Dravet syndrome is a rare, refractory epilepsy typically involving multiple comorbidities, including motor, cognitive, and behavioural impairments. The wide scope of comorbidities associated with this condition, combined with it being a rare disease, can be expected to result in a high impact on caregivers, affecting all aspects of their lives.

Dravet syndrome typically presents with febrile and afebrile, generalized tonic-clonic or hemiconic epileptic seizures in the first year of life in an otherwise healthy child. At around 1 to 2 years of age the patient begins to experience additional seizure types. Cognitive slowing or stagnation, behavioural disorders, motor problems, and other comorbidities appear during childhood. In late childhood or early adolescence there is usually a decrease in seizure frequency. Dravet syndrome is primarily a clinical diagnosis, frequently supported by the identification of a mutation in SCN1A, as the majority of children (70–80%) carry such a mutation. At all stages seizures are usually refractory to standard antiepileptic medication. While some studies have linked a greater degree of cognitive and behavioural impairment to a higher convulsive and non-convulsive seizure frequency, the extent to which comorbidities and their severity arise and develop independently from seizures is still unknown. Also, it is unclear whether a delay in correct diagnosis is correlated with later and more severe comorbidities.

In collaboration with the extensive pan-European network of the Dravet Syndrome European Federation, the study described here sought to acquire, in a large sample size, an overall picture of factors that may have an impact on patients with Dravet syndrome and their caregivers, such as quality of life (QoL), disease severity, socioeconomic and financial impact, and health care resource utilization. This report describes the overall clinical and demographic data collected in the survey and explores associations between disease characteristics (e.g. current seizure frequency and time to diagnosis [TTD]), comorbidities, and QoL. Our hypothesis was that there is an association between ‘severity’ of the disease (as expressed by the current seizure frequency) and the known comorbidities in Dravet syndrome, such as motor and cognitive problems and overall QoL. We also specifically examined whether a delay to the correct diagnosis was associated with a worse outcome.

**METHOD**

**Research design and survey procedure**

The Dravet syndrome caregiver survey was an anonymous cross-sectional study of caregivers of patients with Dravet syndrome and their caregivers in Europe.
syndrome open to participants from 23 June to 15 September 2016 (Appendix S1, online supporting information for survey questions) and available in 10 languages (English, Spanish, Portuguese, French, Dutch, German, Italian, Polish, Croatian, and Romanian) and two dialects (Latin American Spanish and Brazilian Portuguese). Participants were recruited through e-mail invitations to approximately 1000 members of different countries’ patient advocacy groups associated with the Dravet Syndrome European Federation, as well as through Internet-based sources (Facebook and Twitter).

Each language version of the Dravet syndrome caregiver survey was hosted online by the survey platform Formstack. The survey was developed in English and translated by specialist translators into all languages except Croatian, Dutch, and Romanian, which were translated by native-speaking patient advocacy group members. All surveys were tested by local-language speakers before survey launch.

The Dravet syndrome caregiver survey consisted of 150 questions about the caregiver household (demographic information), health status of the patient (including current seizure frequency), current and past treatments, experiences of diagnosis, QoL, social and financial caregiver impact, and health services use. A pilot study of the English version was conducted with 13 families to establish questionnaire validity.

Answers to survey questions were given in checkboxes (multiple choices possible), radio buttons (a single choice only), dropdown lists (single choice only), or free text. Questions were gated and only fully completed surveys (with the exception of question number 109 regarding the cost of non-pharmacological treatments) were accepted for submission by Formstack.

**Seizure frequency**

Parents were asked how often (0, 1–12, 13–30, 31–60, 61–150, or >150 times) their child had experienced a seizure type (tonic-clonic, myoclonic, partial/focal, absence, atonic/ drop attack, and unidentified seizure) in the past 3 months.

**Patient health-related QoL**

As a measure of the health-related QoL of patients with Dravet syndrome, caregivers completed in proxy for their son or daughter the standardized instrument EQ-5D-5L. Index values were based on the UK value set. We elected to use the EQ-5D-5L without the visual analogue scale.

**Data processing**

Responses were retrieved from Formstack in Excel format. Non-English-language data were translated back into English and collated into a single data file. Nine duplicates, identified by matching Internet protocol addresses and identical answers, were removed from the data set.

**Descriptive analysis**

Data are reported as total counts, frequency of responses, and summary statistics (mean and standard deviation (SD)) of the pooled sample and differing age ranges: infant (<2y) pre-school (2–5y, inclusive), middle childhood (6–11y, inclusive), adolescent (12–17y, inclusive), and adult (≥18y).

**Statistical analysis**

Statistical significance of differences between frequencies was determined using a two-tailed z-test for two proportions with a 95% confidence interval using the statistical software XLSTAT (Addinsoft SARL, Paris, France) in Excel. All p-values less than 0.05 were regarded as statistically significant.

