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Living with Dravet syndrome: quality of life and caregiver burden among family caregivers in Europe. Results from the QoL4DRAVET study

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ABSTRACT

Background: Dravet syndrome (DS) is a rare, severe developmental epileptic encephalopathy associated with lifelong clinical complexity and substantial caregiving demands. This study describes the quality of life and caregiver burden among family caregivers of individuals with DS across Europe.

Methods: This cross-sectional, multinational study was conducted as part of the QoL4Dravet – Measuring Quality of Life in Dravet Syndrome project coordinated by the Dravet Syndrome European Federation. 379 family caregivers (322 females and 57 males) completed an anonymous, self-administered online questionnaire from 14 European countries.

Results: Caregiving for individuals with DS was associated with a high and sustained burden extending beyond the diagnostic period. Although diagnosis typically occurred early in life, most individuals with DS in this cohort were already adolescents or adults, underscoring the long-term and persistent nature of the disease. This prolonged trajectory was characterised not only by ongoing seizure activity, complex treatment regimens, and frequent need for rescue medication, but also by the continuous management and rehabilitation of associated neurodevelopmental comorbidities, including behavioural and motor difficulties, cognitive and communication impairments. Caregivers reported pronounced impairments in emotional well-being, sleep, fatigue, and stress, while physical functioning was relatively preserved. Only 26.4% of caregivers were employed full-time, whereas 25.6% identified as full-time caregivers, with marked cross-country variation. Women reported poorer emotional well-being, lower autonomy, and poorer social well-being than men, while no sex differences were observed in physical well-being. Significant cross-country differences were found in emotional well-being and autonomy, with poorer outcomes reported in Poland and more favourable profiles in the Netherlands and Germany.

Conclusions: Caregiving burden in DS is long-term, multidimensional, and shaped by both gendered caregiving roles and national contexts. These findings underscore the necessity for integrated, gender-sensitive, and policy-informed support strategies that cater to caregivers' psychological, social, and occupational needs throughout their life course.

Abbreviations: DS, Dravet syndrome; DSEF, Dravet Syndrome European Federation; QoL, quality of life; QoL4Dravet, QoL4Dravet – Measuring Quality of Life in Dravet Syndrome.

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1. Introduction

Dravet syndrome (DS) is a rare, severe, genetically based developmental epileptic encephalopathy [1] that typically begins in the first year of life, often in infants with previously normal development [2–4]. Although precise global epidemiology is difficult to establish, DS is estimated to affect approximately 1 in 15,000–40,000 individuals [5,6]. Clinically, DS is characterised by early-onset, recurrent, often prolonged, and pharmacoresistant seizures, initially typically febrile and generalised or unilateral clonic or tonic-clonic, with subsequent diversification of seizure types and risk of status epilepticus [2–4,7]. Seizures are frequently triggered by fever, infections, temperature changes, exertion, emotional stress, and environmental factors, including hot baths, flashing lights, and sensitivity to visual patterns [8–10]. Beyond seizures, DS is recognised as a complex neurodevelopmental disorder associated with cognitive, motor, behavioural, and sleep-related impairments [11–14].

Genetically, DS is most often caused by pathogenic SCN1A variants (≈80–90% of cases) and typically arises *de novo*, although variants in other genes may produce DS-like phenotypes, highlighting the importance of comprehensive genetic testing [15–18]. Treatment focuses on reducing seizures and preventing status epilepticus using antiseizure medications, dietary therapies, and selected device-based interventions such as vagus nerve stimulation (VNS) [19–21], yet DS remains frequently drug resistant and is associated with substantial premature mortality [22–24], including sudden unexpected death in epilepsy (SUDEP), with reported rates of approximately 10–15% [25–28].

Because DS is a chronic and severe condition, caregiving demands are intensive and long-term, requiring sustained vigilance, complex treatment management, and frequent medical care [22–24,29,30]. Consequently, the burden of care extends well beyond disease management, affecting multiple physical, psychological, social, and economic domains of caregivers' lives [31–34].

In the physical domain, caregivers commonly report profound fatigue, chronic sleep disruption, and deterioration of their own health due to continuous care demands, particularly night-time vigilance and emergency preparedness [35–38]. These difficulties are consistently associated with limited time for self-care, work restrictions, reduced quality of life, and elevated perceived caregiver burden across physical and other domains [39,40]. Psychologically and emotionally, caregiving is commonly associated with chronic stress, anxiety, depressive symptoms, emotional exhaustion, and anticipatory grief, particularly in the context of severe seizures, progressive developmental slowing, and limited emotional support [35,36,39–41]. Caregivers also report intense fear related to seizures, constant supervision demands, and persistent worries about the child's future, including premature mortality and transition to adult care [37,38]. The economic burden of DS caregiving is substantial, involving both direct healthcare-related costs and indirect losses due to reduced work capacity, absenteeism, or job loss, often disproportionately affecting mothers [35,40,42,43]. Studies consistently show that work restrictions and productivity losses are common and may exceed direct medical costs [37,41,44,45]. Finally, caregiving in DS often disrupts social functioning, with caregivers reporting reduced social participation, strained friendships, and changes in couple and family relationships [38,41,44]. Feelings of isolation, stigma, and being misunderstood are common and may further exacerbate psychological burden and reduce overall quality of life [35,37,40,46].

Beyond its clinical complexity, DS requires sustained and structured engagement with healthcare systems, including coordinated specialist care, emergency management, and long-term multidisciplinary follow-up. Caregivers frequently navigate delays in diagnosis, fragmented care pathways, limited access to expertise, and variable availability of supportive services. Managing pharmacoresistance, polytherapy, and recurrent hospitalisations places caregivers in an active role in treatment decision-making and monitoring. This systemic dimension of care adds an additional layer of burden and uncertainty, underscoring the importance of examining caregivers' experiences within the broader healthcare context [30,35–37,45–47].

Therefore, given the substantial and multidimensional burden of caring for a person with DS, this study aims to assess quality of life and caregiver burden among family caregivers across multiple European countries, with particular attention to physical, psychological, social, and economic well-being. Using a multinational, patient-oriented approach, the study seeks to provide a comprehensive overview of caregivers' experiences and to identify priority areas for targeted support and intervention.

2. Material and methods

2.1. Study design

This study was conducted as part of the multinational QoL4Dravet – Measuring Quality of Life in Dravet Syndrome (QoL4Dravet), an international initiative coordinated by the Dravet Syndrome European Federation (DSEF; https://dravet.eu) aimed at assessing the quality of life of family caregivers of persons with Dravet syndrome across Europe. Data were collected in 14 European countries: Belgium, Croatia, France, Germany, Ireland, Italy, the Netherlands, Norway, Poland, Portugal, Serbia, Spain, Switzerland, and the United Kingdom.

A patient-oriented research approach was adopted, with caregivers and their representative organisation actively involved throughout the research process [48,49]. The DSEF acted as an equal research partner, contributing to the definition of study priorities, the development of the research tool, and the support of data collection, thereby ensuring that the survey addressed issues most relevant to families affected by DS. The identified priorities included the development of a DS-specific questionnaire focusing on caregivers' quality of life and the assessment of seizure-related burden, healthcare utilisation, caregiving constraints, and the broader psychosocial impact of caring for a person with DS.

