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CRITICAL REVIEW

A systematic literature review on the global epidemiology of Dravet syndrome and Lennox–Gastaut syndrome: Prevalence, incidence, diagnosis, and mortality

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Abstract

Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS) are rare developmental and epileptic encephalopathies associated with seizure and nonseizure symptoms. A comprehensive understanding of how many individuals are affected globally, the diagnostic journey they face, and the extent of mortality associated with these conditions is lacking. Here, we summarize and evaluate published data on the epidemiology of DS and LGS in terms of prevalence, incidence, diagnosis, genetic mutations, and mortality and sudden unexpected death in epilepsy (SUDEP) rates. The full study protocol is registered on PROSPERO (CRD42022316930). After screening 2172 deduplicated records, 91 unique records were included; 67 provided data on DS only, 17 provided data on LGS only, and seven provided data on both. Case definitions varied considerably across studies, particularly for LGS. Incidence and prevalence estimates per 100 000 individuals were generally higher for LGS than for DS (LGS: incidence proportion = 14.5–28, prevalence = 5.8–60.8; DS: incidence proportion = 2.2–6.5, prevalence = 1.2–6.5). Diagnostic delay was frequently reported for LGS, with a wider age range at diagnosis reported than for DS (DS, 1.6–9.2 years; LGS, 2–15 years). Genetic screening data were reported by 63 studies; all screened for *SCN1A* variants, and only one study specifically focused on individuals with LGS. Individuals with DS had a higher mortality estimate per 1000 person-years than individuals with LGS (DS, 15.84; LGS, 6.12) and a lower median age at death. SUDEP was the most frequently reported cause of death for individuals with DS. Only four studies reported mortality information for LGS, none of which included SUDEP. This systematic review highlights the paucity of epidemiological data available for DS and especially LGS, demonstrating the need for further research and adoption of standardized diagnostic criteria.

J.R. and E.B. were at the indicated institutions at the time the study was conducted.

KEYWORDS
developmental and epileptic encephalopathy, diagnostic delay, epilepsy, *SCN1A* mutation, SUDEP

1 | INTRODUCTION

Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS) are developmental and epileptic encephalopathies (DEEs) characterized by early onset treatment-resistant seizures, as well as cognitive and behavioral impairment, which usually worsen over time.[1–5] Despite available treatments, both conditions can have a substantial negative impact on the health-related quality of life of the affected individual and their caregivers.[6,7]

DS is characterized by seizure onset usually within the first year of life, with prolonged febrile seizures, and thereafter a seizure pattern that evolves over time, comprising multiple seizure types, including hemiclonic seizures, generalized tonic–clonic seizures, myoclonic seizures, atypical absence seizures, and other types of focal and generalized seizures.[8] Pathogenic variants of the gene encoding the alpha subunit of the voltage-gated sodium channel (*SCN1A*) can be used as genetic biomarkers to aid DS diagnostic confirmation.[9]

LGS is characterized by a triad of clinical features, including multiple seizure types (specifically including tonic seizures), a specific abnormal electroencephalogram (EEG; interictal slow spike–wave complexes <2.5 Hz and paroxysmal fast rhythms 10–20 Hz, mainly during non-rapid eye movement sleep),[4] and intellectual and behavioral impairment.[3] Onset of LGS peaks at 3–5 years of age and can evolve from other epilepsy syndromes, such as infantile epileptic spasms syndrome.[4]

The absence of reliable global epidemiological data for DS and LGS, coupled with considerable changes in the treatment landscape over recent years, means that information is lacking on the number of individuals affected globally and their demographics, diagnostic journeys, and risk of mortality. A greater understanding of the global epidemiology of DS and LGS would provide valuable information for organizations that review novel diagnostic technologies and therapies, as well as for the health systems that deliver them. The aim of this systematic review was to summarize and to evaluate the available global epidemiological data for DS and LGS, including incidence, prevalence, diagnostic data, genetic mutations, mortality, and sudden unexpected death in epilepsy (SUDEP) rates.

Key points

- There was a clear skew of research attention toward DS and a paucity of data for LGS.
- Discovery of *SCN1A* variants as genetic biomarkers for DS has aided diagnosis and may partly explain the higher number of articles identified for DS than LGS.
- Prevalence estimates were higher for LGS than for DS per 100 000 individuals (LGS, 5.8–60.8; DS, 1.2–6.5), but mortality and SUDEP risk may be higher for DS than for LGS.
- Standardized case definition and identification criteria for LGS are required to improve the precision of epidemiological estimates.
- Owing to the underdiagnosis of DS and LGS, the true global incidence, prevalence, and mortality of these conditions may be underestimated.