**Stratification by patient characteristics**

**Scores**

Patient characteristics were assigned numerical values. Based on survey answers, each patient received a score for the frequency of each seizure type (maximum 10 [≥150 in past 4wks], minimum 0 [none in past 3mo]) and for their TTD (maximum 10 [≥4y], minimum 0 [immediate diagnosis]), and a composite score for total seizure frequency (composite seizure frequency [CSF] score) (maximum 39, minimum 0; only countable seizures and seizures with a motor component were used for this score), comorbidities (maximum 18, minimum 0), and non-antiepileptic drug (AED) treatments (maximum 12, minimum 0) (Table I).

**Scores in the lowest and highest strata**

For each characteristic, patient scores (TTD score, CSF score, composite comorbidity score, composite non-AED score and EQ-5D-5L index score) were ranked and patients in the highest and lowest strata were compared. Since multiple patients could have identical scores for a characteristic, the cut-off point for the highest and lowest strata was defined by the score closest to the twentieth or eightieth centile. Thus, the highest and lowest strata for ranked CSF scores contained patients above the eighty-third centile (101 patients; scores 14–39) and below the sixteenth centile (94 patients; scores 0–2) respectively; for EQ-5D-5L index scores, above the eightieth centile (118 patients; scores 0.706–1) and below the twenty-first centile (123 patients; scores 0.157 to −0.594) respectively; for TTD, above the seventy-sixth centile (138 patients; TTD score 10) and below the twenty-eighth centile (164 patients; TTD score 0) respectively; for composite comorbidity scores, above the eighty-first centile (110 patients; scores 7–10) and below the twenty-second centile (126 patients; scores 0–2) respectively; for composite non-AED treatment scores, above the seventieth centile (178 patients; scores 4–10) and below the twenty-seventh centile (155 patients; score 0) respectively (Appendix S2, online supporting information).

**What this paper adds**

- The survey captured about 15% of all patients with Dravet syndrome in Europe.
- Less than 10% of patients had current seizure freedom.
- Patients with a high current seizure burden have more comorbidities and lower quality of life.
Table I: Scoring system for patient characteristics

| Score | Q 4: Tonic–clonic | Q 5: Myoclonic | Q 7: Partial focal | Q 8: Atonic/drop attack | Q 12: Time to diagnosis | Q 11: Motor impairment | Q 119: Speech impairment | Q 125: Learning difficulties | Q 131: Autism | Q 137: ADHD | Q 143: Other behaviour | Q 103: Herbal medicines | Q 104: Vitamins | Q 105: Amino acids | Q 106: Ketogenic diet | Q 107: Other nutrition | Q 108: VNS |
|-------|------------------|---------------|-------------------|-------------------------|------------------------|------------------------|------------------------|-----------------------------|-----------------|-----------------|------------------------|----------------------|----------------|------------------|------------------|------------------|------------------|
| 0     | None             | None          | None              | None                    | 0                      | No                     | No                     | No                           | No              | No              | No                     | No                   | No             | No                | No                | No               | No               |
| 1     | 1–12             | 1–12          | 1–12              | 1–12                    | 6–12mo*                | Yes                    | Yes                    | Yes                          | Yes             | Yes             | Yes                     | Yes                   | No             | Yes               | Yes               | Yes              | Yes              |
| 2     | 13–30            | 13–30         | 13–30             | 13–30                   | 1–2y*                  | Yes                    | Yes                    | Yes                          | Yes             | Yes             | Yes                     | Yes                   | Yes            | Yes               | Yes               | Yes              | Yes              |
| 3     | 31–60            | 31–60         | 31–60             | 31–60                   | 3–4y*                  | Yes                    | Yes                    | Yes                          | Yes             | Yes             | Yes                     | Yes                   | Yes            | Yes               | Yes               | Yes              | Yes              |
| 4     | 61–150           | 61–150        | 61–150            | 61–150                  | >15y*                  | Yes                    | Yes                    | Yes                          | Yes             | Yes             | Yes                     | Yes                   | Yes            | Yes               | Yes               | Yes              | Yes              |
| 5     | >150             | >150          | >150              | >150                    | >4y*                   | Yes                    | Yes                    | Yes                          | Yes             | Yes             | Yes                     | Yes                   | Yes            | Yes               | Yes               | Yes              | Yes              |

See Appendix S1 (online supporting information) for full questions. Composite seizure frequency score = tonic–clonic score + myoclonic score + partial focal score + atonic/drop attack score. Composite comorbidity score = motor impairment score + speech impairment score + learning impairment score + autism score + attention deficit–hyperactivity disorder (ADHD) score + other behaviour impairment score. Composite non-antiepileptic drug treatment score = herbal medicine score + vitamins score + amino acids score + ketogenic diet score + other nutritional therapy score + vagus nerve stimulation (VNS) score. *After the first seizure. **Full answer: ‘In the past but not anymore’. Q, question.