Given the rarity of DS and the lack of comprehensive national patient registries in participating countries, a cross-sectional, observational design was employed using an anonymised, self-administered, computer-assisted online survey. The survey focused on caregivers' self-reported quality of life, burden of care, and use of health and support services related to caring for a person with DS, consistent with previous evidence demonstrating substantial caregiver burden associated with this condition.

2.2. Ethical issues

This survey was conducted in accordance with the principles of the Declaration of Helsinki [50]. The Dravet Syndrome European Federation (DSEF) acted as the coordinating body for the study and reviewed the study protocol internally to ensure compliance with ethical standards and data protection requirements.

Participation was entirely voluntary and anonymous. The study was non-interventional and involved the completion of an anonymous questionnaire, without the collection of identifiable personal or clinical data. In accordance with institutional and national regulations applicable at the time of data collection, formal approval from a local or academic ethics committee was not required for anonymous, non-interventional survey studies of this type.

Before beginning the survey, all participants were presented with an online information sheet and provided informed consent by voluntarily proceeding to complete the questionnaire.

2.3. Research tool

Since no specific instrument exists to assess the quality of life of caregivers of individuals with DS, an original *ad hoc* questionnaire was developed for this survey. The QoL4Dravet questionnaire was designed to comprehensively assess the quality of life of caregivers of individuals

with DS, addressing gaps in existing measurement tools that do not fully capture the complexity of this condition.

The development of the questionnaire followed a multi-phase, collaborative process. Key domains relevant to quality of life in DS were identified through a review of the scientific literature and consultations with stakeholders, including caregivers, patient representatives, and healthcare professionals. The development process also drew on insights from previous research on the social and quality-of-life impact of rare epilepsies, including items adapted from the Childhood Rare Epilepsy Social Impact Assessment (CRESIA) framework [51], which informed the initial pool of candidate items. These domains encompassed sociodemographic characteristics, health status of the affected person, psychological and emotional well-being, social support, physical health and daily functioning, and access to medical care and support services.

The questionnaire was developed through close collaboration between the DSEF and a multidisciplinary scientific team, ensuring both scientific rigour and relevance to lived experiences. Particular emphasis was placed on incorporating caregiver perspectives to reflect the realities of long-term care for individuals with DS. A preliminary version of the questionnaire was reviewed by a multidisciplinary panel of 13 experts proposed by the Board of the DSEF. The panel included researchers with expertise in Dravet syndrome and rare epilepsies, caregivers and family members of individuals with DS, representatives of patient organisations and federations, a psychologist, a health policy expert, pharmaceutical industry representatives, and physicians experienced in the management of DS and rare epilepsies. Several experts fulfilled more than one role. Experts evaluated each item using a dichotomous yes/no assessment regarding its relevance, clarity, wording, and appropriateness. For all negative evaluations, experts were required to provide written justification and suggested modifications. No numerical weighting of expert ratings was applied; items were evaluated using binary yes/no judgements and revised on the basis of qualitative feedback and expert consensus. Following the initial review, comments were incorporated, and a revised version of the questionnaire was circulated for a final validation round. Consensus was achieved when all experts approved the final version of the instrument.

The questionnaire was subsequently piloted among 24 caregivers in Spain and 21 caregivers in Italy between July and November 2024. Based on participant feedback, several refinements were introduced to improve transparency, clarity, precision, inclusiveness, and overall user-friendliness. Some items were revised to include explicit time references (e.g., “during the last two weeks”) to facilitate interpretation. In addition, overlapping or insufficiently informative items were removed, resulting in a reduction from 39 initial items to 27 direct quality-of-life items, complemented by four self-perceived quality-of-life items. The structure of the questionnaire was also refined through redistribution of items across quality-of-life domains to improve conceptual coherence and interpretability, while response options and rating scales remained unchanged.

Although the questionnaire underwent expert review and pilot testing, it was developed as a bespoke instrument specifically for the purposes of this study and has not undergone formal psychometric validation. Consequently, the QoL4Dravet questionnaire should be regarded as an exploratory research tool rather than a validated measurement scale, and the findings should be interpreted accordingly. Nevertheless, a preliminary assessment of internal consistency yielded a Cronbach’s alpha of 0.881 for the full scale, providing initial evidence of reliability. However, this should not be considered a substitute for formal psychometric validation. Formal psychometric validation of disease-specific instruments in rare disease populations is particularly challenging due to small and geographically dispersed populations, marked clinical heterogeneity, and the additional requirements of cross-cultural adaptation and linguistic equivalence in multinational studies.

To ensure accessibility and cultural relevance, the questionnaire was translated into multiple European languages, including Croatian, Dutch, English, French, German, Italian, Norwegian, Polish, Portuguese, Serbian, and Spanish. All language versions underwent a forward-and-backward translation process. Translations were performed and reviewed by bilingual individuals familiar with DS and recommended by the participating national patient organisations. Following translation, all versions were reviewed by local organisations affiliated with DSEF to ensure linguistic accuracy, conceptual equivalence, and cultural appropriateness before implementation.

The QoL4Dravet questionnaire consisted of two main parts. The first part collected sociodemographic information on caregivers and households, as well as clinical and treatment-related characteristics of individuals with DS, including seizure burden, healthcare use, and current therapies. The second part assessed caregivers’ quality of life and caregiver burden using domain-specific items covering physical health, psychological and emotional well-being, social functioning and support, daily functioning and self-care, and economic situation. In addition, the questionnaire included four separate single-item global self-assessment items capturing caregivers’ overall perceptions of physical well-being, emotional well-being, social well-being, and perceived autonomy. Physical well-being referred to caregivers’ overall perception of their physical health (including sleep and energy); emotional well-being refered to their ability to manage emotions and maintain a positive affect; social well-being refered to satisfaction with social relationships and support; and perceived autonomy refered to the sense of independence and self-sufficiency in daily life. This intentional combination allowed the assessment of both specific, experience-based aspects of caregiving and broader, subjective evaluations of overall well-being. The global self-assessment items were analysed separately and were not combined with the domain-specific items. Additional items assessed access to healthcare and support services, as well as the perceived impact of DS on family life. Responses were recorded using standardised Likert-type scales and categorical response options (Supplementary material).

2.4. Participants and setting

Participants were recruited through the DSEF, national Dravet associations, and online caregiver support groups operating across the participating European countries. Eligible participants were parents or family caregivers of individuals with a confirmed diagnosis of DS who were directly involved in providing daily care.

Additional inclusion criteria included the ability to understand the survey language and to complete an online questionnaire using electronic devices. Recruitment was conducted primarily through digital channels, including social media platforms and mailing lists managed by participating patient organisations.

2.5. Data collection

Data were collected over a two-month period, from April to May 2025, using an online survey platform among family caregivers of persons with DS. The Dravet Syndrome European Federation (DSEF) first contacted national patient advocacy organisations in each participating country to invite them to collaborate in the study. These organisations were actively involved in the study implementation process, including the translation of the questionnaire into national languages, the review and cultural adaptation of translated versions, and the dissemination of the survey among caregivers. After obtaining their agreement, an invitation letter including information about the study, instructions for participation, and a link to the online questionnaire was distributed through these organisations. Survey promotion also included social media activities, such as Facebook posts and reminders published by the DSEF and member organisations to enhance reach and participation.

The questionnaire was made available simultaneously in all participating countries and in the relevant language versions. Invitations to participate were disseminated by national patient organisations

through their established communication channels, including social media and mailing lists. Depending on local recruitment needs and response rates, between two and three reminder messages were distributed in each participating country to maximise participation. Recruitment continued until repeated dissemination efforts no longer generated additional survey responses.

