years who was currently in education or training

[e]Only caregivers who cared for an individual aged ≥ 16 years who was unemployed or unable to work

Table 2 Clinical characteristics of individuals with TSC (caregiver proxy-reported)

Characteristic		n (%)[a]
Age of symptom onset (years) ($N = 73$)	Mean (SD)	1.6 (6.0)
Age at diagnosis (years) ($N = 73$)	Mean (SD)	2.5 (6.3)
Number of organs affected by tumours ($N = 73$)	Mean (SD)	3.6 (1.5)
Organs affected by tumours ($N = 73$)	Brain	70 (96)
	Kidney	51 (70)
	Skin	58 (79)
	Heart	21 (29)
	Lungs	9 (12)
	Mouth	12 (16)
	Eyes	29 (40)
Intellectual ability ($N = 71$)	Normal ability	9 (13)
	Mild-moderate disability	35 (49)
	Severe-profound disability	27 (38)
Developmental delay ($N = 71$)	Yes	62 (87)
	Prefer not to answer	3 (4)
Neuropsychiatric comorbidities ($N = 71$)	Autism spectrum disorder	33 (46)
	Attention deficit hyperactivity disorder	7 (10)
	Anxiety	30 (42)
	Depression	9 (13)
	Obsessive compulsive disorder	8 (11)
	Psychotic disorder	2 (3)
	Other	11 (15)
	None	23 (32)
	Don't know	2 (3)
Sleep problems ($N = 71$)	Yes	52 (73)
Seizure-specific characteristic		
Ever had an epileptic seizure ($N = 73$)	Yes	69 (95)
Age (years) at first epileptic seizure ($N = 69$)[b]	Mean (SD)	1.4 (3.7)
Currently receiving treatment for epileptic seizures ($N = 69$)[b]	Yes	65 (94)
Number of epileptic seizures in the previous week ($N = 69$)[b]	Mean (SD)	17.4 (31.6)
	Median (IQR)	4 (1–15)
	≥ 1 seizure	53 (77)
Number of generalised seizures in the previous week ($N = 69$)[b]	Mean (SD)	7.9 (18.8)
	Median (IQR)	0 (0–5)
	≥ 1 seizure	31 (45)
Number of focal seizures with impaired awareness in the previous week ($N = 69$)[b]	Mean (SD)	8.3 (18.3)
	Median (IQR)	1 (0–5)
	≥ 1 seizure	35 (51)
Number of focal seizures without impaired awareness in the previous week ($N = 67$)[b]	Mean (SD)	6.6 (19.8)
	Median (IQR)	0 (0–2)
	≥ 1 seizure	23 (34)

IQR interquartile range, *N* number of individuals, *n* number of individuals in each category, *SD* standard deviation, *TSC* tuberous sclerosis complex

[a]Value presented is the number (proportion) of individuals in each category, unless stated otherwise

[b]Only individuals with TSC who 'ever had an epileptic seizure'

were most common, followed by generalised seizures and focal seizures *without* impaired awareness (Table 2).

3.2 Demographic and Clinical Characteristics of Primary Caregivers and Household Members

Among the caregivers who participated in the survey, a large majority (95%) were female, and most were employed part-time (38%) or a full-time homemaker (33%). Chronic health conditions commonly reported by caregivers included sleep problems (28%), stress (23%), and anxiety (18%). One caregiver was diagnosed with TSC. Most caregivers lived with their partner (70%) and/or other child(ren) in addition to the individual with TSC (47%), with a median (range) of 1.5 (1–6) children in each household. One participant lived with another child with TSC symptoms, in addition to the child with TSC whom they reported on during the survey.

3.3 Care Aspects of the Burden of TSC

A median (range) of 2 (1–11) household members were involved in caring for the individual with TSC (Table 3). Most primary caregivers provided all the care activities described; other household members commonly supported with daily activities and emotional care (Table 3). In addition, 'other' care activities included the provision of all personal care needs, constant supervision and ensuring the safety of the individual, physiotherapy exercises, assistance with finances, and managing behavioural difficulties. Overall, primary caregivers spent a mean (SD) of 104.3 (51.7) hours on care in the previous week, with 7.4 (16.2) hours on seizure-specific care; other household members also spent considerable amounts of time on care (Table 3).