2 | MATERIALS AND METHODS

This systematic review was registered on PROSPERO before initiation (ID: CRD42022316930) and was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[10]

2.1 | Search strategy

The search strings used to identify potential articles for inclusion were a combination of Medical Subject Headings and free-text terms (Table S1).

2.2 | Data sources

Literature searches were performed in the MEDLINE, Embase, and Cochrane Library databases from inception to March 18, 2022. Supplementary searches included relevant website entries (US Food and Drug Administration and European Medicines Agency) and 2017–2022 conference proceedings (International Society for Pharmacoeconomics and Outcomes Research, American Academy of Neurology, International Epilepsy Congress, American Epilepsy Society, European Academy of Neurology, and the Academy of Managed Care Pharmacy congress [including Nexus]). Bibliographic reference lists of review articles published during 2017–2022 were also searched to identify additional relevant studies.

2.3 | Study selection

Noninterventional studies of any design that reported original research on one or more outcomes of interest in a DS or LGS population were eligible for inclusion. Studies that did not include primary or subgroup analyses specific to DS or LGS were excluded. There were no restrictions on publication date, population, or country of origin. Non-English publications were considered if they contained an abstract written in English. Preclinical studies, case reports, reviews, and interventional studies that actively assigned individuals to a given therapy were excluded. For the purpose of this review, use of screening, diagnostic tests (including genetic sampling), or assessments was not defined as an intervention. Full inclusion and exclusion criteria are listed in Table S2.

After removal of duplicates, screening of title and abstracts and full texts was performed independently in duplicate to identify studies that met the selection criteria. Any disagreement between reviewers was resolved through either discussion or deferral to a third independent reviewer.

2.4 | Data extraction and quality assessment

Data on study design, population, and outcomes were extracted by a single reviewer for each included article. The main outcomes of interest for both DS and LGS were incidence and prevalence estimates, diagnostic data (including age at diagnosis and method of diagnosis, e.g., genetic testing), prevalence of genetic mutations, and risk of mortality and SUDEP.

The same reviewer who conducted data extraction also performed a quality assessment based on a series of "risk of bias" questions adapted from the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement,[11] AXIS (Appraisal tool for Cross-Sectional Studies),[12] and Newcastle–Ottawa Quality Assessment Scale.[13] Risk of bias was rated as high, medium, or low across eight categories relating to study design, methodology, and reporting, to reflect potential concerns over reliability and generalizability of reported results.

2.5 | Data synthesis

Owing to heterogeneity in the study populations and methodologies, no quantitative analyses were conducted. A narrative synthesis of findings is provided below for each outcome, with tabulation of results when relevant. When synthesizing results, potential sources of heterogeneity were examined, including demographic characteristics, geographical scope, condition, study methodology, and quality of evidence. Quantitative estimates were standardized to the same scale when possible (e.g., 100 000 person-years for incidence and per 100 000 people for prevalence, mortality, and SUDEP); these standardized estimates were not derived from raw data and therefore are approximate.

3 | RESULTS

3.1 | General findings

The key findings of this systematic review are summarized in Figure 1. After screening 2172 deduplicated records (database registers, $n=1346$; supplementary searches, $n=826$), 91 articles met the predefined inclusion criteria (Figure 2; Table S3). Of these, 67 reported only on DS, 17 reported only on LGS, and seven reported on both disorders. The most frequently reported outcome was genotype characteristics in individuals with DS ($n=62$); the least frequently reported was SUDEP prevalence in individuals with LGS ($n=0$; Figure 3). Most studies were based in Europe ($n=46$), followed by Asia ($n=22$, predominantly China, Japan, and South Korea) and North America ($n=10$, all based in the USA); few were based in South America, Africa, and Oceania (Table S4).

The most notable and common quality concerns across the studies were sample representativeness, disease and outcome measures used, and reporting clarity (Table S5). These concerns were study specific and most commonly arose because of unclear or poorly defined case definitions resulting in a lack of confirmed DS or LGS diagnoses, or use of specific inclusion criteria. No studies were excluded owing to quality concerns; however, notable concerns are reported throughout the Results section, particularly those that affected study generalizability to DS and LGS populations or comparability between studies.