Before accessing the questionnaire, participants were presented with an online information sheet and provided informed consent. Caregivers completed the survey independently using electronic devices. Completion time was approximately 15–20 min.

2.6. Data analysis

Descriptive statistics were used to summarise socio-demographic characteristics, clinical variables, and caregivers' responses to quality-of-life and well-being items. Categorical variables were presented as absolute frequencies and percentages. Continuous variables were summarised using means and standard deviations, medians, and interquartile ranges.

Associations between categorical variables were examined using the chi-square ($\chi 2$) test. This approach was applied to assess the relationship between country of residence and caregivers' occupational status. When statistically significant overall associations were identified, selected country-specific differences were further explored. Pairwise odds ratios (ORs) with 95% confidence intervals were calculated to compare the likelihood of being a full-time caregiver across countries. These analyses were based on the occupational status data presented in Table 2, with each country alternately treated as the reference category. Statistical significance was determined using corresponding p-values.

For certain comparative analyses, only the six countries with the largest sample sizes were included to ensure sufficient statistical power and reliable estimation. Countries with smaller samples were retained in descriptive analyses but excluded from inferential comparisons where cell sizes would have precluded meaningful interpretation.

Caregivers' quality of life and caregiver burden items were analysed descriptively using Likert-scale response distributions across predefined domains, including physical health, psychological and emotional well-being, social well-being, daily functioning, and economic well-being. Comparisons of caregivers' self-reported global well-being across countries were performed using the Kruskal-Wallis analysis of variance due to the ordinal nature of the outcome variables. When the overall Kruskal-Wallis test indicated statistically significant differences, post hoc pairwise comparisons were performed using the Conover-Iman post-hoc test, which incorporates adjustment for multiple comparisons to identify specific country-level differences. No interpretation of between-country differences was made in the absence of statistically significant overall effects. Sex differences in caregivers' self-reported well-being were assessed using the Mann–Whitney *U* test. Results were considered statistically significant at a two-sided p-value < 0.05. Missing data were minimal and confined to individual questionnaire items. No imputation was performed; all analyses were conducted on available data, and denominators in each analysis reflect the number of valid responses per item. All statistical analyses were conducted using JASP (Version 0.18.3) and PQStat (Version 1.8.4).

3. Results

The socio-demographic and clinical characteristics of caregivers and persons with DS are presented in Table 1. Caregivers were predominantly female (85%), with a mean age of 46.5 years (SD 10.2). Most had completed higher education (61.5%), and over three-quarters self-identified as belonging to the middle socioeconomic class (77.3%). Occupational status was heterogeneous, with similar proportions working full-time (26.4%), part-time (25.9%), or acting as full-time caregivers (25.6%). Participants were recruited from 14 European countries, with the largest proportions from France (n = 75), Italy (n =

Table 1
Socio-demographic characteristics of caregivers and persons with DS.

Characteristics	N (%)
DS caregivers	
Sex	
female	322 (85)
male	57 (15)
Age (in years)	
Range	25–76
Mean (SD)	46.5 (10.2)
95%CI for mean	45.4–47.5
median	45.0
Professional activity	
full-time caregiver	97 (25.6)
full-time employed	100 (26.4)
part-time employed	98 (25.9)
self-employed	29 (7.7)
retired	20 (5.3)
unemployed	35 (9.2)
Country of residence	
Belgium (BEL*)	11 (2.9)
Croatia (HRV)	5 (1.3)
France (FRA)	75 (19.8)
Germany (DEU)	56 (14.8)
Ireland (IRL	7 (1.8)
Italy (ITA)	63 (16.6)
Netherlands (NLD)	32 (8.4)
Norway (NOR)	14 (3.7)
Poland (POL)	63 (16.6)
Portugal (PRT)	23 (6.1)
Serbia (SRB)	3 (0.8)
Spain (ESP)	9 (2.4)
Switzerland (CHE)	9 (2.4)
United Kingdom (GBR)	9 (2.4)
Education	
primary education	3 (0.8)
secondary education	143 (37.7)
higher education	233 (61.5)
Self-reported socioeconomic status	
lower class	53 (14)
middle class	293 (77.3)
upper class	33 (8.7)
DS patients	
Sex	
female	203 (53.6)
male	175 (46.2)
prefer not to say	1 (0.3)
Age (in years)	
Range	0.8–52.4
Mean(SD)	14.3 (9.7)
95%CI for mean	13.3–15.3
Median	12.7
Age at DS diagnosis (years)	
Range	0.0–43.5
Mean(SD)	3.1 (5.3)
95%CI for mean	2.6–3.6
25th percentile	0.75
Median	1.3
75th percentile	3.2

(*continued on next page*)

Table 1 (*continued*)

Characteristics	N (%)
Number of current medications	
0	1 (0.3)
1	12 (3.2)
2	44 (11.6)
3	119 (31.4)
4	129 (34)
≥ 5	74 (19.5)
Seizure frequency (last 3 months)	
less than 4	165 (43.5)
between 5 and 9	66 (17.4)
between 10 and 14	46 (12.1)
between 15 and 19	21 (5.5)
≥ 20	81 (21.4)
Seizures requiring rescue medication (last 3 months)	
0	187 (49.3)
1	46 (12.1)
2	36 (9.5)
3	22 (5.8)
4	17 (4.9)
5	7 (1.8)
6	12 (3.2)
7	4 (1.1)
8	11 (2.9)
9	4 (1.1)
≥ 10	33 (8.7)
Hospital admissions or ER visits (last 3 months)	
0	276 (72.8)
1	52 (13.7)
2	21 (5.5)
3	17 (4.9)
4	9 (2.4)
5	2 (0.5)
6	1 (0.3)
≥ 7	1 (0.3)

* Country name abbreviations are presented in accordance with ISO 3166–1 alpha-3.

63), Poland (n = 63), and Germany (n = 56).

The persons with DS, the caregivers were caring for (n = 379), had a mean age of 14.3 years (SD 9.7; range 0.8–52.4) and were slightly more often female (53.6%). The mean age at diagnosis was 3.1 years (SD 5.3), with a median of 1.3 years (range 0.0–43.5). The clinical profile indicated a substantial disease burden, with more than 85% receiving three or more concurrent antiseizure medications. Seizure frequency varied widely: while 43.5% experienced fewer than four seizures in the preceding three months, nearly one-quarter reported 15 or more seizures during the same period. Almost half of the individuals did not require rescue medication; however, a considerable proportion required repeated rescue interventions, indicating ongoing seizure activity and clinical instability. Rates of hospital admissions or emergency department visits were relatively low during the same period, with 72.8% reporting no visits in the preceding three months, 13.7% reported one visit, and fewer than 10% reported three or more visits.

Caregivers' occupational status varied substantially across countries (Table 2). The proportion of full-time caregivers ranged from approximately 7–10% in Belgium, France, Germany, and Norway to nearly half or more in Poland, the United Kingdom, Serbia, and Spain. Full-time employment was particularly prevalent in Portugal, whereas in several other countries, including Belgium, Norway, and Spain, the proportions of full-time and part-time employment were comparable, and part-time employment was more common in Germany, the Netherlands, Italy, and Switzerland. Retirement and self-employment accounted for relatively small proportions across all countries, although self-employment was relatively more frequent in Switzerland. Overall, a significant association was observed between country of residence and caregivers'

Table 2
Caregivers' occupational status by country.