Pharmacological treatment

Half of patients were reported to be taking an average (SD) of three AEDs (3.14 [1.3]), ranging from 0 to 12 per patient, and had previously taken an average of three drugs (3.15) ranging from 0 to 28 per patient. Valproate acid, at least one AED was reported for ambulance calls (Fig. 1c). The most frequent seizure types reported in the past 12 months were myoclonic and absence seizures (each in about 50% of patients), followed by tonic–clonic seizures (78% of patients).) The proportion of patients with at least one tonic–clonic seizure decreased significantly from the pre-school to 74% in the middle-childhood group and adults, whereas that of tonic–clonic seizures did not change significantly across age groups (Fig. 1b). While the proportion of patients with myoclonic seizures decreased significantly from the pre-school to 24% in the middle-childhood group, the proportion remained very drug resistant into adulthood. In older patients, the frequency of myoclonic and absence seizures decreased significantly compared with infants but 14% of adolescents (p = 0.017). Overall, only 9% of patients and fewer young than old were seizure free in the previous 3 months. Only 3% of infants but 14% of adolescents (p = 0.039) were seizure free in the previous 3 months compared with infants who were not statistically significant.

Clinical characteristics

Overall, only 9% of patients and fewer young than old were seizure free in the previous 3 months. Only 3% of infants but 14% of adolescents (p = 0.039) were seizure free in the previous 3 months compared with infants who were not statistically significant.

Emergencies

Half of patients required at least one emergency admission (Table II and Appendix S1). More young than old patients (85% and 78%) reported at least one emergency admission (p = 0.017). The proportion remained very drug resistant into adulthood. In older patients, the frequency of myoclonic and absence seizures decreased significantly compared with infants but 14% of adolescents (p = 0.017). Overall, only 9% of patients and fewer young than old were seizure free in the previous 3 months. Only 3% of infants but 14% of adolescents (p = 0.039) were seizure free in the previous 3 months compared with infants who were not statistically significant.
typically used as first-line treatment,\textsuperscript{4,9,10} is currently taken by 76%. Other first- or second-line treatments such as stiripentol, topiramate, clobazam, or the ketogenic diet, are currently taken by 47%, 34%, 53%, and 7% respectively (Table III and Appendix S4, online supporting information). Across age groups, use of valproate, clobazam, and topiramate (except in infants with 11.8%) were constant, whereas that of stiripentol decreased with age: 31% in the adult versus 51.8% in the pre-school group ($p=0.001$). Also, ketogenic diet use decreased with age (11.8% in infants vs 2% in adults). However, more than 20% of adolescents and adults had tried a ketogenic diet in the past. Vagus nerve stimulation was not used in the younger age groups but considered as a possible treatment option more often in older patients (17% in adults vs 5.9% in middle childhood; $p=0.012$).

Very few (0–2%) patients reported currently taking antiepileptic agents known to exacerbate seizures in Dravet syndrome;\textsuperscript{9} however, many adults had taken these previously, including carbamazepine (54%), lamotrigine (56%), phenobarbital (42%), and vigabatrin (35%) (Table III and Appendix S4). Also of note is that 21% of infants had been exposed to carbamazepine or oxcarbazepine, typical first-line drugs for focal seizures.

The use of pharmacological treatments for the associated comorbidities appeared limited. Only 6% of patients reported currently taking antipsychotics and 6% attention-deficit–hyperactivity disorder (ADHD) medication. Of the various non-AED treatments explored in the survey, only complementary medicine (16%) and vitamin supplements (>50%) were currently taken by more than 10% of patients (Table III).
Comorbidities or impairments

Caregivers were asked whether their son or daughter had a motor impairment, speech impairment, a diagnosis of autism or autistic-like behaviour, a diagnosis of ADHD, or behavioural problems not diagnosed as autism or ADHD. Nearly all (91%) patients older than 5 years of age reported at least one other comorbidity or impairment in addition to seizures as follows: motor impairment (74%), speech impairment (80%), learning difficulties (98%), autism (42%), ADHD (24%), and behavioural difficulties not related to autism or ADHD (51%) (Table II). Patients older than 5 years of age had, on average, four (3.7 [1.2])