In free-text sections, participants shared additional responses regarding their time spent providing general and seizure-specific care (summarised in Figs. 1 and 2; see Supplementary Tables 2 and 3 in ESM5 for specific quotes). Participants described the care they provide as 'all day, every day and often through night as well' and stated they 'need to be available all the time' due to the risk of seizures. Some caregivers reported receiving occasional respite from their caring responsibilities when the individual was at school or being cared for by the other parent, childminder, or support worker. Several caregivers described how their hours of care varied depending on unpredictable seizure frequency. Additionally, several caregivers described the burden associated with nocturnal seizures, with one noting that they consequently slept in the same room as the child.

3.4 Predictors of Total Hours of Care per Week

Seizure frequency was a significant predictor of the total hours of care by the primary caregiver in the bivariate regression analysis (Supplementary Table 4 in ESM5). This significant association remained after intellectual disability was included in the final multivariable model (Table 4), suggesting seizure frequency and intellectual disability have independent effects on the number of hours the primary caregiver spends caring. In the final model, compared with caring for someone with no seizures in the previous week, it was predicted the primary caregiver required an additional 30.8 hours ($p = 0.04$) to care for an individual with 1–12 seizures, and an additional 49.6 hours ($p = 0.01$) for an individual with > 12 seizures over the same time period (Table 4). Caring for individuals with mild–moderate or severe intellectual disability significantly increased the predicted hours of care by 37.7 hours ($p = 0.04$) and 50.1 hours ($p = 0.01$) compared with caring for individuals with no intellectual disability (Table 4).

Seizure frequency was also a significant predictor of the combined total hours of care by all household members in the bivariate regression analysis (Supplementary Table 4 in ESM5). However, when intellectual disability was included in the final multivariable model, the predicted combined total hours of care were significantly increased only for care of an individual with > 12 seizures in the previous week (increase of 74.3 hours compared with care of an individual with no seizures; $p < 0.01$; Table 4). The individual's age was not a significant predictor of total hours of care by the primary caregiver or all household members combined in the bivariate regression analysis (Supplementary Table 5 in ESM5).

3.5 Psychosocial Aspects of the Burden of TSC on Caregivers

Several measures were used to assess the psychosocial burden of TSC, with mean (SD) transformed PedsQL FIM scores for primary caregivers as follows: Total Scale score = 43.3 (19.1); Family Functioning Summary score = 46.2 (23.0); and Parent HRQL Summary score = 45.4 (20.3). These scores were lower (indicating worse HRQL) than those for a community sample of parents of children aged 2–17 years [37], caregivers of children with other conditions associated with developmental delay (e.g. cerebral palsy and attention deficit hyperactivity disorder) [38], and parents of children/adolescents with chronic pain [39]. For the primary caregiver, the mean (SD) and median (range) HADS Anxiety and Depression summary scores were 11.2 (4.8) and 10.5 (2.0–21.0) for anxiety and 7.9 (4.4) and 7.0 (0.0–19.0) for depression. Overall, 50% of primary caregivers were classified as having 'probable clinical caseness' for anxiety and 27% for depression. The summary scores for both measures were higher than the median UK population norms of 6 (women) and 5 (men) for anxiety and 3 for depression (both sexes) [40].

Table 3 Care aspects of the burden of TSC on the primary caregiver, their partner/spouse, and other household members

Characteristic		n (%)[a]
Number of household members involved in care (N = 61)[b]	Mean (SD)	2.3 (1.6)
	Median (range)	2 (1–11)
	1	13 (21)
	2	32 (52)
	3	9 (15)
	≥ 4	7 (11)
Relationship of other household members involved in care to primary caregiver (N = 50)[c]	Partner/spouse	44 (88)
	Other family member	15 (30)
	Other	3 (6)