	BEL	HRV	FRA	DEU	IRL	ITA	NLD	NOR	POL	PRT	SRB	ESP	CHE	GBR	Total
Caregivers' occupational status															
Full-time caregiver	1 (9.1%)	2 (40%)	7 (9.3%)	6 (10.7%)	2 (28.6%)	23 (36.5%)	10 (31.3%)	1 (7.1%)	30 (47.6%)	4 (17.4%)	2 (66.7%)	4 (44.4%)	1 (11.1%)	4 (44.4%)	97 (25.6%)
Full-time employed	4 (36.4%)	1 (20%)	24 (32%)	17 (30.4%)	1 (14.3%)	8(12.7%)	2 (6.3%)	6 (42.9%)	13 (20.6%)	17 (73.9%)	0	2 (22.2%)	2 (22.2%)	3 (33.3%)	100 (26.4%)
Part-time employed	4 (36.4%)	0	21 (28%)	24 (42.9%)	2 (28.6%)	19 (30.2%)	13 (40.6%)	6 (42.9%)	3 (4.8%)	1 (4.3%)	0	2 (22.2%)	3 (33.3%)	0	98 (25.9%)
Retired	1 (9.1%)	0	5 (6.7%)	1 (1.8%)	1 (14.3%)	7 (11.1%)	1 (3.1%)	0	1 (1.6%)	1 (4.3%)	0	1 (11.1%)	0	1 (11.1%)	20 (5.3%)
Self-employed	1 (9.1%)	0	7 (9.3%)	4 (7.1%)	1 (14.3%)	3 (4.8%)	5 (15.6%)	0	4 (6.3%)	0	0	0	3 (33.3%)	1 (11.1%)	29 (7.7%)
Unemployed	0	2 (40%)	11 (14.7%)	4 (7.1%)	0	3 (4.8%)	1 (3.1%)	1 (7.1%)	12 (19%)	0	1 (33.3%)	0	0	0	35 (9.2%)

Chi-square = 156.076, 65 df, $p < 0.001$.

occupational status ($\chi 2 = 156.1$; df = 65; $p < 0.001$), although country-specific comparisons should be interpreted cautiously due to unequal sample sizes across countries.

Pairwise odds ratios for being a full-time caregiver were calculated based on the data presented in Table 2 and are shown in Table 3, with each column representing the reference country. Significant differences were observed across multiple country pairs. Caregivers in Italy and Poland were consistently more likely to be full-time caregivers compared with caregivers from several other countries, whereas caregivers in France, Germany, and the Netherlands showed odds that varied depending on the reference country. In addition, Poland differed significantly from other countries with respect to the proportion of caregivers reporting unemployment, which was significantly higher than in most other participating countries. Overall, these findings demonstrate substantial cross-country variability in caregivers' occupational status, with both the direction and magnitude of differences dependent on the reference country used for comparison.

Caregivers' responses to quality-of-life and caregiver burden items were grouped into five predefined thematic areas for descriptive purposes: physical health, psychological and emotional well-being, social well-being, daily functioning, and economic well-being (Table 4). These groupings were used solely for descriptive presentation and do not represent validated subscales. Responses spanned the full Likert scale, reflecting substantial heterogeneity in caregivers' experiences.

Additional analyses examining associations between caregiver quality of life and clinical variables – including seizure frequency, number of antiseizure medications, use of rescue medications, and hospital/ER admissions – showed that although exploratory Kendall's tau analyses identified a single nominally significant association between rescue medication use and caregiver emotional well-being ($\tau = -0.10$, $p = 0.03$), all correlations were weak in magnitude ($|\tau| \leq 0.10$) and did not show a consistent pattern across quality-of-life domains, suggesting that caregiver QoL is not straightforwardly driven by these clinical disease burden measures (Supplementary Table S1). Similarly, exploratory analyses of selected sociodemographic variables, including caregiver employment status and country of residence, did not identify statistically significant predictors of caregiver quality of life. Attempts to construct multivariable explanatory models were likewise inconclusive because the observed associations were weak and inconsistent and because of limitations related to sample structure.

Within the physical health domain, more than half of caregivers reported dissatisfaction with sleep and rest, frequent physical discomfort, and elevated levels of fatigue. Although most caregivers indicated the ability to perform routine physical activities, many perceived themselves as more vulnerable to illness and reported that health-related problems, including seizure-related complications in the cared-for person, interfered with everyday functioning. Psychological and emotional well-being items revealed marked emotional strain. A considerable proportion of caregivers reported symptoms of anxiety, sadness, stress, dissatisfaction with their current life situation, and emotional overload during the previous two weeks. At the same time, many caregivers also reported periods of positive mood, suggesting a degree of psychological resilience and adaptive coping despite sustained caregiving burden.

In the social well-being domain, a substantial proportion of caregivers indicated experiences of loneliness and only moderate satisfaction with social relationships. Reports of limited support from friends, community resources, and healthcare professionals were also evident, despite generally positive perceptions of comfort and safety within the home environment. Items related to daily functioning suggested difficulties in balancing caregiving responsibilities with personal time, leisure, and self-care. Many caregivers reported limited enjoyment of free time and insufficient time to attend to their own needs. In terms of economic well-being, although a majority rated their financial situation as adequate, a non-negligible proportion reported economic strain.

Self-reported well-being differed by sex across several domains (Table 5). No statistically significant differences were observed between female and male caregivers in physical well-being. In contrast, emotional well-being differed significantly by sex, with female caregivers more frequently reporting poorer emotional well-being than male caregivers ($p = 0.04$). Sex differences were also evident in self-reported autonomy, with female caregivers reporting lower levels of autonomy compared with males ($p = 0.008$). Similarly, social well-being varied significantly by sex ($p = 0.039$), with female caregivers more often indicating poorer social well-being.

Caregivers' well-being was examined across countries using four single-item global self-assessments of physical well-being, emotional well-being, perceived autonomy, and social well-being (Table 6). No statistically significant differences between countries were observed for self-reported physical well-being (Kruskal-Wallis $H = 20.878$, $p = 0.08$), suggesting broadly comparable levels of physical well-being across countries.

In contrast, significant cross-country differences were observed in self-reported emotional well-being (Kruskal-Wallis $H = 29.789$, $p = 0.005$). Caregivers from Poland and Spain reported particularly high proportions of poor emotional well-being, whereas caregivers from the Netherlands and Germany reported good or very good emotional well-being more frequently. Post hoc analyses indicated multiple significant pairwise differences between countries, highlighting pronounced variability in emotional burden across national contexts.

Self-reported autonomy also differed significantly between countries (Kruskal-Wallis $H = 30.247$, $p = 0.004$). Lower levels of perceived autonomy were more frequently reported in Croatia and Poland, with a similar pattern observed in Spain, although estimates for Spain should be interpreted cautiously due to the small sample size. On the other hand, higher levels were more common among caregivers in Italy and the Netherlands. At the same time, estimates from countries with small

Table 3
Pairwise odds ratios for being a full-time caregiver by country (column country as reference).