| Table II: Disease severity |
|---------------------------|
| % Total responses | % Responses within age group |
| I | PS | MC | A | Adult |
|---------------------|-----|-----|-----|-----|-----|
| Epilepsy type and severity | | | | | |
| Seizure free | 9.4 | 3 | 5.7 | 10 | 14 | 11 |
| Frequency of at least one seizure in the past 3mo | | | | | |
| Tonic–clonic | 78.1 | 85.3 | 85.1 | 74.3 | 73.8 | 78.0 |
| Myoclonic | 48.6 | 64.7 | 51.8 | 47.5 | 43.0 | 47.0 |
| Absence | 49.6 | 67.6 | 56.0 | 48.5 | 50.5 | 35.0 |
| Partial/focal | 38.7 | 58.8 | 46.8 | 37.1 | 37.4 | 25.0 |
| Atonic/drop attack | 25.5 | 29.4 | 29.1 | 23.8 | 25.2 | 23.0 |
| Unidentified | 24.5 | 29.4 | 24.8 | 24.3 | 26.2 | 21.0 |
| Time to diagnosis | | | | | |
| Immediate diagnosis | 28.1 | 29.4 | 44.7 | 27.7 | 21.5 | 12.0 |
| Self-diagnosis | 12.0 | 17.6 | 15.6 | 10.9 | 14.0 | 5.0 |
| Time to diagnosis &lt;6mo | 9.3 | 33.3 | 20.5 | 8.9 | 1.2 | 1.1 |
| 6–12mo | 23.1 | 54.2 | 37.2 | 29.5 | 10.7 | 3.4 |
| 1–2y | 19.3 | 8.3 | 30.8 | 23.3 | 19.0 | 5.7 |
| 3–4y | 15.5 | 4.2 | 10.3 | 18.5 | 28.6 | 6.8 |
| &gt;4y | 32.9 | 4.2 | 1.3 | 19.9 | 40.5 | 93.0 |
| Emergency events in the past 12mo | | | | | |
| No emergency admissions | 49.7 | 5.9 | 24.1 | 53.0 | 70.1 | 72.0 |
| No ambulance calls | 53.9 | 17.6 | 41.8 | 51.5 | 73.8 | 67.0 |

Comorbidities and impairments

| % Total responses | % Responses within age group |
|---------------------|---------------------------|
| All age groups | Excluding (a) I or (b) I and PS age group |
|---------------------|---------------------------|
| Motor impairment | 71.7 | (a)72.7 (b)74.3 |
| Speech impairment | 64.0 | (a)66.0 (b)67.0 |
| Does not talk | 14.9 | (a)14.4 (b)13.4 |
| Learning difficulties | 87.8 | (a)91.1 (b)97.8 |
| Autism | 33.6 | (a)35.6 (b)42.1 |
| ADHD | 20.2 | (a)21.3 (b)23.5 |
| Behaviour | 45.6 | (a)47.1 (b)51.1 |
| No other comorbidities or impairments | 7.5 | (a)7.8 (b)9.3 |
| EQ-5D-5L (mobility dimension) | | |
| 1. I have no problems in walking about | 21.4 | (a)21.1 (b)20.5 |
| 2. I have slight problems in walking about | 30.7 | (a)31.1 (b)30.6 |
| 3. I have moderate problems in walking about | 28.3 | (a)29.5 (b)29.3 |
| 4. I have severe problems in walking about | 12.3 | (a)12.9 (b)14.2 |
| 5. I am unable to walk about | 7.4 | (a)5.5 (b)5.4 |

