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Review

The clinical, economic, and humanistic burden of Dravet syndrome – A systematic literature review

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ABSTRACT

Dravet syndrome (DS) is a developmental and epileptic encephalopathy with evolving disease course as individuals age. In recent years, the treatment landscape of DS has changed considerably, and a comprehensive systematic review of the contemporary literature is lacking. Here we synthesized published evidence on the occurrence of clinical impacts by age, the economic and humanistic (health-related quality-of-life [HRQoL]) burden, and health state utility. We provide an evidence-based, contemporary visualization of the clinical manifestations, highlighting that DS is not limited to seizures; non-seizure manifestations appear early in life and increase over time, contributing significantly to the economic and humanistic burden of disease. The primary drivers of HRQoL in DS include seizure severity, cognition, and motor and behavioral problems; in turn, these directly affect caregivers through the extent of assistance required and consequent impact on activities of daily living. Unsurprisingly, costs are driven by seizure-related events, hospitalizations, and in-home medical care visits. This systematic review highlights a paucity of longitudinal data; most studies meeting inclusion criteria were cross-sectional or had short follow-up. Nonetheless, available data illustrate the substantial impact on individuals, their families, and healthcare systems and establish the need for novel therapies to address the complex spectrum of DS manifestations.

1. Introduction

Dravet syndrome (DS) is a severe, life-long developmental and epileptic encephalopathy that begins in infancy and evolves with accumulating morbidity that significantly impacts individuals and their families [1,2]. Dravet syndrome is a rare disease, recently determined to occur in 1:15,500 live births [3]. More than 85% of people living with DS present with pathogenic variants in the *SCN1A* gene (SCN1A+ DS) encoding the α subunit of the $Na_V1.1$ sodium channel, which is primarily expressed in GABAergic inhibitory interneurons [4–6]. Impairment of $Na_V1.1$, results in a profound loss of GABAergic signaling, which is implicated in the pathogenesis of disease. Dravet syndrome is thus conceptualized as a channelopathy because the effects of the variants on the sodium channel appear to contribute to the disorder independent of the seizures [7].

Abbreviations: DS, Dravet Syndrome; SUDEP, sudden unexpected death in epilepsy; SE, status epilepticus; HRQoL, health-related quality of life; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; AES, American Epilepsy Society; EPNS, European Paediatric Neurology Society; AAN, American Academy of Neurology; NICE, National Institute for Health and Care Excellence; PECOS, Population, Exposure, Comparator, Outcomes, Study design; SMEI, Severe Myoclonic Epilepsy in infancy, SMEB, borderline SMEI; STROBE, Strengthening the Reporting of Observational studies in Epidemiology; TC, tonic-clonic; FC, focal clonic; ID, intellectual disability; ASD, autism spectrum disorder; ADHD, attention-deficit hyperactivity disorder; IQ, intelligence quotient; DQ, development quotient; GQ, global quotient; ASMs, antiseizure medications; CPI, consumer price indices; FMS, functional mobility scale; PedsQL, Pediatric Quality of Life Inventory; VAS, visual analog scale; CG, Crouch gait.

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The symptomatic expression of DS is complex due to its evolving heterogeneity as individuals age. People living with DS experience a high seizure burden in the first year of life with seizure types evolving over time [8]. Additional DS manifestations typically begin shortly after seizure onset, including neurodevelopmental stagnation or decline, behavioral and sleep difficulties, and motor impairment, which worsen and become more detectable throughout childhood [2,6,9]. Individuals with DS have an increased risk of death in early childhood [9,10], most frequently due to sudden unexpected death in epilepsy (SUDEP) and status epilepticus (SE) [10,11]. Despite a growing body of evidence [12–16], the phenotypic heterogeneity of DS [17–19] makes characterizing the natural history and burden of disease challenging. In addition, the past few years have seen a rapidly changing treatment landscape with the approval of therapies such as fenfluramine, cannabidiol, and stiripentol, which have demonstrated efficacy in reducing the seizure burden in DS [20]. However, seizure freedom is rarely achieved and little impact is observed in motor function and neurodevelopmental manifestations of DS [20–22]. Previous portrayals of the clinical burden and evolution were largely based on expert opinion [12–16,23], and, to date, an evidence-based visualization of the clinical burden of DS by age across the contemporary literature is lacking.

Health-related quality of life (HRQoL), defined as the impact of health status on an individual's or groups' well-being over time [24], among individuals living with DS is significantly lower compared with the general population [25]. Caring for people living with DS exerts substantial physical, emotional, and time burdens on the entire family unit [26–31]. While the detrimental effects of informal caregiving on caregivers' mental health and HRQoL have been shown, no systematic review has summarized the substantial humanistic burden reported among those living with DS. Furthermore, a synthesis of the literature on direct and indirect cost impacts of DS is currently lacking.

The objectives of this contemporary and comprehensive systematic review were two-fold (1) to characterize the spectrum and evolution of DS manifestations, and (2) to define the clinical, humanistic, and economic costs of living with, and caring for, DS.

2. Materials and methods

We conducted a systematic literature review following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for designing, performing, and reporting systematic reviews to guide the conduct of this review [32,33].

2.1. Data source

The search was implemented on December 4, 2020, in MEDLINE (MEDLINE and MEDLINE in-process [OVID SP]) and EMBASE to identify published data on the clinical, economic, and humanistic burden of DS by age and genotype (where available) from database inception to December 3, 2020. To ensure the latest data available were captured (up to December 3, 2020), conference abstracts were screened for inclusion. In addition to the conference abstracts identified through MEDLINE and EMBASE, the search was supplemented by a search for abstracts from congresses – on or before December 3, 2020 – including the American Epilepsy Society (AES), European Paediatric Neurology Society (EPNS), and American Academy of Neurology (AAN). Conference abstracts published before 2018 were excluded.

2.2. Search strategy

An intentionally broad search strategy (Supplemental Table 1) was developed to comprehensively capture relevant literature. The search included medical subject headings for the population of interest (DS or DS+ SCN1A) and study design filters adapted from the National Institute for Health and Care Excellence (NICE) guidelines for developing literature search strategies [34]. The searches were restricted to English and also French, given the breadth of data published in these languages. There were no restrictions based on geographical region or publication date, but animal studies were excluded.

2.3. Study selection

Two researchers independently reviewed all abstracts identified by the search strategy against the study-specific PECOS (Population, Exposure, Comparator, Outcomes, Study design) criteria (Fig. 1). Exclusion of manuscripts based on study outcomes was performed during full text review. Full text of studies that met inclusion criteria during abstract screening were screened for inclusion by two reviewers using study-specific PECOS. If screening researchers differed when categorizing studies for inclusion/exclusion in either abstract or full-text review, a third researcher provided arbitration. In order to narrow the focus to contemporary studies describing individuals with DS based on current diagnosis criteria/language, we excluded older studies using terms such as Severe Myoclonic Epilepsy in infancy (SMEI) or borderline SMEI (SMEB) during full text screening. De-duplication, abstract screening, and full text screening were conducted using Microsoft Excel.