Characteristic		All household members (N = 69)[d]	Primary caregiver (N = 69)	Partner/spouse (N = 44)[e]	Other household members (N = 15)[f]
Care activities performed in the previous week	Daily activities	–	64 (93)	37 (84)	11 (73)
	Medication and medical care	–	64 (93)	29 (66)	4 (27)
	Seizures[g]	–	58 (89)	31 (72)	7 (47)
	Emotional	–	63 (91)	36 (82)	11 (73)
	Other	–	14 (20)	3 (7)	2 (13)
Total hours of care in the previous week[h]	Mean (SD)	128.4 (67.7)	104.3 (51.7)	41.3 (38.7)	16.9 (26.6)

		All household members (N = 61)[d]	Primary caregiver (N = 61)	Partner/spouse (N = 33)[e]	Other household members (N = 12)[f]
Hours of seizure-specific care in the previous week[g,h]	Mean (SD)	11.2 (28.3)	7.4 (16.2)	6.8 (17.0)	4.0 (7.8)

N number of caregivers analysed, *n* number of caregivers who reported in each category, *SD* standard deviation, *TSC* tuberous sclerosis complex

[a] Value presented is the number (proportion) of caregivers who reported in each category, unless stated otherwise

[b] The primary caregiver was added to the number of other household members involved in the care provided

[c] Only caregivers who reported that other people in the household are involved in caring for the individual with TSC

[d] Sum of hours of care provided by the primary caregiver, partner, parent/siblings, (other) children, and/or other relatives

[e] Only caregivers who reported that their partner/spouse is involved in caring for the individual with TSC

[f] Only caregivers who reported that their parent, sibling, (other) children, and/or other relative is involved in caring for the individual with TSC

[g] Only caregivers who reported that the person they care for ever had epileptic seizures
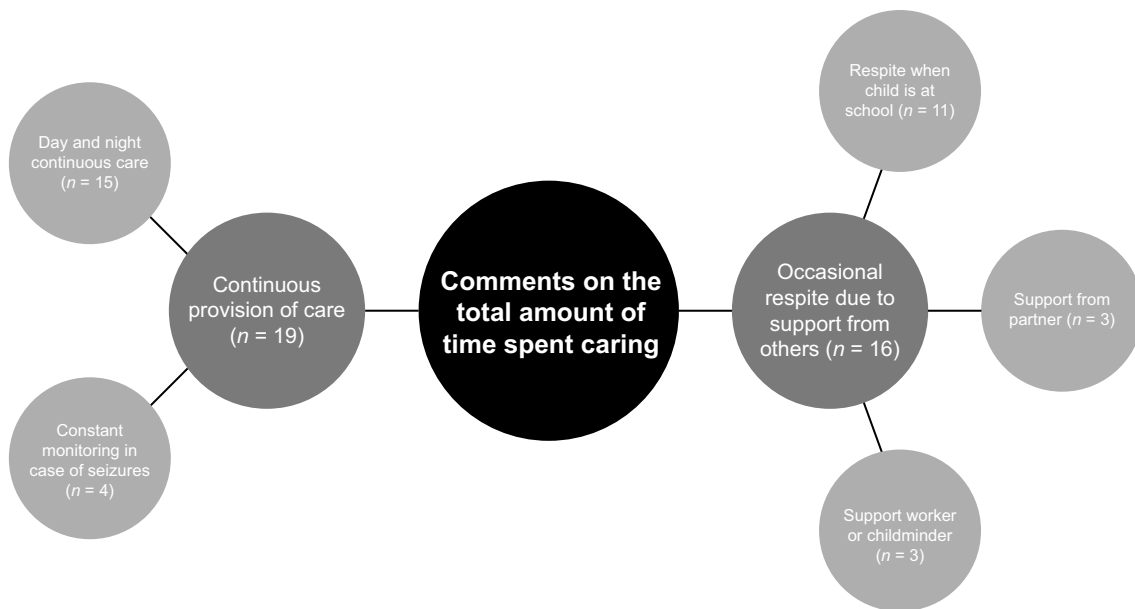
[h] Hours per day were converted to hours per week