Because of rounding, percentages might not add up to exactly 100. For all answers to disease-severity questions see Appendix S3 (online supporting information). Seizure free is defined as a participant who selected the option ‘none’ for all questions (4–9) asking about seizures in the past 3mo. Participants answered ‘yes’ or ‘no’ to the question ‘Did the doctor you first saw recognize Dravet syndrome?’. Participants answered ‘yes’ or ‘no’ to the question ‘Did you (parents or other family members) at some point suggest the diagnosis of Dravet syndrome to your doctor?’. Time to diagnosis after the first seizure. Percentage of patients that were not immediately diagnosed, i.e. whose caregivers answered ‘no’ to the question ‘Did the doctor you first saw recognise Dravet syndrome?’. Caregivers selected either ‘yes’ or ‘no’ to the question ‘Does your son/daughter have a motor impairment (such as problems walking about)?’. Does not include patients who do not talk at all. Caregivers selected either ‘Yes, my son/daughter’s speech is impaired’, ‘No’, or ‘My son/daughter does not talk at all’ to the question ‘Does your son/daughter have a speech or language impairment? (e.g. impaired articulation or a voice impairment?)’. Caregivers selected either ‘yes’ or ‘no’ to the question ‘Does your son/daughter have learning difficulties?’. Caregivers selected either ‘yes’ or ‘no’ to the question ‘Has your son/daughter been diagnosed with autism/autistic like symptoms?’. Caregivers selected either ‘yes’ or ‘no’ to the question ‘Has your son/daughter been diagnosed with attention-deficit-hyperactivity disorder (ADHD)?’. Caregivers selected either ‘yes’ or ‘no’ to the question ‘Does your son/daughter experience behavioural problems that have NOT been diagnosed as autism or ADHD?’. No other diagnoses is defined as a participant who selected the option ‘no’ for all for all questions (111, 119, 125, 131, 137, 143) asking about diagnoses. I, infant (≤2y); PS, pre-school (2–5y); MC, middle childhood (6–11y); A, adolescent (12–17y); Adult, adult (≥18y).
| Pharmacological treatment | % Total responses | % Responses within age group |
|---------------------------|-------------------|-----------------------------|
|                           |                   | I  | PS  | MC  | A   | Adult   |
| Patients taking AEDs      | 98.1              | 97.1 | 98.6 | 98.0 | 99.1 | 97.0    |
| Current and previous AEDs |                   |    |     |     |     |         |
| Valproic acid             |                   |    |     |     |     |         |
| Current                   | 75.5              | 82.4 | 82.3 | 75.2 | 68.2 | 72.0    |
| TP                        | 13.7              | 2.9  | 9.2  | 12.4 | 22.4 | 17.0    |
| Clobazam                  |                   |    |     |     |     |         |
| Current                   | 52.7              | 61.8 | 55.3 | 54.5 | 44.9 | 51.0    |
| TP                        | 19.0              | 5.9  | 14.2 | 21.3 | 23.4 | 21.0    |
| Stripectol                |                   |    |     |     |     |         |
| Current                   | 47.1              | 41.2 | 51.8 | 55.4 | 42.1 | 31.0    |
| TP                        | 11.1              | 8.8  | 5.7  | 12.4 | 13.1 | 15.0    |
| Topiramate                |                   |    |     |     |     |         |
| Current                   | 34.2              | 11.8 | 28.4 | 38.6 | 42.1 | 33.0    |
| TP                        | 25.7              | 8.8  | 14.2 | 26.7 | 34.6 | 36.0    |
| Bromide                   |                   |    |     |     |     |         |
| Current                   | 9.6               | 8.8  | 11.3 | 10.9 | 9.3  | 5.0     |
| TP                        | 4.6               | 0.0  | 0.7  | 5.0  | 9.3  | 6.0     |
| Cannabinoida              |                   |    |     |     |     |         |
| Current                   | 2.7               | 0.0  | 2.1  | 4.5  | 2.8  | 1.0     |
| TP                        | 2.2               | 0.0  | 0.7  | 3.5  | 2.8  | 2.0     |
| Other cannabis derivativesb|                |    |     |     |     |         |
| Current                   | 7.0               | 2.9  | 7.1  | 10.4 | 3.7  | 5.0     |
| TP                        | 4.1               | 2.9  | 2.8  | 6.9  | 0.9  | 4.0     |
| Carbamazepine             |                   |    |     |     |     |         |
| Current                   | 1.7               | 2.9  | 2.1  | 1.5  | 0.9  | 2.0     |
| TP                        | 26.4              | 8.8  | 9.2  | 19.3 | 42.1 | 54.0    |
| Oxcarbazepine             |                   |    |     |     |     |         |
| Current                   | 1.2               | 0.0  | 0.7  | 1.0  | 0.9  | 3.0     |
| TP                        | 10.1              | 11.8 | 6.4  | 9.9  | 8.4  | 17.0    |
| Phenytoin                 |                   |    |     |     |     |         |
| Current                   | 0.5               | 0.0  | 0.7  | 1.0  | 0.0  | 0.0     |
| TP                        | 8.0               | 11.8 | 5.7  | 3.5  | 8.4  | 19.0    |
| Lamotrigine               |                   |    |     |     |     |         |
| Current                   | 1.7               | 0.0  | 0.0  | 1.0  | 2.8  | 5.0     |
| TP                        | 27.9              | 5.9  | 8.5  | 20.8 | 47.7 | 56.0    |
| Vigabatrin                |                   |    |     |     |     |         |
| Current                   | 0.3               | 0.0  | 0.7  | 0.5  | 0.0  | 0.0     |
| TP                        | 11.3              | 0.0  | 2.1  | 8.4  | 10.3 | 35.0    |
| Phenobarbital             |                   |    |     |     |     |         |
| Current                   | 1.7               | 5.9  | 0.7  | 2.0  | 1.9  | 1.0     |
| TP                        | 23.5              | 5.9  | 17.7 | 18.8 | 28.0 | 42.0    |
| Rufinamide                |                   |    |     |     |     |         |
| Current                   | 0.2               | 0.0  | 0.7  | 0.0  | 0.0  | 0.0     |
| TP                        | 1.5               | 0.0  | 0.7  | 1.0  | 1.9  | 4.0     |
| Other antiepileptic treatment |               |    |     |     |     |         |
| Ketogenic diet            |                   |    |     |     |     |         |
| Current                   | 6.5               | 11.8 | 6.4  | 9.4  | 3.7  | 2.0     |
| Not anymorec              | 17.5              | 2.9  | 9.2  | 18.8 | 27.1 | 21.0    |
| VNS                       |                   |    |     |     |     |         |
| Current                   | 7.4               | 0.0  | 0.7  | 5.9  | 12.1 | 17.0    |
| Not anymorec              | 1.9               | 0.0  | 0.0  | 0.5  | 5.6  | 4.0     |
| Other drugs and treatments |               |    |     |     |     |         |
| Antipsychotics            |                   |    |     |     |     |         |
| Current                   | 6.3               | 2.9  | 1.4  | 6.9  | 10.3 | 9.0     |
| Not anymorec              | 2.4               | 0.0  | 0.0  | 2.0  | 1.9  | 8.0     |
| Stimulants or antistimulantsd|             |    |     |     |     |         |
| Current                   | 5.5               | 2.9  | 0.7  | 8.9  | 8.4  | 3.0     |
| Not anymorec              | 3.6               | 0.0  | 0.7  | 4.5  | 5.6  | 5.0     |
| Complementary medicinee   |                   |    |     |     |     |         |
| Current                   | 16.6              | 14.7 | 14.2 | 18.3 | 16.8 | 17.0    |
| Not anymorec              | 7.0               | 5.9  | 2.8  | 7.4  | 9.3  | 10.0    |
| Vitamin supplements       |                   |    |     |     |     |         |
| Current                   | 51.7              | 44.1 | 47.5 | 53.5 | 52.3 | 56.0    |
| Not anymorec              | 9.2               | 11.8 | 5.0  | 9.4  | 15.0 | 8.0     |
| Amino acidsf              |                   |    |     |     |     |         |
| Current                   | 8.4               | 14.7 | 9.9  | 10.4 | 5.6  | 3.0     |
| Not anymorec              | 8.4               | 5.9  | 5.0  | 6.4  | 13.1 | 13.0    |
of the six surveyed impairments or comorbidities. Of interest, 13% of all patients older than 5 years of age were reported as not speaking at all.