2.4. Data extraction

Two researchers independently extracted all available data of interest from the eligible studies, including study author and year of publication; study design, period, location, and follow-up length; sponsor; baseline clinical and demographic characteristics; sample size; intervention, outcomes measured (including details on the outcome measures/assessment of the outcome and definitions, where available), and results. Mean, median, standard deviation, and range were extracted for continuous variables; number of individuals and the proportion were extracted for dichotomous and categorical variables. We also extracted patient-level data when available. Outcomes included those specified in the PECOS criteria, extracted by age and genotype (Fig. 1). Discrepancies between the data extracted by the two data reviewers were resolved through discussion with a third researcher until consensus was reached. Data extraction was completed in Microsoft Excel.

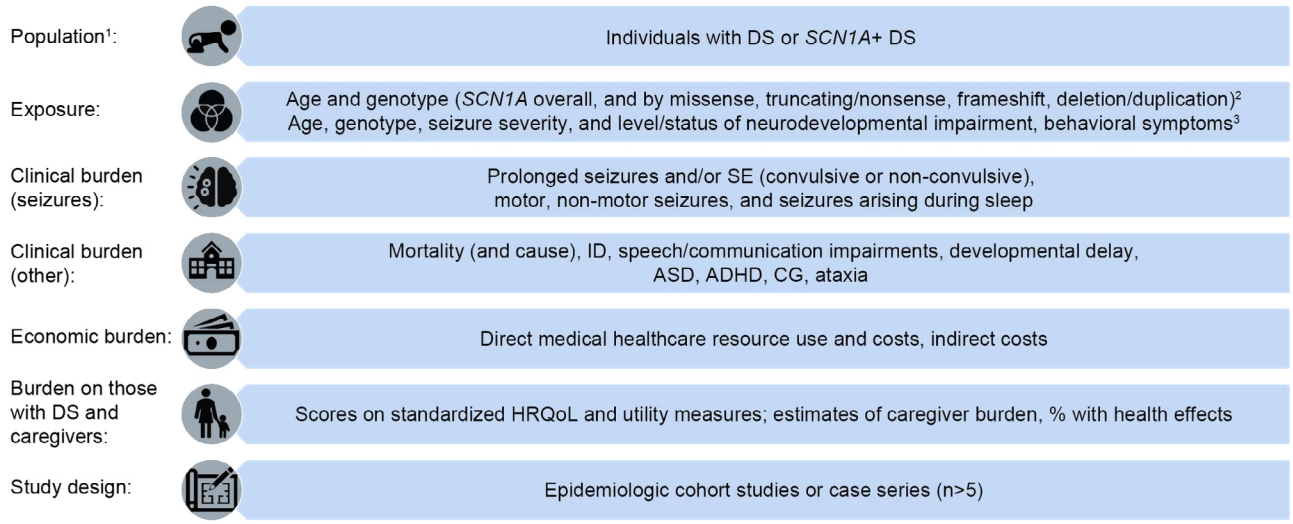
2.5. Quality assessment

The strength of the available evidence from publications included in the final analysis was assessed using the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Statement for observational studies [35].

2.6. Synthesis

Data were stored in Microsoft Excel and synthesized using an iterative approach. The frequency of key study and patient characteristics were tabulated.

To synthesize data on the clinical burden, the occurrence of DS symptoms was summarized in narrative, according to genotype (if available) and age (in years [y] or by age category: onset/infancy [<2y], early childhood [2–4y], middle childhood [5–9y], adolescence [10–17y], and adulthood [>18y]). For seizure-related outcomes, occurrence was summarized according to type (motor [e.g. tonic, tonic-clonic (TC), focal clonic (FC), myoclonic], non-motor seizures [e.g. absences], and seizures arising during sleep)



Notes: 1, excluding studies using out of date terminology such as SMEI; 2, for studies reporting on clinical burden outcomes; 3 for studies on economic and humanistic burden outcomes; 4, while all identified studies reporting on HRQoL among individuals with DS were assessed by caregiver proxy, this was not a requirement during initial abstract and full text screening
Abbreviations: ADHD = Attention deficit hyperactivity disorder; ASD = Autism spectrum disorders; CG = Crouch gait; DS = Dravet syndrome; HRQoL = Health related quality of life; SE=status epilepticus; SUDEP=Sudden unexpected death in epilepsy

Fig. 1. PECOS (Population, Exposures/Comparators, Outcomes, Study design) criteria.

or duration (prolonged seizures and/or status epilepticus [SE; convulsive and non-convulsive]). Note that as epilepsy classifications/definitions have changed over time, we used current ILAE classification to group/synthesize seizure-related outcomes across the identified studies.

Other non-seizure-related outcomes of interest included the occurrence of developmental delays, intellectual disability (ID), communication/speech impairments, autism spectrum disorder (ASD) diagnosis or traits, attention-deficit hyperactivity disorder (ADHD) diagnosis or traits, delay in achieving motor milestones, ataxia, and crouch gait. Intellectual disability data were summarized based on intellectual/cognitive and adaptive functioning outcomes where available; or scores on measures of intellectual/cognitive development, adaptive functioning, or development along with intelligence quotient (IQ), development quotient (DQ), and global quotient (GQ) scores. Communication and speech impairment were summarized by the prevalence of speech motor impairment, as well as expressive and receptive communication impairments. Additionally, causes of mortality (e.g., SUDEP), where reported, were tabulated.

Patterns of the timing of clinical events were described using the age at first occurrence, age-specific rates, and/or scores on relevant outcome measures by age, as published in the original studies. We developed a visualization to display the occurrence (the percentage of patients with the outcome by age) and age at onset of seizure- and non-seizure-related outcomes. Estimates from the largest and/or most robust studies (e.g., from longitudinal studies, or from large cross-sectional studies reporting events by age strata) were plotted for each outcome.