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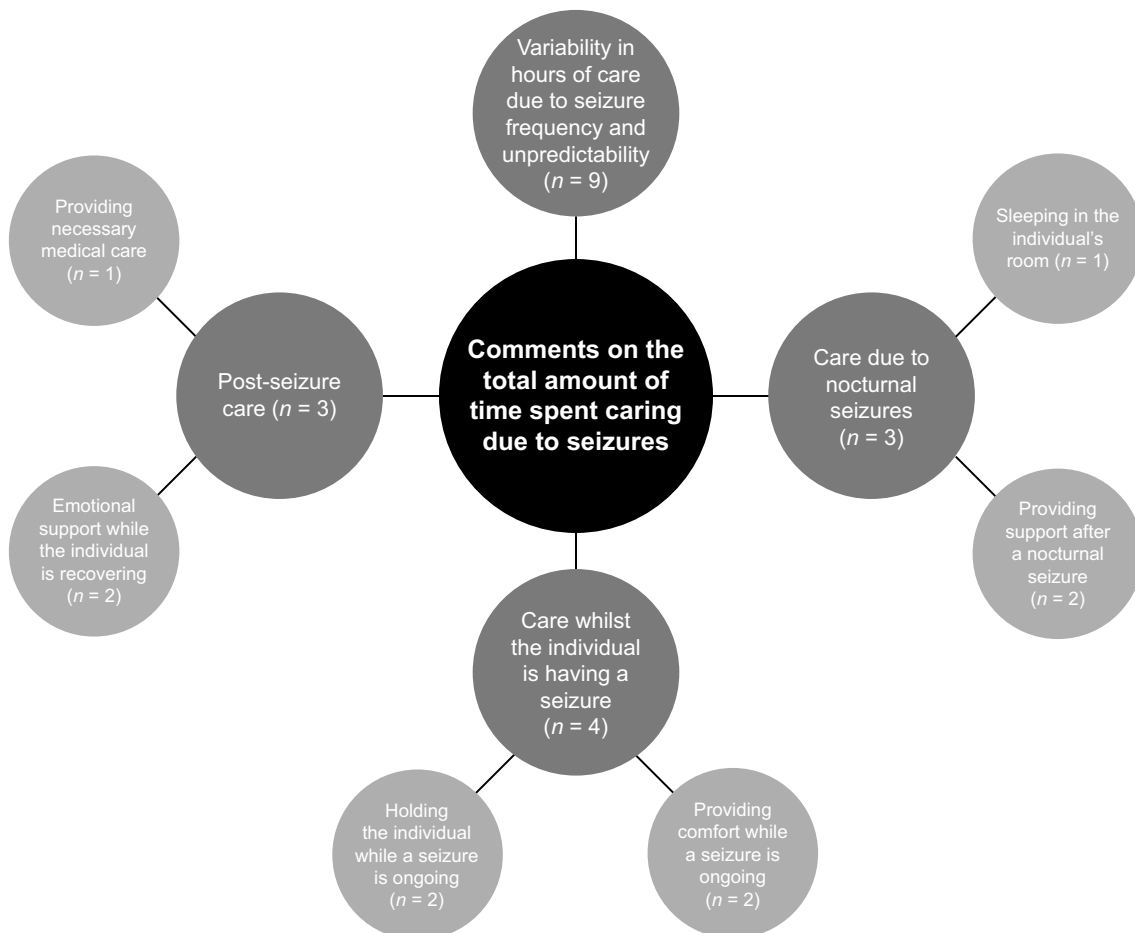**Fig. 1** Comments regarding the total amount of time spent caring