	FRA	DEU	ITA	NLD	POL	PRT
OR of being full-time caregivers						
FRA	x	ns	5.586 [2.200, 14.183] p = 0.0003	ns	8.831 [3.513, 22.200] p < 0.0001	ns
DEU	ns	x	4.792 [1.780, 12.896] p = 0.0019	3.788 [1.224, 11.720] p = 0.0208	7.576 [2.842, 20.197] p < 0.0001	ns
ITA	0.179 [0.071, 0.455] p = 0.0003	0.209 [0.078, 0.562] p = 0.0019	x	ns	ns	ns
NLD	ns	0.264 [0.085, 0.817] p = 0.0208	ns	x	ns	ns
POL	0.113 [0.045, 0.285] p < 0.0001	0.132 [0.050, 0.352] p < 0.0001	ns	ns	x	0.232 [0.071, 0.758] p = 0.0156
PRT	ns	ns	ns	ns	4.318 [1.319, 14.140] p = 0.0156	x

ns: not significant.

sample sizes (e.g., Ireland, Portugal, Norway, Switzerland, and the United Kingdom) should be interpreted cautiously. No statistically significant differences were detected for self-reported social well-being across countries (Kruskal-Wallis H = 18.965, p = 0.12), suggesting comparable levels of social well-being across the participating countries.

4. Discussion

The findings of this multinational study highlight the complexity and multidimensional nature of caregiving for individuals with DS, extending far beyond the initial diagnostic period. Despite relatively early diagnosis in many cases, caregivers in this cohort reported substantial clinical, occupational, psychological, and social challenges. Overall, caregiving burden in DS appears to be driven by the chronic and pharmacoresistant course of the condition, its associated neurodevelopmental and behavioural impairments, high demands on caregivers' time and employment, pronounced impairments in emotional well-being, and marked gender- and country-specific differences in perceived quality of life. Hence, these findings highlight a pressing need for increased awareness, enhanced coordination of care, and more responsive, context-sensitive support systems for caregivers.

Firstly, the results indicate that caregiving for a person with DS is intensive and associated with a substantial clinical burden. Although the median age at diagnosis in our cohort was relatively early (1.3 years), the mean age of persons with DS in the sample was 14.3 years, with cases extending into adulthood (up to 52 years). The broad age range represented in the sample suggests that substantial caregiving burden is observed among caregivers of individuals with DS not only during childhood but also during adolescence and adulthood. In the present cohort, substantial medical complexity was observed: more than 85% of individuals were treated with three or more antiseizure medications, nearly one in five required five or more drugs, and over one-fifth experienced at least 20 seizures within the preceding three months. Moreover, almost half of the persons with DS required rescue medication during the same period, reflecting ongoing seizure severity and unpredictability despite treatment.

Importantly, the clinical burden observed in this study should also be considered in the context of diagnostic trajectories experienced by many families. Previous studies show that although seizure onset typically occurs early in life and some children receive a diagnosis within the first year, many families experience diagnostic delays lasting several years, with diagnoses sometimes made in adolescence or adulthood [46,52–55]. This reflects broader evidence from rare disease and epilepsy research, in which the diagnostic process is frequently described as an "odyssey" characterised by multiple specialist consultations, misdiagnoses, and prolonged uncertainty [30,56–59], with neurological and epileptic conditions being particularly prone to delay [30,47,55,60–62].

Although advances in molecular diagnostics and increasing awareness among paediatric neurologists have shortened diagnostic timelines for some families [19–21,54,63–65], DS is still often diagnosed primarily based on clinical presentation, with genetic confirmation delayed

Table 4
Caregivers' quality of life and caregiver burden.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Physical health					
I am satisfied with my sleep and rest.	80 (22)	146 (40.1)	50 (13.7)	84 (23.1)	4 (1.1)
My quality of life depends on medication, medical equipment, or medical interventions.	41 (11.3)	28 (7.7)	58 (16)	160 (44.2)	75 (20.7)
I frequently show signs of physical discomfort, often appearing uneasy or restless.	28 (7.7)	91 (25.1)	87 (24)	114 (31.5)	42 (11.6)
Seizures and seizure-related symptoms make it difficult for me to perform everyday activities.	25 (6.9)	37 (10.2)	64 (17.7)	128 (35.5)	107 (29.6)
I perceive myself as more prone to illness than others.	31 (8.6)	121 (33.6)	76 (21.1)	88 (24.4)	44 (12.2)
I can carry out everyday physical activities (e.g., walking, climbing stairs, carrying objects).	12 (3.3)	30 (8.3)	19 (5.3)	164 (45.4)	136 (37.7)
I experienced a high level of fatigue in the past two weeks.	1 (0.3)	27 (7.5)	158 (43.8)	121 (33.5)	54 (15)
Mental health and emotional well-being					
I generally feel happy.	26 (7.2)	72 (19.8)	127 (35)	130 (35.8)	8 (2.2)
In the past two weeks, I have felt intense sadness that interfered with my daily life.	19 (5.2)	86 (23.8)	48 (13.3)	136 (37.6)	73 (20.2)
I am dissatisfied with my current life circumstances.	24 (6.6)	78 (21.5)	99 (27.3)	120 (33.1)	41 (11.3)
In the past two weeks, I have felt ashamed because of socially unacceptable actions related to my situation.	63 (17.4)	135 (37.2)	74 (20.4)	71 (19.6)	20 (5.5)
In the past two weeks, I have felt stressed and overwhelmed by my responsibilities.	9 (2.5)	30 (8.3)	50 (13.9)	137 (38)	135 (37.4)
I see myself as upbeat and full of energy.	44 (12.2)	108 (29.9)	106 (29.4)	90 (24.9)	13 (3.6)
I generally experience a sense of psychological well-being.	41 (11.4)	111 (30.8)	120 (33.3)	84 (23.3)	4 (1.1)
In the past two weeks, I have experienced periods of good mood.	12 (3.3)	30 (8.3)	58 (16.1)	209 (57.9)	52 (14.4)
In the past two weeks, I have experienced symptoms of anxiety.	18 (5)	62 (17.2)	60 (16.6)	150 (41.6)	71 (19.7)
Social well-being					
In the past two weeks, I have experienced feelings of loneliness, isolation, and abandonment.	27 (7.4)	68 (18.7)	58 (16)	147 (40.5)	63 (17.4)
My social relationships are satisfactory.	48 (13.3)	117 (32.4)	80 (22.2)	98 (27.1)	18 (5)
I feel comfort and joy when being at home.	12 (3.3)	35 (9.7)	77 (21.3)	179 (49.4)	59 (16.3)
I receive support from my friends.	50 (13.9)	97 (26.9)	112 (31)	83 (23)	19 (5.3)
I receive sufficient support from my home, community, and healthcare services.	40 (11.1)	89 (24.7)	94 (26)	105 (29.1)	33 (9.1)
Daily functioning					
In the past two weeks, I have enjoyed my leisure time.	85 (23.5)	93 (25.7)	76 (21)	86 (23.8)	22 (6.1)
I can manage my daily tasks and responsibilities.	33 (9.1)	83 (23)	75 (20.8)	133 (36.8)	37 (10.2)
I am satisfied with my personal achievements.	30 (8.3)	89 (24.7)	105 (29.1)	119 (33)	18 (5)
In the past two weeks, I have had enough time for self-care.	86 (23.9)	120 (33.3)	77 (21.4)	67 (18.6)	10 (2.8)
Economic well-being					
My economic situation covers my basic needs and allows for some discretionary spending.	28 (7.7)	57 (15.7)	71 (19.6)	164 (45.3)	42 (11.6)
My family's financial resources are sufficient to cover my personal care and health-related expenses.	20 (5.5)	41 (11.3)	53 (14.6)	177 (48.9)	71 (19.6)

or incomplete. Diagnostic delays have been associated with ineffective treatment strategies, frequent medication changes, unnecessary hospitalisations, and exposure to contraindicated therapies, including sodium channel blockers that may worsen seizures and prognosis [46,52,53,55,65]. Recent research on caregivers' experiences of the diagnostic odyssey further suggests that substantial disease burden may remain despite early diagnosis, as DS continues to be a chronic, pharmacoresistant, and clinically demanding condition [30].