Estimates of the economic, patient and caregiver burden of DS, as well as any reported health effects among caregivers were summarized by age, genotype, seizure severity, and level of neurodevelopmental impairment. For the economic burden, costs related to DS-specific healthcare resource use (seizure-related costs, e.g., costs for medical claims with a diagnosis code for epilepsy or seizures, and pharmacy costs for antiseizure medications [ASMs], etc.; non-seizure-related costs, e.g. costs for speech therapist appointment, etc.), as well as all-cause costs (i.e. both DS-specific and non-DS-related healthcare resource use) were considered. Indirect costs (e.g. costs due to lost caregiver time) were also captured. Costs were presented as reported in the studies. For ease of comparison, annualized costs were presented in a common currency (USD; conversion rates 2021-03-25) and inflated to 2020 values (using country specific annual consumer price indices [CPIs]; direct costs were inflated using CPI for health; indirect costs were inflated using CPI overall). Drivers of costs as reported in the original articles were described.

To summarize the impact of DS on quality of life on individuals living with DS and their caregivers, scores on relevant HRQoL instruments were reported. Trends in HRQoL over time and by age were reviewed. Qualitative data on caregiver burden were summarized descriptively. Factors reported to be key drivers of symptom progression and burden were collated across studies.

Finally, data on health state utility values were reviewed. Health state utility values quantify how strongly a person values, or prefers being in, a particular health state associated with a given health condition. Health state utility values are measured on a scale between 0 and 1. These were presented according to respondent type (patient vs. proxy vs. caregiver), instrument, and other patient and caregiver characteristics, as available.

3. Results

3.1. Studies identified

The database search yielded 3824 records, of which 3084 (80.6%) were excluded during abstract review and 644 (16.8%) during full-text review – the majority of these did not meet population and study design criteria. Seven additional abstracts from conference proceedings were included to the 90 manuscripts and 6 conference abstracts identified through MEDLINE and EMBASE, totaling 103 studies eligible for review (Fig. 2). Publication dates ranged from 2006 to 2020. Sixty-five percent ($n = 67$) of identified studies were published in the last 5 years of search implementation (2016–2020; Supplemental Fig. 1). Major themes reported in

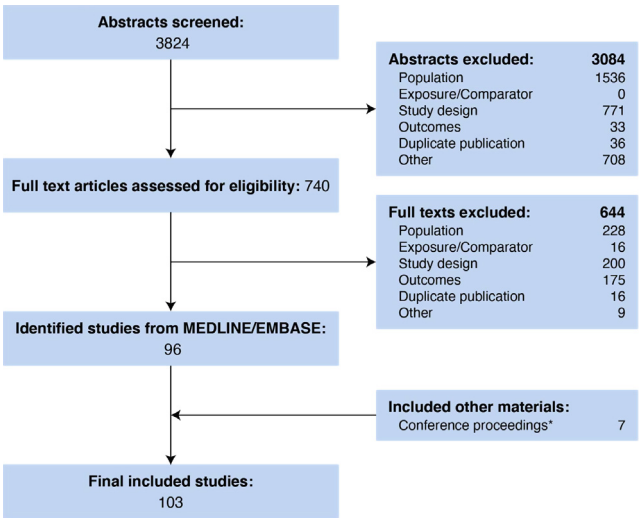
the studies included the natural history of DS ($n = 8$); the burden of DS ($n = 24$; comorbidities, economic and/or humanistic burden); frequency and semiology of seizures ($n = 18$); neurodevelopmental progression ($n = 20$); and other outcomes ($n = 33$; e.g., including mortality, gait, genetic sequencing, and incidence). Most studies were European ($n = 51$), followed by 18 from the USA, 7 with international samples, and 27 from other countries (e.g. Australia, China). Study characteristics, baseline demographics, and clinical characteristics are summarized in Supplemental Table 2, and a summary of the outcomes reported on each study in Supplemental Table 3. While conference abstracts may not include detailed information, they offer the most up-to-date primary findings of a study and were therefore screened for inclusion, resulting in 13 conference abstracts eligible for review [36–48]. The quality of included studies is summarized in Supplemental Tables 4 and 5.

3.2. Evolution and presentation of clinical semiology

Of the studies identified ($n = 103$), 94 included estimates on the patterns of timing of clinical events. While several of these were prospective studies ($n = 14$), most were small cross-sectional studies, had a short follow-up period, or were chart reviews of adults (Supplemental Tables 2 and 3) [2,9–11,17–19,25–30,36–55,57,59–69,71–85,87,94,124,126–185]. The contemporary published data highlight the dramatic clinical impact of DS attributable to seizure- and non-seizure-related manifestations. Figs. 3 and 4 illustrate the age-specific evolution of clinical manifestations of DS using evidence from longitudinal studies ($n = 11$) [9,17,19,49–56] and large cross-sectional studies ($n = 13$) [25,30,37,57–63] reporting events by age. Comparison between studies was hampered by differing patient ages, definitions, outcome measures, and duration of follow-up.

3.3. Seizure-related outcomes

While the early occurrence of seizures is a defining feature of DS, seizure types evolve over time, and importantly, persist into adulthood. Seizures typically shift from prolonged, provoked, focal seizures occurring while awake during childhood, to short generalized onset seizures occurring in sleep during adolescence and adulthood. Generally, the frequency and severity of seizures decreases from later childhood/adolescence to adulthood yet prolonged periods of seizure freedom remain uncommon. Most studies reporting on seizure-related outcomes described the percentage of patients with seizures, or age at first seizure, rather than seizure rates by age. The age-specific evolution of seizures over time is depicted in Fig. 3.



Notes: * Conference abstracts from congresses – on or before December 3, 2020 – including the American Epilepsy Society (AES), European Paediatric Neurology Society (EPNS), and American Academy of Neurology (AAN)

Fig. 2. PRISMA diagram.

SE (defined as one seizure or sequential seizures without return to baseline level of consciousness lasting ≥ 30 min) was described in 40 studies (Supplemental Table 3). Only 13 studies assessed SE longitudinally and the remaining 27 had a cross-sectional design. SE is common in infancy [19,64,65] and occurrence gradually diminish with age after childhood. The mean age at onset of SE ranged from 5 to 11 months [64,65], and 77% experienced one or more episodes by 1.5 years of age [19].

Prolonged seizures (defined at a minimum as seizures lasting ≥5 min) were described in only 19 studies, and only 2 were longitudinal (Supplemental Table 3). The mean age at onset ranged from 5 to 8.5 months [65,66], and 80% experienced one or more prolonged seizures before 1 year of age [52]. Prolonged seizures affect virtually all of those with DS in infancy through middle childhood [52,60], and while they appear to decline with age, supportive data on the occurrence of prolonged seizures after childhood are scarce.