Case definitions varied for both conditions across the included studies. In total, 27.5% of studies (25/91) used the International League Against Epilepsy (ILAE) criteria at least partly for their case definitions of DS or LGS, although no formally accepted criteria were available until 2022.[14–38] Most used the 2017 revised criteria (seven articles),[14,20,22,26,33–35] followed by the 1989 criteria (six articles)[15,16,23,24,30,31] and the 2010 revised version (three articles).[18,29,32] The ILAE version used was not reported in seven articles,[17,19,21,25,27,28,36] and a mix of criteria iterations was used in two articles.[37,38] Except for five articles, the most recent ILAE criteria available were used.[16,23,29,30,37]

DS case definitions were based on clinical diagnosis and review of medical records across most studies, with a mix of diagnostic criteria using International Classification of

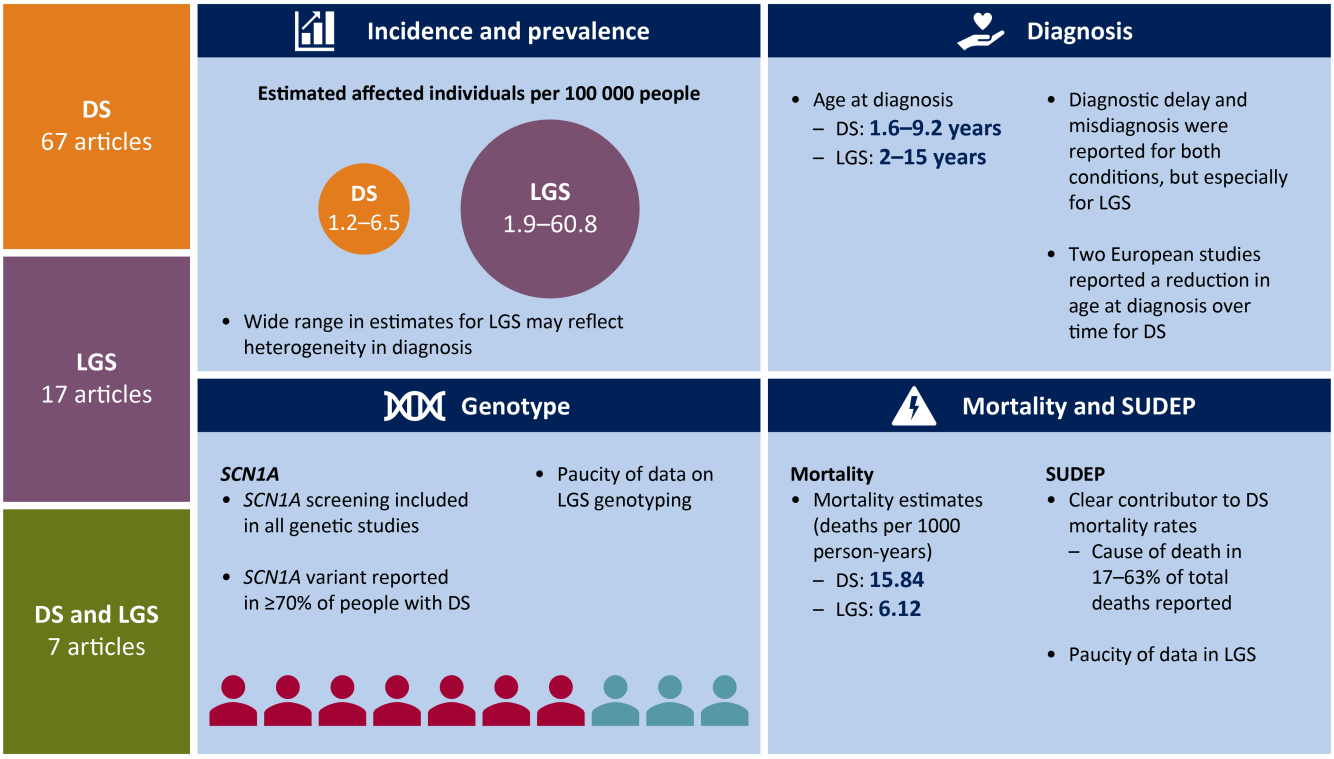


FIGURE 1 Summary of key findings for each epidemiological outcome reported. DS, Dravet syndrome; LGS, Lennox–Gastaut syndrome; *SCN1A*, gene encoding the sodium voltage-gated channel alpha subunit 1; SUDEP, sudden unexpected death in epilepsy.