Taken together, these findings indicate that DS remains a lifelong condition characterised by high seizure burden and complex treatment regimens. Consequently, caregiver burden appears to extend beyond the diagnostic phase and remains evident among caregivers of older children, adolescents, and adults with DS, underscoring the need to conceptualise caregiver burden in DS within a life-course perspective, as suggested by both the present findings and previous literature.

Secondly, the findings demonstrate that caregiving for a person with DS entails substantial occupational and economic costs, which vary markedly across countries. In the present cohort, only 26.4% of caregivers were employed full-time, whereas 25.6% identified themselves as full-time caregivers, underscoring the extent to which DS care constrains participation in the labour market. Notably, the proportion of full-time caregivers differed strikingly between countries, ranging from below 10% in some Western European countries to nearly half or more in others. This heterogeneity suggests that caregiver burden may be influenced not only by disease severity but also by broader contextual factors. For example, countries with a higher likelihood of caregivers being out of paid employment may differ with respect to access to formal respite care, opportunities for flexible employment, welfare arrangements, and other contextual factors that were not assessed in the present study [43–45,66,67].

Although the present study did not directly assess policy or health-system characteristics, cross-country differences may be influenced by variation in national approaches to disability and rare disease support. Evidence from several European contexts indicates that even where formal support exists, caregivers, predominantly mothers, continue to experience substantial career disruption, financial strain, and unmet support needs [42–45,66,68]. This pattern is consistent with previous research demonstrating profound work-related and financial consequences of DS caregiving, including lost income, reduced working hours, disrupted career trajectories [42,43,66,69,70], poorer quality of life and increased emotional distress [41,44,45,71,72]. Evidence from European and non-European contexts further shows that between one-quarter and one-third of caregivers report job loss, while many others experience missed workdays, reduced salaries, or forced job changes due to caregiving demands [34,35,43,44,66]. Importantly, many of these costs remain "hidden," as they are insufficiently captured by healthcare expenditure metrics and are instead absorbed by families through long-term employment instability, reduced pension contributions, and constrained career advancement.

Thus, the occupational impact of DS caregiving cannot be understood solely in clinical terms. The observed cross-country differences suggest that factors beyond clinical characteristics may contribute to caregiver burden; however, the present study was not designed to identify the specific structural, policy, or health-system determinants underlying these differences. Consequently, the results underscore the need for policy-sensitive and context-specific interventions, such as flexible employment arrangements, income protection schemes, and formal caregiver support, rather than uniform models of support.

Thirdly, this study indicates that caregivers' quality of life is significantly impaired in key areas related to sleep, fatigue, stress, and emotional well-being, while physical functioning and the ability to perform basic daily activities are relatively better preserved. This pattern suggests that DS caregiving burden manifests primarily as chronic psychological and emotional strain rather than physical incapacity. While a growing body of evidence demonstrates that psychological and emotional well-being are the most severely affected aspects of caregiver well-being in DS, studies report significantly reduced psychological quality of life, elevated levels of anxiety and depressive symptoms, and marked sleep disturbances among caregivers, often exceeding impairments observed in physical health domains [36,39,45–47,66,70]. Across international studies, approximately 60–80% of caregivers report clinically significant sleep problems, fatigue, or symptoms of anxiety and depression, a range that is consistent with the proportion observed in the present study (62.1%), whereas severe physical health limitations are reported by a smaller proportion [36,46]. Systematic reviews further confirm that emotional exhaustion, persistent stress, and impaired sleep are central features of DS caregiving regardless of disease stage or seizure severity [32,34,68].

Qualitative studies complement these findings by documenting caregivers' lived experiences of enduring anxiety, helplessness, guilt, fear of seizure unpredictability and SUDEP, loneliness, and emotional overload, with many reporting long-term emotional exhaustion [33,36,37,39,41,44]. Thus, while caregivers often adapt physically to the demands of daily care, the constant vigilance, sleep deprivation, and emotional responsibility associated with DS are far more difficult to mitigate and remain major drivers of distress [36,45,68,71]. Thus, these results underscore that caregiver burden in DS is predominantly emotional and psychological in nature, highlighting a critical gap in support systems that prioritise medical management over mental health care. The absence of statistically significant associations between current clinical severity indicators and caregiver quality of life should be interpreted with caution. Clinical severity was assessed using caregiver-reported measures reflecting the preceding three months and may not fully capture the cumulative burden associated with years of caregiving. Nevertheless, the findings may also suggest that caregiver burden in DS is not solely determined by current seizure activity or treatment intensity, but reflects a chronic and multidimensional experience shaped by long-term psychological, social, and occupational demands.

Lastly, the present study reveals sex- and country-specific differences in caregivers' self-reported well-being, suggesting that the lived burden of DS caregiving is shaped by both gendered caregiving roles and national contexts. While physical well-being did not differ significantly by sex, women reported poorer emotional well-being, lower autonomy, and poorer social well-being than men. This pattern aligns with extensive evidence showing that mothers more often assume primary caregiving roles and experience higher psychological burden, stronger disease-related emotions, and greater work restrictions than fathers [36,39,46,73]. These differences reflect the feminisation of informal care and the unequal distribution of caregiving responsibilities observed across rare paediatric and genetic conditions [74–79].

Cross-country analyses further demonstrated substantial heterogeneity in emotional well-being and autonomy, with particularly high

Table 5
Caregivers' self-reported well-being by sex.

	Poor	Fair	Good	Very good	Excellent	p
Self-reported physical well-being						
female	70 (22.9)	126 (41.2)	94 (30.7)	15 (4.9)	1 (0.3)	ns
male	8 (14.5)	21 (38.2)	21 (38.2)	5 (9.1)	0	
Self-reported emotional well-being						
female	75 (24.5)	129 (42.2)	87 (28.4)	13 (4.2)	2 (0.6)	0.04
male	8 (14.5)	21 (38.2)	24 (43.6)	0	2 (3.6)	
Self-reported autonomy						
female	69 (22.8)	72 (23.8)	90 (29.7)	47 (15.5)	19 (8.3)	0.008
male	5 (9.1)	9 (16.4)	23 (41.8)	13 (23.6)	5 (9.1)	
Self-reported social well-being						
female	89 (29.1)	103 (33.7)	85 (27.8)	24 (7.8)	5 (1.6)	0.039
male	10 (18.2)	16 (29.1)	23 (41.8)	6 (10.9)	0	

ns: not significant.

Table 6
Caregivers' self-reported well-being across countries.