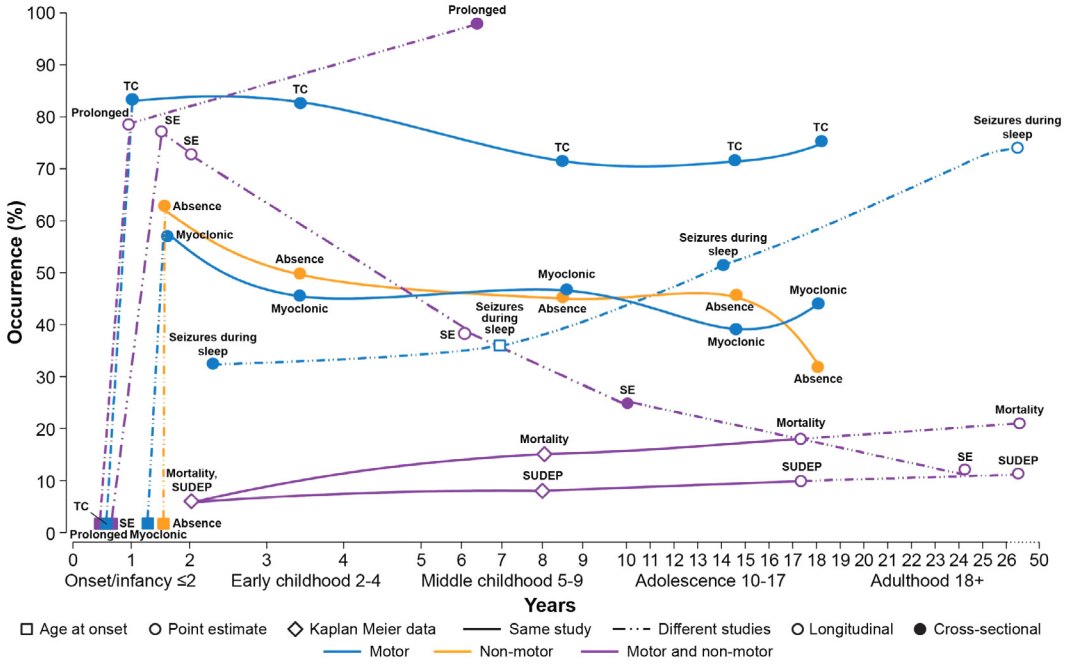
The most commonly described seizure types were TC, FC, absence, and myoclonic seizures. Tonic-clonic (generalized or unspecified) seizures were described in 48 studies (Supplemental Table 3), with a mean age at onset ranging from 5 to 9 months [67,68]. One study found that 86% of infants experienced TC seizures [2], which remain frequent during childhood [2,17,69], but tend to decrease in adulthood. Focal clonic seizures, described in 17 studies, occur most commonly at onset and in early childhood then diminish with age. Generalized TC seizures are more common than FC seizures. In one study, at onset, generalized TC and FC seizures were reported in 54% and 32% of infants with DS, respectively [39]. Absence seizures (atypical or unspecified) were described in 35 studies, and myoclonic seizures, in 43 studies (Supplemental Tables 2 and 3); these seizures appear to be less common than TC seizures, with occurrence peaking in childhood, diminishing by adolescence, and few reports in adulthood.

Seizures arising during sleep were described in 14 studies (3 of which were longitudinal; Supplemental Table 3). These begin on average at 7 years of age and appear to occur in up to 50% of children and almost 90% of adults living with DS. They tend to be brief, most commonly TC or tonic, and occur in clusters.

3.4. Non-seizure-related outcomes

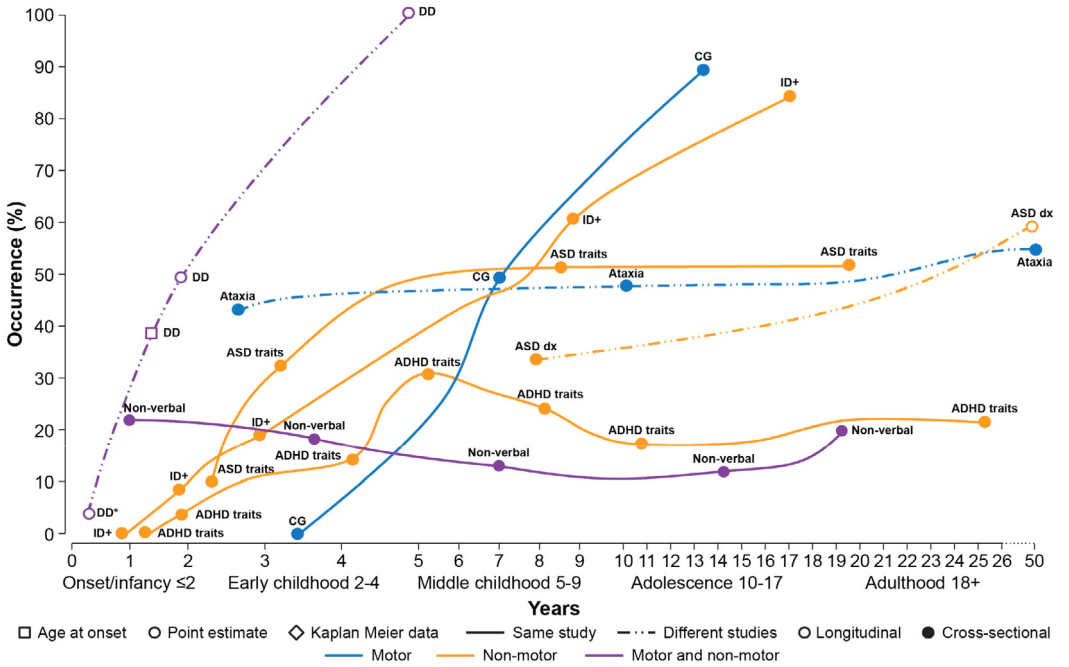
Contemporary data on non-seizure-related outcomes highlight that the clinical burden of DS is not limited to seizures. Most patients have developmental delays [70], profound impairments and disturbances in intellectual functioning [9], adaptive functioning, speech [2], behavior [2,9], and gait [57,61] observed by middle childhood and adulthood (Fig. 4). Most children with DS attend special schools and most adults live with their parents or in specialized facilities [49,67,71,72]. The majority of studies of non-seizure-related manifestations reported on frequency by age, rather than mean age at occurrence, and definitions and measures varied greatly.

Twenty studies that focused on characterizing neurodevelopmental progression reported the age at or frequency of ID and/or developmental delays, and only 9 studies were longitudinal (Supplemental Table 3). Developmental delays frequently present in the first 2 years of life [9,70], and may appear before 1 year of age in some individuals [56,73]. Deficits in cognitive scores (IQ, DQ, and GQ scores) – as commonly measured by the Wechsler Intelligence Scale for Children, clinician-reported Likert scale, Vineland Adaptive Behavior Scales, Griffiths Mental Development Scale,



Abbreviations: TC, tonic-clonic; SE, status epilepticus; SUDEP, Sudden Unexpected Death in Epilepsy.