Fig. 2 Comments regarding the total amount of time spent caring due to seizures

Table 4 Multivariable regression model for total hours of care per week

Characteristic		Total hours of care per week by primary caregiver			Total hours of care per week by all household members[a]		
		β	95% CI	P value	β	95% CI	P value
Intercept[b]		40.0	7.2–72.8	–	59.9	15.8–104.1	–
Epileptic seizures in the previous week	0 seizures	–	–		–	–	
	1–12 seizures	**30.8**	**1.7–59.9**	**0.04[c]**	28.1	−11.0 to 67.3	0.16[c]
	> 12 seizures	**49.6**	**15.2–84.0**	**0.01[c]**	74.3	**28.0–120.6**	**< 0.01[c]**
Intellectual disability	None	–	–		–	–	
	Mild–moderate	**37.7**	**1.9–73.6**	**0.04[d]**	36.1	−12.1 to 84.3	0.14[d]
	Severe	**50.1**	**10.6–89.6**	**0.01[d]**	51.0	−2.2 to 104.1	0.06[d]
		RMSE = 42.20; adjusted R^2 = 0.26; N = 65			*RMSE = 56.73; adjusted R^2 = 0.24; N = 65*		

β correlation coefficient, *CI* confidence interval, *N* number of observations, *RMSE* root-mean-square error, *TSC* tuberous sclerosis complex

[a]Sum of hours of care per week provided by the primary caregiver, partner, parent/siblings, (other) children, and/or other relatives

[b]Mean total hours of care per week when caring for individuals with TSC who had 0 seizures in the previous week and no intellectual disability

[c]Relative to those caring for individuals with TSC who had 0 seizures in the previous week

[d]Relative to those caring for individuals with TSC with no intellectual disability

In bivariate regression analyses, participants who cared for an individual with > 12 epileptic seizures in the previous week had significantly lower PedsQL FIM scores than those who cared for an individual who had no seizures in the same period (Supplementary Table 6 in ESM5). However, for all PedsQL FIM scores, there was no significant difference between those who cared for individuals with 1–12 epileptic seizures versus no seizures, in the previous week (Supplementary Table 6 in ESM5). The associations for caregivers of individuals with > 12 epileptic seizures in the previous week remained significant for all PedsQL FIM scores when neuropsychiatric comorbidity was included in the final multivariable model (Table 5). This seizure frequency was significantly associated with lower PedsQL Total Scale, Family Functioning Summary, and Parent HRQL Summary scores, compared with caring for an individual who had no seizures (all p = 0.03; Table 5). Caring for an individual with a neuropsychiatric comorbidity was also significantly associated with lower PedsQL Total Scale, Family Functioning Summary, and Parent HRQL scores, compared with caring for an individual with no neuropsychiatric comorbidities (p < 0.01–0.02; Table 5). The age of the individual with TSC was not a significant predictor of any PedsQL FIM scores in the bivariate regression analysis (Supplementary Table 7 in ESM5).

Bivariate linear regression models for HADS Anxiety and Depression summary scores demonstrated a statistically nonsignificant increase in both scores with increased seizure frequency (both p > 0.05; Table 6). Bivariate logistic regression models for HADS 'probable clinical caseness' suggested greater odds for HADS Anxiety 'caseness' when caring for an individual with > 12 seizures in the previous week, compared with caring for an individual with no seizures (p = 0.05; Table 6). Seizure frequency had no evident association with HADS Depression 'caseness' (Table 6). Further exploratory multivariable regression analyses showed results for associations between seizure frequency and HADS Anxiety and Depression summary scores, and seizure frequency and HADS Anxiety and Depression 'caseness' remained stable after accounting for any other individual and caregiver characteristic variables associated with the HADS response variables at the p = 0.10 level (data not shown).

Older age of the individual with TSC was significantly associated with lower caregiver HADS Anxiety Summary score in the bivariate analysis (p = 0.02; Supplementary Table 8 in ESM5) and when adjusting for seizure frequency (p = 0.02; Supplementary Table 9 in ESM5). For HADS Anxiety 'caseness', HADS Depression Summary score, and HADS Depression 'caseness', the age of the individual with TSC did not have a significant effect in the bivariate analysis (Supplementary Table 8 in ESM5) or when adjusting for any other variables of the individuals with TSC or caregivers, including seizure frequency (data not shown).

3.6 Caregiver and Household Non-Healthcare-Related Costs and Productivity Impacts

In terms of non-healthcare-related costs and care support, 41% of households received professional social care (Table 7). Households who received social care received a mean (SD) of 5.1 (10.8) hours of private-funded care and 20.5 (26.9) hours of state-funded care per week. Overall, a median (range) of £550 (0–9999) was spent per year on non-healthcare-related out-of-pocket costs for the individual with TSC (Table 7).