Mobility impairments with respect to walking were further explored in the EQ-5D-5L section of the survey. Very few (5%) patients older than 5 years were unable to walk, most indicating slight (31%), moderate (29%), or severe problems (14%). Twenty-one per cent indicated no problems in walking (Table II).

More males than females 2 years of age or older had a speech impairment, including not talking at all (84% vs 76%; \( p=0.035 \)), autism (40% vs 31%; \( p=0.028 \)), and ADHD (28% vs 14%; \( p<0.001 \)). Motor impairments, learning difficulties, and behavioural difficulties were reported in similar proportions by both sexes (Appendix S5, online supporting information).

**Patient QoL**

The mean EQ-5D-5L index value for all patients 2 years of age or older was 0.42 (0.29) and ranged from less than 0 to 1 (Appendix S3). No large difference in index values across age groups was observed.

**TTD and comorbidities**

This survey data suggest that physician awareness of Dravet syndrome has markedly improved over time. Doctors immediately recognized Dravet syndrome in 45% of preschool versus only 12% of adult patients. Furthermore, in contrast to 83% of adults, only 20% of middle-childhood patients not diagnosed at their first visit reported receiving a Dravet syndrome diagnosis over 4 years after their first seizure (Table II). In infants, the diagnosis of Dravet syndrome was made in 88% within the first year after presentation.

**Associations between disease characteristics, comorbidities, and QoL**

Associations between disease characteristics, comorbidities, and QoL were explored by comparing patients with the highest and lowest disease burden, as expressed by seizure frequency, comorbidities, TTD, treatment pattern (number of current, failed, seizure-exacerbating or non-AED medications), and QoL.

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### Table III: Continued

| Nutritional therapy \( ^a \) | % Total responses | % Responses within age group |
|-----------------------------|-----------------|---------------------------|
| Current                     | 7.0             | I  | PS | MC | A  | Adult |
| Not anymore\( ^c \)         | 4.5             | 5.9 | 7.1 | 5.4 | 7.5 | 10.0 |

Because of rounding, percentages might not add up to exactly 100. A full list of treatments is given in Appendix S4 (online supporting information). \( ^a \) Purified compound. \( ^b \) Including cannabidiol oil. \( ^c \) Taken in the past but not anymore. \( ^d \) Stimulants or anti-stimulants for attention-deficit-hyperactivity disorder other than or in addition to a ketogenic diet. \( ^e \) Complementary medicine such as herbal medicine. \( ^f \) Amino-acid supplements. \( ^g \) Nutritional therapy. \( ^1 \) infant (<2y); PS, pre-school (2–5y); MC, middle childhood (6–11y); A, adolescent (12–17y); Adult, adult (≥18y); TP, taken previously; VNS, vagus nerve stimulation.

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**High and low seizure frequency burden**

A wide range of seizure frequency in the previous 3 months was reported, from no seizures to multiple occurrences of each seizure type, and patients with high and low seizure frequencies (high and low seizure frequency are represented in this study by the highest and lowest strata of CSF scores respectively) reported emergency events, comorbidities, and QoL to different extents.

Patients in the highest versus the lowest CSF stratum more frequently reported at least one emergency admission (56% vs 36%; \( p<0.006 \)) or ambulance call (55% vs 30%; \( p<0.001 \)) in the previous 3 months. Patients older than 5 years of age in the highest CSF stratum reported more comorbidities (4.08 [0.97]) than in the lowest (3.41 [1.28]). More patients older than 2 years of age in the highest than lowest CSF stratum reported a motor (83% vs 53.8%; \( p<0.001 \)) and speech impairment (including not talking at all; 89.4% vs 71.4% \( p<0.005 \)) (Fig. 1d and Appendix S5).