Diseases (ICD), Ninth Revision or Tenth Revision (ICD-10) codes (five articles),[18,30,39–41] ILAE diagnostic criteria (20 articles),[14,16,18–23,25–30,32–35,37,38] or *SCN1A* mutation presence (two articles).[34,42]

Case definitions for LGS also varied across all included studies, with most individuals being identified based on medical records. Eleven studies used ILAE criteria as part of their diagnostic criteria,[14–17,22,24,31,33,36–38] five assessed presence of slow spike–wave activity via EEG,[43–47] two used unspecified diagnosis codes,[41,48] and two studies included patients with a diagnosis of probable or suspected LGS based on ICD-10 or UK National Health Service (NHS) Read codes for epilepsy/status epilepticus and rufinamide or felbamate prescription.[49,50] NHS Read codes use a standardized coding system for clinical terminology, whereby each code refers uniquely to a specific term and can be used to record an individual's personal and medical history data (e.g., occupation, symptoms and past history, diagnostic or surgical procedures performed, medical conditions).[51] Case definition for LGS was not reported by two studies.[52,53]

3.2 | Incidence and prevalence

Incidence or prevalence data were provided in 10 articles each for DS and LGS (Tables 1 and 2). There were no observed patterns in estimates by demographic or study characteristics for either condition; however, comparisons were difficult given the high degree of heterogeneity in case definition and methodology used across studies.

DS was estimated to affect fewer than seven per 100 000 individuals across all 10 articles, with ranges of 2.17–6.5 per 100 000 individuals for incidence proportion estimates (eight articles)[18,26,28,30,40,54–56] and 1.2–6.5 per 100 000 individuals for prevalence estimates (four articles)[30,39,41,55] (Table 1). The number of individuals with DS used to calculate these estimates varied considerably in size across studies, with those used to calculate DS incidence proportion ranging from six to 285 individuals and for DS prevalence ranging from 42 to 724 individuals. The methodologies used to calculate estimates were also highly variable, with studies using various sources for total study populations (e.g., total number of live births, number of members enrolled in insurance databases, or total number of individuals alive at the end of the study period in a longitudinal study).

No clear geographical patterns were identified. Several countries and regions were underrepresented, with studies limited to Europe (seven articles),[18,26,30,39,54–56] North America (two articles),[40,41] and Asia (one article).[28] Studies were published between 2012 and 2021, with no apparent trend in estimates over time, although one population-based study that included 53 individuals with