Item	BEL	HRV	FRA	DEU	IRL	ITA	NLD	NOR	POL	PRT	SRB	ESP	CHE	GBR	Total
Self-reported physical well-being															
poor	1 (9.1%)	1 (20%)	9 (12.5%)	9 (16.7%)	0	10 (15.9%)	5 (18.5%)	1 (8.3%)	26 (42.6%)	7 (31.8%)	0	4 (50%)	2 (25%)	3 (33.3%)	78 (22.9%)
fair	6 (54.5%)	1 (20%)	34 (47.2%)	22 (40.7%)	2 (33.3%)	33 (52.4%)	7 (25.9%)	8 (66.7%)	18 (29.5%)	9 (40.9%)	2 (66.7%)	2 (25%)	1 (12.5%)	2 (22.2%)	147 (41.5%)
good	4 (35.4%)	3 (60%)	26 (36.1%)	21 (38.9%)	2 (33.3%)	15 (23.8%)	13 (48.1%)	3 (25%)	14 (22.9%)	3 (13.6%)	1 (33.3%)	2 (25%)	5 (62.5%)	3 (33.3%)	115 (30.7%)
very good	0	0	3 (4.2%)	2 (3.7%)	2 (33.3%)	5 (7.9%)	2 (7.4%)	0	3 (4.9%)	2 (9.1%)	0	0	0	1 (11.1%)	20 (5.5%)
excellent	0	0	0	0	0	0	0	0	0	1 (4.3%)	0	0	0	0	1 (0.3%)
Kruskal-Wallis ANOVA							H = 20.878, p = 0.08								
Self-reported emotional well-being															
poor	4 (36.4)	1 (20%)	11 (15.3%)	8 (14.8%)	0	12 (19%)	1 (3.7%)	3 (25%)	32 (52.5%)	5 (22.7%)	0	4 (50%)	0	2 (22.2%)	83 (21.9%)
fair	5 (45.5)	2 (40%)	39 (54.2%)	19 (35.2%)	5 (83.3%)	26 (41.3%)	12 (44.4%)	6 (50%)	11 (18%)	11 (50%)	2 (66.7%)	2 (25%)	5 (62.5%)	5 (55.6%)	150 (39.6%)
good	2 (18.2)	2 (40%)	21 (29.2%)	25 (46.3%)	1 (16.7%)	17 (27%)	12 (44.4%)	2 (16.7%)	18 (29.5%)	3 (13.6%)	1 (33.3%)	2 (25%)	3 (37.5)	2 (22.2%)	111 (29.3%)
very good	0	0	1 (1.4%)	2 (3.7%)	0	7 (11.1%)	0	0	0	3 (13.6%)	0	0	0	0	13 (3.4%)
excellent	0	0	0	0	0	1 (1.6%)	2 (7.4%)	1 (8.3%)	0	0	0	0	0	0	4 (1.1%)
Kruskal-Wallis ANOVA							H = 29.789, p = 0.005								
p for group differences	DEU*NLD*		NLD*POL**	BEL* POL***ESP*		POL***	BEL* FRA* POL***ESP*		FRA** DEU*** ITA*** NLD***CHE*			DEU*NLD*	POL*		
Self-reported autonomy															
poor	4 (36.4%)	2 (40%)	15 (20.8%)	9 (16.7%)	1 (16.7%)	7 (11.3%)	6 (23.1%)	5 (41.7%)	15 (24.6%)	2 (9.1%)	0	2 (25%)	3 (37.5%)	3 (37.5%)	74 (20.7%)
fair	1 (9.1%)	3 (60%)	22 (30.6%)	12 (22.2%)	2 (33.3%)	14 (22.6%)	2 (7.7%)	3 (25%)	9 (14.8%)	8 (36.4%)	0	2 (25%)	0	3 (37.5%)	81 (22.6%)
good	2 (18.2%)	0	27 (37.5%)	21 (38.9%)	0	14 (22.6%)	5 (19.2%)	4 (33.3%)	25 (41%)	6 (27.3%)	2 (66.7%)	3 (37.5%)	3 (37.5%)	1 (12.5%)	113 (31.6%)
very good	4 (36.4%)	0	5 (6.9%)	10 (18.5%)	2 (33.3%)	16 (25.8%)	7 (26.9%)	0	10 (16.4%)	2 (9.1%)	1 (33.3%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	60 (16.8%)
excellent	0	0	3 (4.2%)	2 (3.7%)	1 (16.7%)	11 (17.7%)	6 (23.1%)	0	2 (3.3%)	4 (18.2%)	0	0	1 (12.5%)	0	30 (8.4%)
Kruskal-Wallis ANOVA							H = 30.247, p = 0.004								
p for group differences		DEU* IRL* ITA*** NLD*** PRT* SRB*	ITA***NLD***	HRV*NOR*	HRV*	HRV*** FRA*** NOR*** POL*GBR*	HRV*** FRA*** NOR***GBR*	DEU* ITA*** NLD*** PRT* SRB*	ITA*	HRV*NOR*	HRV*NOR*			ITA*NED*	
Self-reported social well-being															
poor	3 (27.3%)	1 (20%)	15 (20.8%)	11 (20.4%)	2 (33.3%)	15 (23.8%)	3 (11.1%)	5 (41.7%)	27 (44.3%)	6 (27.3%)	0	5 (62.5%)	5 (22.7%)	4 (44.4%)	99 (27.4%)
fair	4 (36.4%)	2 (40%)	26 (36.1%)	16 (29.6%)	3 (50%)	25 (39.7%)	11 (40.7%)	1 (8.3%)	14 (23%)	6 (27.3%	2 (66.7%)	1 (12.5%)	5 (62.5%)	3 (33.3%)	119 (33%)
good	4 (36.4%)	2 (40%)	25 (34.7%)	20 (37%)	1 (16.7%)	15 (23.8%)	9 (33.3%)	4 (33.3%)	18 (29.5%)	5 (22.7%)	1 (33.3%) 5 (22.7%)	5 (22.7%)	0	2 (22.2%)	108 (29.9%)
very good	0	0	6 (8.3%)	4 (7.4%)	0	6 (9.5%)	4 (14.8%)	2 (16.7%)	2 (3.3%)	5 (22.7%)	0	0	1 (12.5%)	0	30 (8.3%)
excellent	0	0	0	3 (5.6%)	0	2 (3.2%)	0	0	0	0	0	0	0	0	5 (1.4%)
Kruskal-Wallis ANOVA							H = 18.965, p = 0.12								

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

proportions of poor emotional well-being reported by caregivers in Poland and Spain, whereas caregivers in the Netherlands and Germany more often reported good or very good emotional well-being; autonomy was more frequently reduced in Croatia, Poland, and Spain, and more often preserved in Italy, the Netherlands, and Norway. For instance, the relatively high proportion of caregivers outside paid employment observed in Poland may reflect a combination of contextual factors, including labour-market conditions, cultural expectations regarding family caregiving, and welfare arrangements; however, these factors were not examined in the present study. Such cross-national variability suggests that caregiver burden may be influenced by factors extending beyond clinical characteristics alone. However, because contextual variables such as health-care organisation, access to support services, and welfare arrangements were not measured, the present findings should be interpreted cautiously and cannot determine the mechanisms underlying these differences [34,37,41,45,46].

Taken together, these findings argue against a "one-size-fits-all" approach to caregiver support and highlight the need for individualised, gender-sensitive, and context-aware interventions that integrate psychological support with measures enhancing caregivers' autonomy, social participation, and ability to reconcile long-term care with employment and family life [32,33].