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Table 5 Multivariable regression model for PedsQL FIM scores

Characteristic		PedsQL Total Scale score			Family Functioning Summary score			Parent HRQL Summary score		
		β	95% CI	P value	β	95% CI	P value	β	95% CI	P value
Intercept[a]		60.4	49.8–71.0	–	66.1	52.8–79.4	–	63.5	52.5–74.5	–
Epileptic seizures in the previous week	0 seizures	–	–	–	–	–	–	–	–	–
	1–12 seizures	−6.3	−17.5 to 4.9	0.26[b]	−9.9	−23.8 to 4.1	0.16[b]	−5.3	−16.9 to 6.2	0.36[b]
	> 12 seizures	−13.9	−26.6 to −1.1	0.03[b]	−17.3	−33.2 to −1.4	0.03[b]	−15.1	−28.4 to −1.9	0.03[b]
Neuropsychiatric comorbidity	No	–	–	–	–	–	–	–	–	–
	Yes	−13.9	−23.4 to −4.4	0.01[c]	−14.5	−26.3 to −2.7	0.02[c]	−15.2	−25.0 to −5.3	<0.01[c]
		RMSE = 16.47; adjusted R² = 0.17; N = 58			RMSE = 20.53; adjusted R² = 0.13; N = 58			RMSE = 17.11; adjusted R² = 0.18; N = 59		

β correlation coefficient, CI confidence interval, FIM Family Impact Module, HRQL health-related quality of life, N number of observations, PedsQL Pediatric Quality of Life Inventory, RMSE root-mean-square error, TSC tuberous sclerosis complex

[a]Mean score when caring for individuals with TSC who had 0 seizures in the previous week and no neuropsychiatric comorbidity

[b]Relative to those caring for individuals with TSC who had 0 seizures in the previous week

[c]Relative to those caring for individuals with TSC with no neuropsychiatric comorbidities

Most primary caregivers reported they had either stopped working completely (45%), reduced their working hours (51%), and/or changed their job (22%) to better accommodate their caring responsibilities. It was reported that 9% of partners involved in care had stopped working completely, 23% had reduced their working hours, and 9% changed their job. A similar percentage (20%) of other household members (of working age) had reduced their working hours. Primary caregivers who worked reported missing a mean (SD) of 7.8 (7.9) hours of work per week due to caregiving, with their partners missing 3.9 (7.9) hours of work per week and other household members missing 1.8 (3.3) hours of work or school per week.

4 Discussion

This study describes the burden experienced by caregivers and families of individuals with TSC in the UK. The data suggest that care and psychosocial burden is substantial and can increase when seizures are frequent and TAND manifestations are present.

The survey was developed to better understand the impact of TSC on primary caregivers and other family members, and how this varies by disease severity, with a focus on seizure frequency, and age of the individuals with TSC. Increased seizure frequency was associated with an increase in the number of hours spent caring, by primary caregivers and all household members combined. Greater seizure frequency was also associated with reduced family functioning and caregiver HRQL. These findings support previous studies reporting a correlation between parental stress and seizure occurrence [27], and improvements in parental outcomes following seizure reduction [18, 21]. One study demonstrated seizure occurrence in individuals with TSC in the last 6 months was associated with elevated parental stress [27]. In another study of 11 individuals with TSC, seizure frequency was reduced and parental satisfaction improved, following vagus nerve stimulation [18]. Furthermore, following epilepsy surgery, seizure frequency and time spent caring for individuals with TSC and epilepsy were reduced, and the family quality of life improved [21].