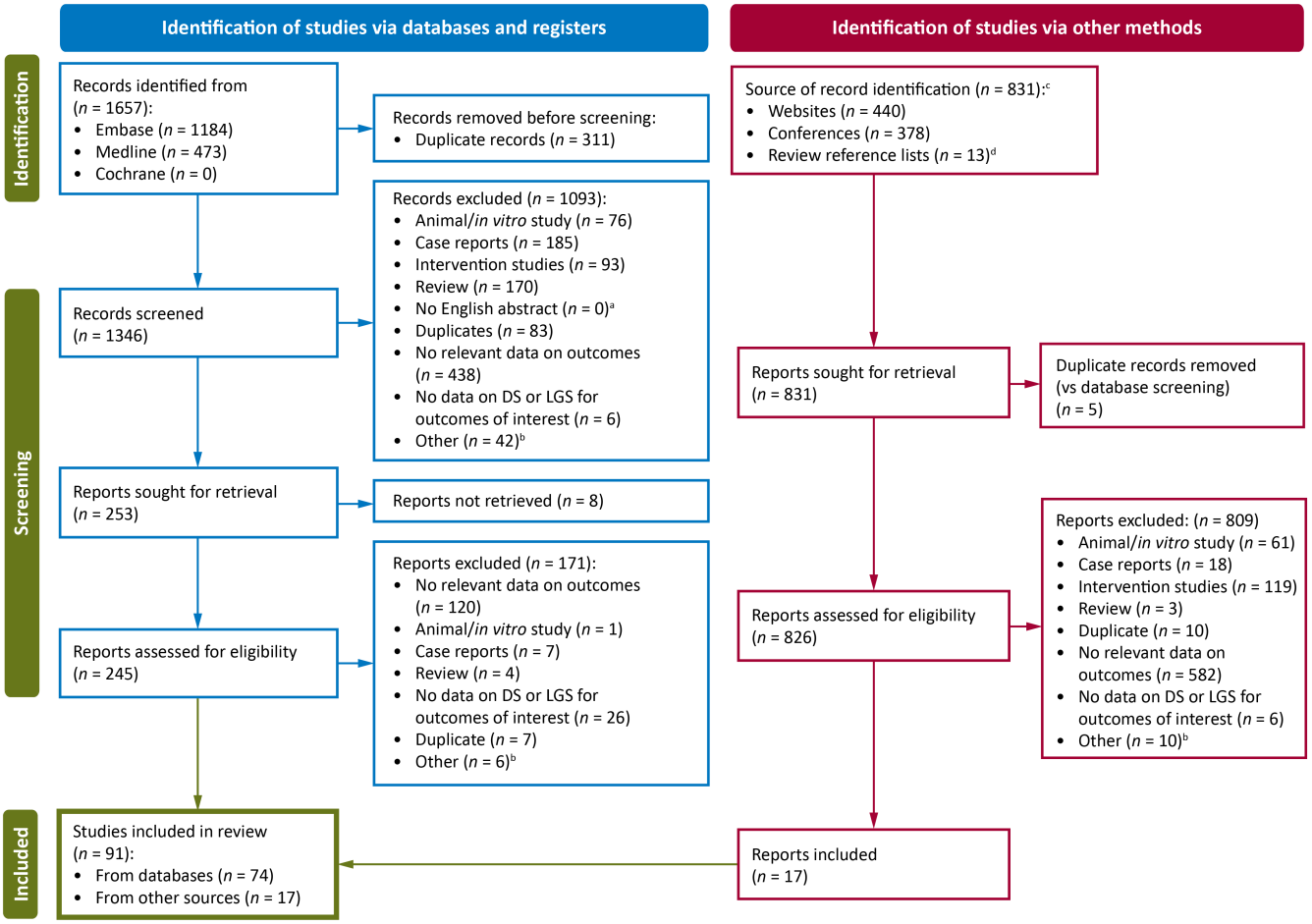
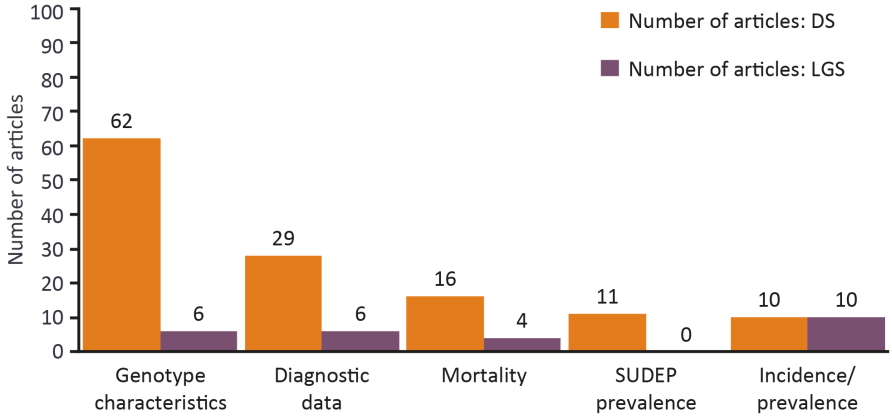


FIGURE 2 PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram. [a]Articles without abstracts were considered if the full text was in English, and articles not in English were considered if there was an abstract in English. [b]In the database search, other reasons for exclusion at title and abstract screening were erratum or letter to editor ($n = 3$) and no abstract available and judged not to be relevant based on title alone ($n = 39$); at full-text screening, other reasons were interim analysis of data in another record ($n = 5$) and uses severe myoclonic epilepsy of infancy rather than Dravet syndrome (DS; $n = 1$); in the additional search, other reasons were full information unavailable ($n = 10$). [c]Hand screening carried out by a single reviewer. [d]Assessed reference lists of all reviews published 2017–2022 and on relevant topics. LGS, Lennox–Gastaut syndrome.

FIGURE 3 Number of studies reporting on the outcomes of interest for Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS). SUDEP, sudden unexpected death in epilepsy.