Fig. 3. Clinical evolution of seizure-related manifestations and mortality in DS: Data from 8 longitudinal studies and 6 large (n > 50) cross-sectional studies.



Abbreviations: DD, developmental delay; ID: Intellectual disability; ASD, Autism spectrum disorder; ADHD, Attention deficit hyperactivity disorder; CG, crouch gait.
Notes: *before onset, +severe/profound.

Fig. 4. Clinical evolution of non-seizure-related manifestations in DS: Data from 3 longitudinal studies and 9 large (n > 30) cross-sectional studies.

and Brunet-Lezine scales – become apparent in early childhood and are profoundly impacted by adulthood. In one study, approximately 50% of adolescents (mean age of patients 11 years) had a severe ID (based on an IQ/DQ score of ≤24) [74]. In another, more than 80% of those >15 years of age had a severe/profound learning disability (based on a 5-point Likert scale rated by clinicians) [9]. Potential predictors of early decline leading to severe ID included the age at onset of developmental delay [9,70], presence of motor disorder [9], longer contraindicated medication use in early childhood [70], occurrence of SE [9], presence of truncating variants [74], later age of independent walking [75], and more impaired verbal skills when compared with other individuals with DS. Additionally, a recent cross-sectional study found that individuals with DS with ASD diagnosis had greater decline in intellectual and adaptive functioning than those individuals with DS without ASD diagnosis [58].

Speech or communication impairments, described in 31 studies (four longitudinal; Supplemental Table 3), are common and occur in 80% of individuals with DS [2]. Delays in language development and communication are observed before 2 years [2,17,76], and motor speech production deteriorates with age [77]. Up to 15% of individuals with DS rely on nonverbal forms of communication, such as gestures [76–78]. This is supported by the Dravet syndrome caregiver survey (DISCUSS), which reports 13% of participants (age range, 5–48 years) are non-verbal [2].

ASD and ADHD diagnoses or traits were described in 23 studies (Supplemental Tables 2 and 3). While the prevalence of ASD and ADHD diagnosis was infrequently described, 20% of those with DS are diagnosed with ADHD, and up to 40% of children and 62% of adults with DS are diagnosed with ASD. In one study, autistic features were observed in 69% of individuals with DS overall, and in up to 28% of those younger than 5 years [9]. The proportion of individuals with ASD and ADHD diagnoses or traits appears to increase with age, peaking in middle childhood, and plateauing or decreasing in adulthood [2,9].

Sixteen studies reported the frequency of delayed achievement of motor milestones and 24 studies reported on ataxia or crouch gait (Supplemental Tables 2 and 3). By 2 years of age, up to 50% of children with DS have delays in fine (e.g., hand-eye coordination) and gross (e.g., sitting and walking independently) motor development [79]. Motor function deteriorates with age [76,79]; most people with DS exhibit gait anomalies and ataxia in early childhood [57], with progression to crouch gait in up to 80% of adolescents [19,57,61,80]. Use of ambulatory devices are common, with up to half of adolescents requiring a wheelchair to cover distances of 500 m or more [as assessed using the functional mobility scale (FMS) scale] [81].

3.5. Mortality

Twenty studies reported on mortality (Supplemental Table 3), 4 of which were large generalizable studies specifically focused on estimating mortality in DS [9–11,82]. The risk of death in childhood is 13-fold higher among those with DS than age-matched healthy controls [48]; SUDEP is the most common cause of death in children, followed by SE. Overall, studies suggest there is a 15% risk of mortality by 17 years [10,48], increasing to 18% by 40 years of age among those who survive to adulthood. Fig. 3 illustrates the evolution of all-cause mortality in DS and the risk of SUDEP alone, both of which persist into adulthood [9,10,48,95].

3.6. Economic burden

The economic burden of DS was reported in 11 studies (Supplemental Table 3, Supplemental Fig. 2), 8 of which described direct costs. Five studies from the US focused primarily on all-cause costs [28,38,42,45,83], and 3 studies from Europe focused on DS-specific costs [27,30,48,84]. Publication dates ranged from 2018 to 2019 and reported on studies conducted between 2010 and 2018. Drivers of direct costs included medically treated seizure events, emergency medication, seizure frequency, level of disability, history of SE, nursing care level, number of non-seizure manifestations, and caregiver depression. The published mean annual all-cause costs ranged from $31,433 (in a US commercially insured population with a mean age of patients 12 years) [83] to $77,914 (in a US commercially insured population, mean age of patients 15 years) [45]. All-cause costs varied depending on insurance type (e.g., Medicaid coverage vs. commercial coverage), as well as the age and severity of the sample at the time of study. Across studies, seizure-related costs contributed to a large proportion of all-cause costs. All-cause medical costs for individuals living with DS were nearly 12 times greater than for age-matched members of the general population [42], with seizure-related costs as the main driver [38,45,83]. Mean annual DS-specific costs ranged from $15,885 (among the European subset of the international DISCUSS survey; mean age of DISCUSS cohort, 10.6 years) [27] to €29,872 (in a German multicenter study, mean age of patients 10.1 years) [30]. Dravet syndrome-specific costs varied based on the extent of informal care/home health data represented in the total estimate. One study reported on the percentage of costs attributable to seizure- vs. non-seizure-related care, with approximately 50% of DS-specific costs attributed to non- seizure-related healthcare resource use [27]. Dravet syndrome-specific costs were 1.5-fold higher among those with DS compared with drug-resistant epilepsy (e.g. individuals with recurrent seizures for whom physicians reported a lack of response to treatment changes) and 5-fold higher than patients with seizures in remission (e.g. individuals with complete seizure control for $\geq$1 year at the time of study entry) [30].

Three studies; two European [30,84] and one from the US [28], reported on indirect costs associated with DS. The drivers included seizure frequency, level of disability, and number of additional symptoms. Mean annual indirect costs ranged from €19,160 (from a German multicenter survey in which 40% of mothers reported missing >37 days of work per year due to DS (mean age of patients 10.1 years) [30] to $81,582 (from a US survey where all caregivers experienced lost leisure time and missed a mean of 48 days of work per year due to DS, mean age of patients 11.7 years) [28]. A study by Whittington et al. was unique in including 'lost leisure time' in their indirect cost estimate [28], which accounted for 64%, and resulted in a substantially higher burden compared with studies considering missed work only [30].

Estimates of direct and indirect costs were highly variable due to differences in population, study designs, and the structure of the healthcare systems included.