In the current study, associations were identified between intellectual disability and hours spent caring by primary caregivers, neuropsychiatric comorbidities and family functioning, and neuropsychiatric comorbidities and caregiver HRQL. Previous research has shown parental stress to be correlated with children with TSC having a history of psychiatric diagnosis, low intellectual function, and elevated behavioural issues [27]. In addition, decreased quality of life in children and adolescents with TSC correlates with lower quality of life and increased symptoms of depression in their caregivers [24]. Overall, the present study found the impact

Table 6 Bivariate regression models for HADS Anxiety and Depression summary scores (linear model) and 'probable clinical caseness' (logistic model), by seizure frequency

Characteristic		HADS Anxiety summary score			HADS Depression summary score		
		β	95% CI	P value	β	95% CI	P value
Intercept[a]		9.7	7.1–12.3	–	6.4	4.1–8.8	–
Epileptic seizures in the previous week	0 seizures	–	–		–	–	
	1–12 seizures	1.2	−1.9 to 4.3	0.44[b]	1.0	−1.8 to 3.9	0.48[b]
	> 12 seizures	3.3	−0.3 to 6.9	0.07[b]	3.1	−0.1 to 6.4	0.06[b]
		RMSE = 4.67; adjusted R^2 = 0.03; N = 58			*RMSE = 4.25; adjusted R^2 = 0.03; N = 58*		

Characteristic		HADS Anxiety 'probable clinical caseness'			HADS Depression 'probable clinical caseness'		
		OR	95% CI	P value	OR	95% CI	P value
Intercept[a]		0.4	0.1–1.2	0.12	0.3	0.1–0.9	0.05
Epileptic seizures in the previous week	0 seizures	–	–		–	–	
	1–12 seizures	2.7	0.7–11.6	0.16[b]	0.8	0.2–4.3	0.74[b]
	> 12 seizures	**5.0**	**1.1–27.0**	**0.05**[b]	2.4	0.5–14.3	0.29[b]
		RMSE = 2.08; R^2 = 0.10; N = 58			*RMSE = 2.45; R^2 = 0.07; N = 58*		

β correlation coefficient, *CI* confidence interval, *HADS* Hospital Anxiety and Depression Scale, *OR* odds ratio, *N* number of observations, *RMSE* root-mean-square error, *TSC* tuberous sclerosis complex

[a]Mean score/OR when caring for individuals with TSC who had 0 seizures in the previous week

[b]Relative to those caring for individuals with TSC who had 0 seizures in the previous week

Table 7 Non-healthcare-related costs and care support received

Characteristic		
Requirement for additional childcare (N = 65)	Yes, *n* (%)	8 (12)
Yearly out-of-pocket costs (GBP) (N = 64)	Mean (SD)	1357.7 (1945.3)
	Median (range)	550 (0–9999)
	Prefer not to answer, *n* (%)	22 (34)
Professional social care (N = 59)	Yes, *n* (%)	24 (41)
Hours of private-funded care per week (N = 24)[a]	Mean (SD)	5.1 (10.8)
Money spent on private-funded care per week (GBP) (N = 24)[a]	Mean (SD)	41.6 (89.7)
	Prefer not to answer, *n* (%)	5 (21)
Hours of state funded care per week (N = 24)[a]	Mean (SD)	20.5 (26.9)

GBP British pound sterling, *N* number of caregivers analysed, *n* number of caregivers who reported in each category, *SD* standard deviation, *TSC* tuberous sclerosis complex

[a]Only caregivers who reported that the individual with TSC receives professional social care

of TSC on caregivers and other family members is multifaceted; the presence of epileptic seizures had an impact on caregiver burden that was independent of the effect of TAND manifestations, namely intellectual disability and neuropsychiatric comorbidities.

The age of the individual with TSC was not significantly associated with any care or psychosocial aspects of caregiver burden, except HADS Anxiety Summary score. Older age has previously been associated with worse HRQL in individuals with TSC [13, 31], possibly due to the increased prevalence of different manifestations over an individual's lifespan, which may impact both physical and mental health [31]. Worse physical HRQL scores have been reported for caregivers of adults with TSC [23], which could be related to the caregiver themselves getting older. However, previous research has found no difference in mental HRQL scores between caregivers of paediatric and adult individuals with TSC [23], which is generally consistent with our findings. Overall, it appears the impact of caring for an individual with TSC, and the need for supervision due to their seizures and TAND manifestations, persists over time.