**High and low comorbidity burden**

Having more comorbidities was associated with higher seizure frequencies. More patients older than 5 years of age in the lowest than the highest stratum for composite comorbidity scores reported no seizures in the past 3 months (20% vs 7%; \( p=0.044 \)) (Appendix S5). The severity of patients’ motor impairment (as indicated in the walking mobility section of the EQ-5D-5L questionnaire) was also associated with seizure frequency. No patients older than 5 years and unable to walk reported no seizures in the previous 3 months versus 10%, 5%, 14%, and 20% in patients with severe, moderate, slight, or no problems walking respectively.

**High and low QoL**

Less than 3% of patients in the lowest versus 15% in the highest EQ-5D-5L stratum were seizure free in the previous 3 months \( p=0.002 \). Patients in the lowest stratum also reported more seizures of each type (Appendix S5). More patients older than 2 years of age in the lowest than the highest stratum reported at least one or more seizure type (tonic–clonic [71% vs 86%; \( p=0.008 \]), myoclonic [34% vs 67%; \( p<0.001 \)], absence [38% vs 62%; \( p<0.001 \)], partial focal [31% vs 49%; \( p=0.005 \)], and atonic seizure [18% vs 32%; \( p=0.022 \)].
**Long and short TTD**

Overall, there were no clear differences in disease characteristics for patients in the highest versus the lowest TTD stratum.

**Treatment patterns**

Patients older than 5 years using a high number of non-AED treatments tended to have a higher disease burden: patients with the highest use (expressed as a high non-AED treatment composite score) reported more motor (87% vs 64%; \(p<0.001\)) and speech impairments (85% vs 69%; \(p=0.009\)) than those not using any non-AED treatments (Appendix S5). Patients grouped by treatment patterns (high or low number of current, failed, or seizure-exacerbating medications) did not display statistically significant differences in disease characteristics (data not shown).

**DISCUSSION**

This survey is the first large pan-European study of families caring for an individual with Dravet syndrome and provides representative data on clinical, social, QoL, and economic impact. Italy, the UK, Germany, France, the Netherlands, and Spain were each represented by 10% or more of the sample, indicating a broad coverage of families in Europe.

The survey confirms Dravet syndrome to be a very severe and difficult-to-treat epilepsy syndrome throughout childhood and into adulthood, with seizures remaining frequent despite appropriate treatment.\(^5\) Even in adults, only 11% of patients were reported to be seizure free. Seizure types also remain very similar across age groups, with generalized tonic–clonic seizures being most frequently reported.

The survey revealed that patients’ overall seizure frequency decreases with age, as previously described,\(^11\) as do ambulance calls and emergency admissions. However, emergency admissions remain notably high in adults, of whom 28% reported at least one emergency admission in the previous 12 months. While this figure is much less than the 94% reported for infants, it is nevertheless very high compared with the 7% of epilepsy-related emergency admissions previously reported for all patients with epilepsy.\(^12\) Although the exact reason for the emergency admission was not asked, we found that ambulance calls and emergency admissions were higher in the stratum with the highest current seizure frequency.

Almost all patients suffer from several comorbidities and the QoL in all age categories is low. Only 31% of school-age patients attended mainstream school. The proportion of patients reporting a diagnosis of autism, ADHD, other behavioural problems or learning disabilities aligns with those reported by Brunklaus et al. for a cohort of 241 patients with \(SCN1A\) mutation-positive Dravet syndrome.\(^13,14\) However, the proportion with motor impairments (including ataxia) was higher than described by others,\(^14\) and may be owing to the difference between parents’ perceptions and clinical criteria applied by the authors. Similar to the study findings of Brunklaus et al.\(^13,14\) the proportion of patients reporting each comorbidity increased with age, although these plateaued or even decreased in adults for diagnoses of autism (51% in adolescents, 38% in adults), ADHD (22% in adolescents and 19% in adults), or other behavioural problems (55% in adolescents and 51% in adults) (Table II), possibly reflecting a difference in the cohort makeup (age distribution was not reported in Brunklaus et al.).\(^13\)

Dravet syndrome exhibits a range of severities in terms of seizure frequency and comorbidities,\(^15\) and there is evidence that in addition to the \(SCN1A\) phenotype,\(^5\) the magnitude of cognitive and behavioural impairment in Dravet syndrome is related to seizure frequency.\(^16\) We therefore hypothesized that the patients with the highest current seizure frequency in our population reflect a subpopulation of patients with more severe Dravet syndrome and are thus expected to show a higher number of concurrent comorbidities. To some extent, our study confirms this hypothesis. Indeed, patients in the highest seizure stratum displayed a more severe motor and speech profile than those in the lowest. The causality of this relationship cannot be explored using the questions asked in the survey, and other studies would be required to distinguish between epileptic versus non-epileptic manifestations of the disease. For example, ataxia and crouching gait seen in Dravet syndrome may be related to \(SCN1A\) mutations,\(^17\) whereas spastic paralysis, seen in a small number of patients with Dravet syndrome, may be the sequelae of acute encephalopathy caused by status epilepticus.\(^18-20\) Our analysis of patients in the lowest and highest seizure strata also did not reveal a significant difference between the two groups for autism, ADHD, and other behavioural problems. These discrepancies indicate that seizure frequency is not the only factor to explain comorbidities, as already shown in other smaller studies.