3.7. HRQoL

Nine studies described the HRQoL among people with DS (Supplemental Tables 3 and 6), only one of which was longitudinal. In every study, HRQoL was assessed by caregiver proxy. Overall, HRQoL deficits occur when children are young (<5 years), increase with age, and persist through life. Available HRQoL data show that impairments experienced by those living with DS appear to be greater than those experienced by other individuals with epilepsy, and children in the general population [30,85]. Key drivers of HRQoL deficits include disease progression, behavioral symptoms, and degree of disability.

Data on HRQoL were relatively few and most frequently assessed using the Pediatric Quality of Life Inventory (PedsQL; 4 studies) [25,81,85,86]. Additional HRQoL scores based on the Kiddy/Kid-KINDL [30,84] and IPES3 [85] are presented in Supplemental Table 6. Total PedsQL scores decrease with age, with the largest declines observed in scores of physical, cognitive, and social functioning domains [25,85,86]. Significantly lower PedsQL total scores were observed among those with behavioral and gait problems [25,81].

3.8. Burden of DS on caregivers

Thirteen studies (11 of which were qualitative) reported the burden of DS on caregivers (Supplemental Tables 3 and 7). As most people with DS require 24-h care, the impact on caregivers is substantial [26,27]. The drivers of caregiver burden (Fig. 5) vary according to the age of the individual living with DS [78], as does the impact on caretaker activities of daily living, including ability to work [27,29]. One study reported that, across the age-span of people living with DS, the most difficult aspects of caregiving include the impact on other siblings, dealing with cognitive and

developmental delays, arranging for alternative care, communication challenges, coordinating medical and ancillary care, managing behavior problems, and tending to the personal care of the individual living with DS [29]. Another study described the most difficult aspects of caregiving by disease stages or phases (defined by both age of the individual living with DS and seizure severity) [78]. The first stage begins in the first year of life with the onset of prolonged seizures and the most difficult aspects of caregiving include seizure control and uncertainty about diagnosis [78]. After approximately 1 year of age, the second phase emerges with other seizure types along with developmental, behavioral, and sleep issues. During the third stage in early adolescence, better seizure control is achieved but increased intellectual disability and behavioral problems drive caregivers' social isolation from family and friends [78].

Anxiety, depression, and sleep problems are frequently reported by DS caregivers [26,29,30,57,84,87]; approximately 38–60% report having anxiety/depression [30,57]. Given that they often sleep with their child to monitor seizures, the quality and quantity of caregivers' sleep is greatly impacted [26,57,87]. Nocturnal monitoring devices are often used to help alleviate this [26,57,87]. Most caregivers report difficulties in daily activities (91%), family relationships (70%), and social life (80%) [27]. Mothers, in particular seem to be impacted both personally and professionally; compared with fathers, they report a greater impact of caregiving on their social life, relationships with family and friends, time and energy, professional life, and health [26,30]. Approximately 33–44% of mothers vs. 18% of fathers are unemployed [26,27,29,30], and around 31–51% of mothers resign from or interrupt work for their caregiving duties compared with 7% of fathers.

3.9. Utility values

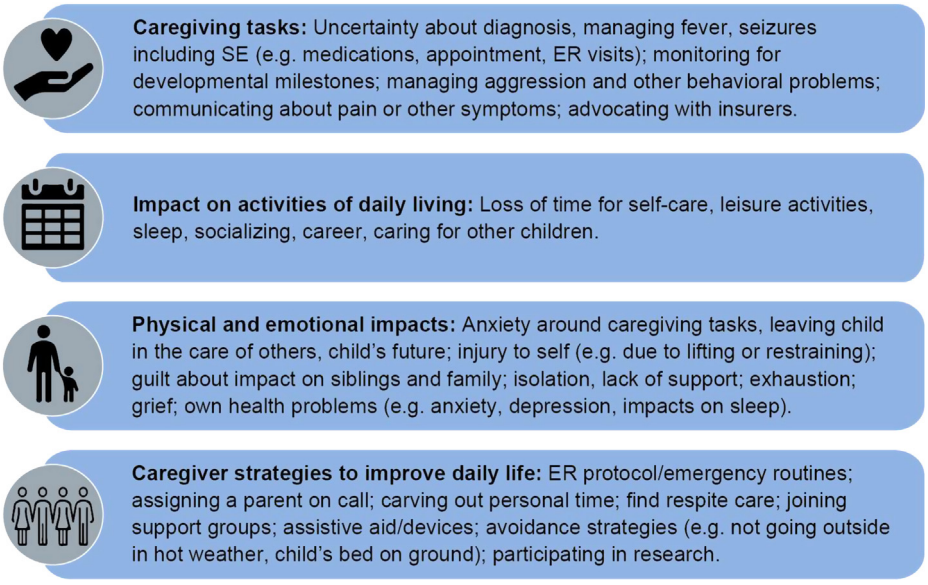
Data on health state utility values in DS are limited: three studies reported utility estimates for those with DS [2,41,44], and three reported caregiver utility values (Supplemental Tables 3 and 7) [29,30,84]. Dravet syndrome-specific utility estimates were assessed using the EQ-5D-5L [2,41] and visual analog scale (VAS) [44], and caregiver utility was measured using the EQ-5D-5L [29] and EQ-5D-3L [29,30,84]. There was no clear trend in utility by age among individuals with DS [2,41,44], but VAS scores declined with increasing seizure frequency [44]. Caregiver utility values ranged from 0.78 (US single center survey, mean age of patients 11.7 years) [29] to 0.9 (German multicenter survey, mean age of patients 10.1 years) [30,84]; utility values were not stratified by caregiver or patient characteristics [29]. Utility values for the entire range of health states experienced by those living with DS, and what effect this has on their caregivers, are not available.

4. Discussion

Dravet syndrome has been the focus of an increasing amount of research in recent years [88–93] yet, large gaps remain in our understanding of disease manifestations, their evolution, and the humanistic and economic impact on individuals, families, and health systems. Bridging these gaps is crucial to ensure that trials of disease-modifying therapies address what is most meaningful to all stakeholders. This contemporary systematic review provides a comprehensive, evidence-based illustration of the features of DS across ages. While seizures significantly impact the lives of people living with DS and their families, as a channelopathy, the clinical burden of DS is not driven by seizures alone [2,17,19,50,54,67,94]. Non-seizure manifestations are fundamental contributors to the clinical, economic, and humanistic burden of DS [2,9,49,72].

The persistent risk of premature mortality in DS into adulthood is an important clinical outcome identified here [9,10,48,95]. Yet, the risk factors that lead to early SUDEP, the most common cause of mortality in DS, relative to other childhood epilepsies are unclear [96]. To date, studies describing the potential risk factors (e.g. presence of *SCN1A* variants, cardiac dysfunction) relied on small cohort studies or case reports [14], highlighting the urgent need for large longitudinal studies to better characterize DS mortality and assist the development of risk-mitigation strategies.