4.1. Limitations

Although this study represents one of the largest multinational investigations of caregivers of persons with DS conducted in Europe to date, several limitations should be acknowledged. First, although the questionnaire was developed through a rigorous, multidisciplinary, and patient-oriented process involving clinicians, researchers, caregivers, and patient representatives, it constitutes a bespoke instrument developed specifically for this study and has not undergone formal psychometric validation. Consequently, its psychometric properties, including construct validity, have not been formally established. This limits the ability to interpret the findings as scores derived from a validated instrument, constrains comparisons with studies using validated measures, and suggests that the results should be interpreted as exploratory. Although a preliminary assessment of internal consistency yielded a Cronbach's alpha of 0.881, this provides only limited evidence of reliability and does not substitute for formal psychometric validation, including assessment of construct validity and measurement invariance. At the same time, the development of disease-specific instruments in rare disease populations presents substantial methodological challenges due to small and geographically dispersed populations, marked clinical heterogeneity, reliance on proxy reporting, and the need for cross-cultural adaptation across multiple languages. These challenges are particularly pronounced in multinational studies, where establishing linguistic equivalence and measurement invariance across countries requires additional validation procedures that are often difficult to implement in small rare-disease populations. Future studies should therefore focus on the formal psychometric evaluation and validation of the QoL4Dravet questionnaire. Second, despite the relatively large sample size ($n = 379$), the total population of caregivers of individuals with DS in Europe is much higher, although it remains unknown. Consequently, the representativeness of the sample cannot be fully established, which limits the generalizability of the findings. Third, the study employed a cross-sectional design and did not include a control group. This restricts the ability to directly attribute observed impairments in quality of life and caregiver burden specifically to DS or to compare their magnitude relative to other caregiving contexts. Fourth, recruitment was conducted through the Dravet Syndrome European Federation (DSEF), national Dravet associations, and online support groups, primarily via digital channels. This recruitment strategy may have introduced selection bias, as caregivers who are not affiliated with patient organisations, are less socially connected, or have limited access to digital technologies, may be underrepresented. As a result, the experiences of more isolated or socioeconomically disadvantaged caregivers may not be fully captured. Furthermore, more than three-quarters of participants self-identified as belonging to the middle socioeconomic class. This may indicate an underrepresentation of caregivers from more socioeconomically disadvantaged backgrounds, who may experience greater caregiving burden and fewer support resources, thereby potentially limiting the representativeness of the findings. In addition, the relatively short recruitment period may have contributed to selection bias, as caregivers experiencing acute medical emergencies or periods of particularly intensive caregiving may have been less likely to participate. Although multiple reminder messages were distributed and response rates plateaued before recruitment was closed, the experiences of the most burdened caregivers may nevertheless be underrepresented. Fifth, all data were based on self-report measures, which are inherently subjective and may be influenced by recall bias, social desirability bias, or current emotional state. In addition, detailed data on the neurodevelopmental profile of individuals with DS (e.g., severity of cognitive impairment, behavioural difficulties, motor functioning, or communication abilities) were not systematically collected, which limits the ability to analyse how specific clinical characteristics of the affected person may influence caregiver burden. Consequently, the study does not allow assessment of the relative contribution of neurodevelopmental impairments, functional limitations, and seizure-related factors to caregiver quality of life and burden, thereby limiting the explanatory depth of the findings. Sixth, the sample consisted predominantly of women, which reflects the feminisation of caregiving but limits the capacity to explore gender-specific differences in greater depth. In addition, caregivers of adults with DS were underrepresented, as most respondents were caring for children or adolescents, which may restrict the applicability of the findings to later stages of the disease course. Seventh, the distribution of participants across countries was uneven, with relatively small samples from several countries. This limits the robustness of cross-country comparisons and increases the risk that observed differences reflect sampling variability rather than true systemic or cultural effects. Additional analyses examining potential predictors of caregiver quality of life did not identify statistically significant associations. Furthermore, the feasibility of robust multivariable modelling was limited by the multinational design, uneven country-level sample sizes, small subgroup sizes, and skewed distributions of certain outcome variables. Consequently, the study was not able to reliably determine the independent contribution of individual clinical and sociodemographic factors to caregiver quality of life. Finally, while this study provides a broad quantitative overview of caregivers' quality of life and burden, it cannot fully capture the complexity and nuance of lived caregiving experiences. Further in-depth qualitative research is therefore needed, particularly to explore longitudinal trajectories of caregiving burden, coping strategies, and interactions with healthcare systems over time.

Despite these limitations, this study has several important strengths. It represents one of the largest multinational investigations of caregivers of persons with DS conducted in Europe to date, providing a rare and comprehensive overview of caregiving experiences across different national contexts. This study was designed as patient-oriented research, with close collaboration between researchers, clinicians, patient organisations, and caregivers, ensuring high relevance to the lived experiences and priorities of families affected by DS. The use of an anonymous, self-administered survey created a safe space for caregivers to share their experiences, which may have had a reflective or therapeutic value for participants who are often insufficiently heard within healthcare systems. Finally, the questionnaire captured a broad range of clinical, psychological, social, economic, and healthcare-related dimensions, allowing for a multidimensional understanding of caregiver burden and quality of life in DS.

5. Conclusions

This multinational study demonstrates that caregiving for individuals with Dravet syndrome is a long-term, multidimensional challenge that extends far beyond the diagnostic phase and persists across the life course. Caregiver burden is likely driven by the chronic and pharmacoresistant nature of DS, sustained clinical complexity, including neurodevelopmental impairments and associated comorbidities, substantial occupational and economic consequences, and pronounced impairments in emotional well-being, with clear gender- and country-specific differences. The findings underscore several key implications for practice and policy.

1. Caregiver burden in DS should be recognised as a long-term and evolving process, requiring continuity of support rather than time-limited interventions focused solely on diagnosis or early childhood.
2. There is a clear need for integrated care models that combine medical management with systematic psychological support for caregivers, including routine screening for emotional distress, sleep problems, and caregiver burnout.
3. Cross-country differences highlight the importance of comprehensive, policy-sensitive systems that support people with DS across the life course while easing the burden on families, with greater emphasis on flexible employment options, income protection, respite care, and formal recognition of unpaid caregiving work.
4. Observed sex differences call for gender-sensitive interventions, acknowledging the disproportionate burden borne by mothers and the structural factors that constrain their autonomy, employment, and well-being.

Overall, improving outcomes for families affected by DS requires coordinated efforts at clinical, psychosocial, and policy levels, moving beyond a one-size-fits-all approach toward context-aware, caregiver-centred models of long-term support.

CRediT authorship contribution statement

Jan Domaradzki: Writing – review & editing, Writing – original draft, Supervision, Project administration, Formal analysis, Conceptualization. **Dariusz Walkowiak:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Formal analysis, Data curation. **Jon Andoni Duñabeitia:** Writing – review & editing, Validation, Methodology, Conceptualization. **Colin Reilly:** Writing – review & editing, Methodology, Conceptualization. **Carsten Konrad:** Writing – review & editing, Methodology, Conceptualization.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and involved voluntary, anonymous participation in a non-interventional online survey; therefore, in accordance with applicable institutional and national regulations, formal approval from an ethics committee was not required. As part of the study governance, the Dravet Syndrome European Federation (DSEF), which coordinated the project, reviewed the study protocol and survey procedures internally to ensure adherence to ethical standards, participant protection, and data protection regulations. Participants provided informed consent by voluntarily proceeding to complete the questionnaire.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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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.2026.111176.

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