This survey also highlighted both primary caregivers and their partners spend a substantial amount of time caring each week. Primary caregivers commented that they must always be available, and the only occasions when they had respite from their caring duties was when the individual was at school or being cared for by someone else. This appeared to impact their work productivity and career, as a large proportion of primary caregivers and their partners had given up their job or reduced their working hours. This supports previous findings that caring for individuals with TSC can affect the careers of caregivers [41]. For example, a survey conducted in the US reported work and school absenteeism and impairment to productivity in caregivers of patients with TSC [29]. This was also reflected in the association between increased seizure frequency and neuropsychiatric comorbidities and lower PedsQL FIM scores, highlighting the impact of TSC on various aspects of family functioning, such as social interaction and relationships.

There were several limitations of this study that should be considered when interpreting the results. The small sample size may have limited the statistical power to identify characteristics of individuals with TSC and caregivers that were associated with caregiver burden. As such, the multivariable regression analyses should be considered with caution. Moreover, since study participants were recruited through newsletters and social media advertisements from the TSA, a UK-based charity, caregivers recruited in this study may not represent those without access to social media, and they may have better knowledge and support than caregivers not involved in the TSA. Further, the generalisability of these findings from a UK caregiver sample may be limited due to differences between health and social care systems between countries.

Further research is required to investigate the impact of life stage of the individual with TSC on the nature and extent of the caregiver and family burden of TSC. Additionally, due to the cross-sectional design, it was not possible to determine any causal relationship between seizure frequency and caregiver burden. The participant dropout rate during survey completion was also high and may have resulted in sample bias. The prevalence of epilepsy, TAND manifestations, and kidney manifestations reported in this study was relatively high compared with previous TSC studies, although it should be noted that reporting and categorisation of manifestations varies between studies [6, 42–44].

To conclude, this study provides valuable insights into the burden of TSC on caregivers and other family members. In particular, the findings suggest that seizure frequency impacts on time spent caring, family functioning, and caregiver HRQL, independent of TAND manifestations. Further research with a larger sample size could measure the impact of seizure frequency on caregiver burden more robustly to better understand the nature and extent of caregiver burden over the lifespan of individuals with TSC.

Declarations

Conflict of interest All authors met the International Committee of Medical Journal Editors (ICMJE) authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship. Sally Bowditch, Edward Dziadulewicz, and Kishan Vyas are employees of Jazz Pharmaceuticals, Inc. Sally Bowditch and Edward Dziadulewicz hold stock/stock options in Jazz Pharmaceuticals, Inc. Hanna Skrobanski, Lena Hubig, and Siu Hing Lo are employees of Acaster Lloyd Consulting Ltd, which received payment from GW Pharmaceuticals, now a part of Jazz Pharmaceuticals, Inc., in the conduct of this study. Louise Fish is an employee of Genetic Alliance UK and was an employee of the Tuberous Sclerosis Association (TSA) when the study was conducted, and Pooja Takhar is an employee of the TSA; the TSA has received sponsorship for events, an unrestricted educational grant, and consulting fees from GW Pharmaceuticals, now a part of Jazz Pharmaceuticals, Inc.

Ethics approval This study received ethical approval from the WIRB-Copernicus Group Independent Review Board (tracking number: 20211736).

Consent All participants provided informed, written consent prior to participating in the survey, which included consent for participation in the survey and for anonymous data to be used in future publications.

Availability of data and material All relevant data are provided with the manuscript and supporting files. Jazz has established a process to review requests from qualified external researchers for data from Jazz-sponsored clinical trials in a responsible manner that includes protecting patient privacy, assurance of data security and integrity, and furthering scientific and medical innovation. Additional details on Jazz Pharmaceuticals' data-sharing criteria and process for requesting access can be found at: https://www.jazzpharma.com/science/clinical-trial-data-sharing/.

Code availability Not applicable.

Author contributions HS and SHL contributed to the conception/design of the study. All authors contributed to the acquisition, analysis, or interpretation of data. All authors drafted or critically revised the manuscript for important intellectual content and approved the final version to be published. All authors agree to be accountable for all aspects of the work.

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