Additional outcomes that greatly contribute to the burden of DS include the evolving nature of seizure subtypes, their timing, and frequency. Seizure freedom remains unattainable for most individuals with DS (>90%) [2,25] despite significant frequency reduction following the introduction of newer ASMs such as stiripentol, cannabidiol, and fenfluramine [91–93]. In contrast to a previous review [12], we show a higher frequency of generalized TC seizures



Abbreviations: ER, Emergency room

Fig. 5. Drivers of Caregiver burden.

before the age of 1 year (85% by 1 year of age [2], vs 65% [12]). In addition, we report a gradual decrease in the rate of SE events after childhood as opposed to the sharp decrease at 1 year of age previously published [12]. Unfortunately, to date, most studies assessing seizures are cross-sectional and only reflect a snapshot of the seizure burden of DS. This may be, in part, due to the challenges and cost associated with longitudinal studies. Daily seizure diaries are burdensome and certain seizure types – myoclonic or absence seizures, or seizures during sleep – may go unnoticed or may not be recorded accurately. Given the contribution of generalized TC seizures and SE to increased mortality through infancy, childhood, and adulthood [97,98], longitudinal data are needed to characterize the occurrence and frequency over the course of the disease.

As a developmental and epileptic encephalopathy, DS is not limited to seizures. Multiple reports illustrate the significant cognitive impairment and neurodevelopmental symptoms that appear early in life and increase over time [9,18,19]. In some instances, these developmental symptoms are present even prior to seizure onset [18,56]. Approximately 20% of individuals remain nonverbal through adolescence [2] and over 80% have profound learning disability by adulthood [9]. Because developmental symptoms may be challenging to identify in very young children with DS, prompt referral to specialists that are able to implement additional therapy or assistive devices, such as seating and mobility aids, is essential to offer individuals and their families better and persistent HRQoL. Although the introduction of newer ASMs has shown a potential modest improvement in some aspects of executive function [22], true disease modification remains an aspirational goal that may only be enabled by therapies targeting the underlying pathophysiology of the DS [99].

Behavior manifestations associated with DS –ASD, ADHD, and obsessive–compulsive disorder (OCD) – have been linked to dysfunction in *SCN1A* with onset usually occurring secondary to seizures [67]. However, how behavioral problems develop with age remains unclear as most estimates come from cross-sectional studies. Yet, the available data underline the high frequency of both ASD and ADHD traits among those living with DS. Autism spectrum disorder is observed in almost 30% of children before the age of 5 years and up to 60% of adults with DS, while ADHD is observed in 15% of children and 20% of adults [2,9]. Very few studies provide contextual or detailed information on OCD or obsessive behavior specifically and no discernible trends were identified in terms of genotype or age for OCD. Data on OCD traits are scarce. Estimates of OCD/obsessive traits ranged widely from 24% to 69% [49] and deserve further examination in future studies.

While the core features of DS have been well described in the literature [9,13,67,100], delineating their precise evolution by age is still needed, especially with the advent of clinical trials of potentially disease-modifying therapies in which treatment effect may differ across age groups. Large longitudinal natural history studies would help describe the clinical evolution of DS, as well as the impact of approved therapies. Building off currently available data on the frequency and timing of seizure- and non-seizure-related outcomes in DS will be important to help shape endpoint selection, optimal timing for assessments, and eventually, optimal timing of treatment with potentially disease-modifying therapies. A recent small prospective study (published after our search was conducted) of 34 children with DS followed up for the first 6 years of life [101], identified a group of patients who showed an initial mild decline between the second and the third years of life, specifically concerning visuomotor abilities, later progressing toward global involvement of all abilities. The authors concluded that in the initial phase of the disease, visuomotor defects might play a major role in determining developmental decline. Natural history studies currently underway or in development will shed further light on clinical prognosis of DS [46,102–105]. Preliminary findings from ENVISION (2-year observational study of young children with DS aged 6–60 months) suggest that regardless of *SCN1A* variant type, global evidence of developmental stagnation is evident as young as two years of age across domains of communication, language, socialization, and motor and adaptive functioning compared with neurotypical peers. In addition, seizure frequency continues to increase with age, despite the use of multiple and newer antiseizure medications [105]. Three-month data from the BUTTERFLY study (2-year observational study of children aged 2–18 years with DS) show that some participants appear to gain some neurodevelopmental and adaptive function skills later in life, relative to neurotypical peers, but not within normative ranges [106]. The HORIZONS study is planned to follow up children and adults living with DS in the United Kingdom for 3 years and will further help define the full range and evolution of disease manifestations.

The diverse clinical manifestations of DS are intrinsically linked with the economic and health system burden of DS. Caring for those living with DS requires substantial healthcare resource use, driven by hospitalizations and in-home medical care visits. Currently available estimates for mean annual total costs (both indirect and direct costs) range widely but are around €49,092 (or approximately $57,800 USD) [30]. These estimates do not comprehensively account for the varied clinical manifestations in DS nor the cost of more recently approved ASMs, so it is likely that they do not represent true current costs [107–111]. For example, the cost of some of the newly available ASMs can be as high as $96,000 per year, an amount that greatly exceeds previous estimates of overall annual total costs [109–111]. Furthermore, though not directly estimated among the identified studies, in other populations with epilepsy the average cost per one childhood SE hospital admission – which is commonly seen in infants and children with DS – is $8000 for convulsive SE [112] and $298,000 for refractory SE [113], suggesting that seizure-related costs alone in DS may be substantially underestimated.

The costs of managing the neurodevelopmental aspects of DS were infrequently reported, including attendance at special schools for children, supportive living/residential community homes for adults, informal or home care, speech language pathologist and physical therapy visits, and assistive devices. While Strzelczyk et al. [30] stratified costs by the number of additional non-seizure-related symptoms, a stratification by the type or severity of these symptoms has not been reported. For context, evidence from those with ASD + ID (without DS) indicates substantial costs associated with of special school among children (accounting for 30% of total costs [€34,225] for those aged 4–11 years and 65% of total costs [€50,233] for those aged 12–17 years) and living accommodation among adults (50% of total costs [€86,099]) [114]. Furthermore, for those that survive into adulthood, costs were infrequently reported, which limits our understanding of the long-term economic impact of DS. Only Strzelczyk et al. [30] stratified by age, finding elevated mean annual direct costs among adults with DS compared with adults with epilepsy [30]. Costs associated with managing neurodevelopmental aspects of DS, considered throughout the lifetime of those with DS, are presently unaccounted for in existing analyses and should be established to fully understand the true economic burden of the disease.