One other important factor to be considered in this respect is the TTD. Early diagnosis of Dravet syndrome is associated with earlier access to appropriate drug therapy (e.g. avoiding sodium channel blockers) and earlier access to, for instance, specialized rehabilitation programmes. Patients in the Dravet syndrome caregiver survey cohort experience a diagnostic journey typical of rare diseases,\(^21,22\) involving late or initially incorrect diagnoses. Encouragingly, and possibly a reflection of increased awareness and genetic testing availability, the TTD in younger patients is far less than in older patients, indicating improvements in diagnosis.

As expected, most of the adult population received a diagnosis 4 years or more after the first seizure. However, surprisingly, there was no clear correlation for the overall group between delay in diagnosis and occurrence of comorbidities.

Antiepileptic medication use among respondents was consistent across age groups and in accordance with
existing clinical guidance. Currently, only a minority of patients are taking drugs known to possibly exacerbate seizures. As expected, many patients in older age groups were reported to be taking contraindicated medicines at some point in their medical history. Whether previous treatment with contraindicated medicines affected disease progression or comorbidity development was not explored in this study. While AED efficacy and side effects were also not explored in the survey, some of the reported treatment patterns raise interesting questions, for example, whether the decreasing use of stiripentol with age reflects a lower retention rate because of efficacy or side effects.

Over 50% of patients also take vitamin supplements. More recent but unlicensed therapies, such as cannabidiol, are not (yet) frequently used in European patients. Previous studies have shown that children with Dravet syndrome have a worse health-related QoL than healthy children. Similarly in this survey, QoL for patients is much lower than in the general population. The average EQ-5D-5L index score of patients older than 2 years was 0.46 points lower than an average population, and 0.38 points lower than patients with epilepsy. The wide range of EQ-5D-5L values may reflect the broad range of severity found in Dravet syndrome, as patients with the lowest EQ-5D-5L values reported the occurrence of more seizures than patients with the highest EQ-5D-5L values. This observation also supports evidence that seizure burden is a large determinant of QoL for people with epilepsy.

This study has some methodological limitations. Most participants (84%) reported belonging to a patient advocacy group, whose members possibly represent more engaged caregivers, more informed and with access to expert care. One can also speculate that families experiencing particular challenges with the condition may be more likely to join advocacy groups. These factors may have introduced a bias, with more affected patients included in our survey. That said, we do see that families with seizure-free children also participated in our survey. The infant group was small (6% of submissions, 34 children) compared with the other age groups, which were more evenly represented by between 15% and 35% of the cohort. The smaller number possibly reflects the survey’s recruited population of primarily patient advocacy group members, to which parents of infants might not yet belong.

A further limitation is that diagnostic information about the patients was reported by parents and not expert physicians. Thus, details about ADHD and autism diagnoses were not requested, and the survey relied on parents’ ability to identify their child’s seizure type and recall its frequency. Indeed, tonic-clonic seizures were the most frequently reported type, possibly reflecting the difficulty of parents in differentiating between tonic, tonic-clonic, myoclonic, and focal seizures, which generalize to bilateral tonic-clonic seizures. Absences may also be very difficult to measure. We attempted to mitigate this limitation by only asking about seizure frequency in the last 3 months and in our composite score for seizure frequency we only included seizure types which can be counted reliably. Furthermore, when examining possible associations between seizures and other outcomes, we only considered the two extremes in the population (the highest or lowest strata of patient characteristic scores, each constituting about 20% of the total population).

We estimate that this survey captured about 15% of the population of patients with Dravet syndrome under the age of 18 years in the ‘European Union Five’ (France, Germany, Italy, Spain, UK) assuming a prevalence of 1 in 45 700 in a population of 340 million, of which about 20% are under the age of 18. This makes it the largest survey ever conducted with families impacted by Dravet syndrome. Further analysis suggests we have not under-sampled because at 250 responses, the median for all variables assessed, such as participating countries and age groups, were the same as at 500 responses (data not shown).

This survey, the largest and most comprehensive of its kind carried out to date, provides a representative depiction of the clinical profile and QoL of families with children with Dravet syndrome in Europe. We found evidence that a high current seizure burden is associated with more comorbidities (especially motor and speech) and lower QoL. The study therefore clearly identifies the need for effective treatment options to reduce the seizure burden in Dravet syndrome.

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**SUPPORTING INFORMATION**

The following additional material may be found online:  
**Appendix S1:** Dravet Syndrome caregiver survey questionnaire items.  
**Appendix S2:** Patient numbers in the highest and lowest strata of ranked characteristics.  
**Appendix S3:** Seizure frequencies, frequency of emergencies, patient education, and EQ-5D-5L index scores.  
**Appendix S4:** Current and previously taken antiepileptic drugs (full list).  
**Appendix S5:** Patient proportions in highest and lowest strata of ranked characteristics.
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