The impact of DS on HRQoL of individuals and their families is increasingly being recognized [25–27,29,30,57,78]. The primary drivers of HRQoL in DS include epilepsy severity, cognition, and motor and behavioral problems. Interestingly, Sinoo et al. reported that the impact of epilepsy severity on HRQoL varies according to cognitive status. Thus, treating seizure severity alone is unlikely to adequately address the HRQoL deficits of DS; disease-modifying therapies that address the spectrum of manifestations are needed. In the quantitative studies included here, HRQoL was reported by parental or caregiver proxy; future assessments and

examination of drivers of patient burden should aim to further characterize the experience from those living with DS.

Due to the severity and extent of both seizure- and non-seizure-related outcomes in DS, the impact on caregivers is substantial. The nature and intensity of caregiving tasks, the impact on caregiver's health, and activities of daily living – including ability to work – change as DS evolves [78]. While the HRQoL effects have only begun to be investigated, anxiety, depression, and sleep problems among DS caregivers are more frequently reported than in the general population or even among other caregiving populations [84,87]. For example, individuals living with DS have more problems with waking during the night than those with other childhood epilepsies, which may explain the worse sleep quality reported by DS caregivers [87]. Similar to findings of a recent systematic review of the burden and health impacts among DS caregivers, we found that most data on caregiving burden are qualitatively- and self-reported [78], with no clinician-assessed studies of caregiver health impacts identified. Studies in other therapeutic areas have demonstrated that caregiver health is negatively affected by caregiving demands [115,116] and studies to characterize this more accurately would be of value in DS.

Utility assessments translate HRQoL scores into measurements of value [117], and further information on how utilities evolve alongside clinical symptoms would help describe the value for targeted therapies. Caregivers of those with DS report lower utility values (0.78) than the general population [29], comparable to those reported in caregivers of severely ill children (e.g., 0.81 in Duchenne muscular dystrophy and 0.71 in childhood onset rare genetic conditions) [118,119]. Similarly, utility values among people with DS are low (0.38–0.42) [2,41], and comparable to other rare pediatric neurodevelopmental disorders [118,120]. Importantly, utility data in DS are presented for a limited selection of health states; only one study described patient VAS scores by seizure frequency which were lower as frequency increased, the remaining studies reported utility data overall or by age [44,121]. Utility assessments for health states that consider a range of seizure- and non-seizure-related manifestations will be required for cost effectiveness analyses of emerging treatments.

While the importance of seizure reduction should not be minimized, potential mitigation strategies are needed to address the broader impacts of DS on the lives of patients and families. Cognitive and developmental sequelae are significant and persistent in DS, and may have a greater impact on HRQoL than just seizure burden. The absence of approved therapies that address the underlying channelopathy means there remains a significant unmet need to prevent or manage non-seizure manifestations in DS [22], underscoring the importance of true disease modification rather than seizure reduction alone.

This systematic review includes a broad and comprehensive scope, creating a more holistic picture of the impact of DS on individuals and their families. Previously published visualizations on the clinical evolution of DS were based primarily on expert consensus [12]. Our evidence-based visualization of the evolution of DS clinical manifestations was developed using the most robust studies identified for each outcome. Furthermore, this is the first systematic review to incorporate estimates of the economic and humanistic burden of DS as well as utility values [12,13,15,16,122,123]. We used a comprehensive approach to identify the evidence base and included evidence published over the last 15 years to concentrate on individuals treated with contemporary medications and management approaches. Finally, we focused on describing the most commonly and consistently reported outcomes related to the clinical burden of DS, using a framework that can be updated as high-quality evidence on other relevant outcomes continue to emerge (e.g., OCD spectrum traits, sleep, and dysautonomia) [47,62,87,124,125]. By integrating measures of the economic and humanistic burden of DS with data on the evolution of clinical manifestations, we were able to identify gaps in knowledge and needs for therapy within the field. These include the need for (1) longitudinal studies of both seizure and non-seizure outcomes to characterize the phenotype of DS across age ranges and aid development of risk-mitigation strategies; (2) economic burden studies that capture the cost of emerging ASMs and stratify by the rate of SE, presence and severity of non-seizure relate outcomes, and age; (3) estimates of caregiver burden by patient age or disease stage; and (4) patient and caregiver utility values for all relevant health states.

As with any systematic review, we were limited by the heterogeneity and reporting accuracy across the included studies. Comparisons and syntheses in this review were hampered by (1) differences between healthcare systems, (2) differences in the characteristics of study samples; (3) differences in the selected outcome measurements, (4) small patient populations, (5) lack of robust longitudinal studies following patients for a broad set of relevant outcomes across age ranges, and (6) potential evolution of the natural history of the disease resulting from earlier diagnosis and use of appropriate ASMs. Other potential biases include variability in measures and definitions used across studies, ceiling and floor effects of selected outcome measures, and lack of assessment among patients with very poor function. Formal meta-analyses were not conducted because there are limited data measuring similar parameters in the same fashion across studies. Recent introduction of genetic testing and DS-specific ICD-10 codes should improve confidence in diagnosis of DS in future studies; however, lack of genetic confirmation may have affected the population included in retrospective studies of adults with DS. It is important to note that natural history studies such as BUTTERFLY, ENVISION, and HORIZONS [46,102–104], currently underway or nearing initiation, will address many of these limitations and knowledge gaps by prospectively following people with genetically confirmed DS across a range of outcomes over long follow-up durations.

5. Conclusions

This systematic review illustrates the dramatic impact of DS on individuals, their families, and healthcare systems, by characterizing the clinical, economic, and humanistic burden, and summarizing health state utility values not previously shared. To characterize the frequency and timing of clinical aspects, this study provides a contemporary, evidence-based visualization of the evolution of DS clinical manifestations, illustrating the persistent risk of premature mortality, the evolving nature of seizures, as well as the significant cognitive and developmental morbidity that appear early in life and increase over time. It is important to closely follow and monitor individuals with DS and their families through various stages of the complex and evolving disease to accurately and fully characterize the burden of DS. These data in turn will help establish the target patient population that is expected to experience the greatest potential benefit from novel disease-modifying therapies, shape development of studies that ensure access to existing and emerging therapeutics, and support understanding of long-term outcomes that are needed to inform important treatment decisions or family support initiatives for people living with DS and their families.

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Data statement

All data presented in this systematic review are derived from published studies and may be available from the first author upon reasonable request.

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Conflict of Interest

MCV, BM, JSG, ESJ, and SR are employees of Encoded Therapeutics. SMS and AMD are employees of Broadstreet HEOR, which received funds from Encoded for the conduct of this study. JS and SMZ received consulting fees related to this work.

Appendix A. Supplementary data

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