DS in Sweden reported an increased cumulative incidence over time. This increase was accompanied by decreases in the median age at diagnosis and age at which *SCN1A* screening was performed.[55]

Incidence and prevalence estimates were higher for LGS than for DS, although they were highly variable across the 10 studies with available information. The LGS incidence proportion ranged from 14.49 to 28 per 100 000

TABLE 1 Incidence and prevalence of DS.

Study	Location	Identification of DS	Case definition for DS (all required unless specified)	Population, *n*	Study timing information	Estimate
Incidence proportion per 100 000 live births[a]						
North America						

Wu et al. (2015)[40]	USA (California)	Based on hospital medical records and child neurologist identification	• ≥2 health care encounters <12 months of age with seizure diagnosis (ICD-9 code for epilepsy, convulsion, or febrile convulsion; excluded if experienced <1 month of age) and prescription for ASM only at 24 months of age
			• ≥4 of 5 DS-specific criteria
			  • Normal/near-normal cognitive and motor development before seizure onset
			  • ≥2 febrile or afebrile seizures <1 year of age
			  • Seizure semiology (myoclonic, hemi-clonic, or generalized tonic–clonic seizures)
			  • ≥2 seizures lasting >10 min
			  • Failure to respond to first-line AEDs with continued seizures >2 years of age
			• No alternative reason for seizure diagnosis (e.g., tumor)
				DS: 8
				Total: 125 547
					Included children born Jan 1, 2007–Jun 30, 2010, ranging from >3 years to <18 years of age	6.37 (95% CI = 3.23–12.50)
						SCN1A-positive cases: 4.78 (95% CI = 2.19–10.42)

Europe						
Bayat et al. (2015)[56]	Denmark	Based on records at Danish Epilepsy Center Filadelfia (where all children with DS are referred)	• *SCN1A*-positive mutation • Seizure onset in infancy triggered by fever and prolonged, with later occurrence of other seizure types (febrile and afebrile) including focal seizures, myoclonic seizures, atypical absences, and tonic–clonic seizures • Normal motor and cognitive development before seizure onset, with subsequent slowing including plateauing or regression of skills	DS: 17 Total: all live births (NR)	Included children born 2004–2009 (4–9 years of age)	4.55

TABLE 1 Continued

Study	Location	Identification of DS	Case definition for DS (all required unless specified)	Population, *n*	Study timing information	Estimate
Bjurulf et al. (2022)[55]	Sweden	Based on DS register, pediatric neurologists, and the Dravet Syndrome Association Sweden	• Normal EEG and no pre-existing cerebral lesion • Normal development until first seizure occurring <1 year of age • Refractory clonic or tonic–clonic seizures affecting one or both sides simultaneously or alternately • Exclusion of other identified epilepsy syndromes, including negative *PCDH19* analysis in *SCN1A*-negative participants	Total individuals with DS: 55 (incidence calculation: 53) Total: all live births (NR)	Included individuals born 2000–2018	2.17 (year of birth 2000–2009) 3.03 (year of birth 2010–2018) No significant difference between time periods ($p = .03$)
Brunklaus et al. (2012)[54]	UK	Based on referral for *SCN1A* testing center	• *SCN1A*-positive mutation • Seizure onset in infancy, mainly triggered by fever and often prolonged with later occurrence of other seizure types (febrile and afebrile), including focal seizures, atypical absences, and tonic–clonic seizures • Normal cognitive and motor development before seizure onset, with subsequent slowing including plateauing or regression of skills	DS: 88 Total: all live births (~720 000 per year)	Included children born 2003–2007 (3–7 years of age)	2.44
Gaily et al. (2016)[18]	Finland (Helsinki)	Based on hospital medical records	• ICD-10 code for epilepsy <24 months of age, with first seizure <12 months of age • DS confirmed by 2 of the authors based on ILAE 2010 criteria	DS: 6 Total: 127 730 live births	Included children born 1997–2006	4.7 *SCN1A*-positive: 1.6
Rosander & Hallböök (2015)[30]	Sweden (Gothenburg)	Based on hospital medical records	• ICD-10 codes and ILAE 1989 criteria	DS: 42 Total: all live births (555 934 per year)	Included children with DS diagnosed 2007–2012 (1–17 years of age)	3.03 (95% CI = 1.78–4.90)
Symonds et al. (2021)[26]	UK (Scotland)	Based on HCP identification and records of EEG <4 years of age	• ILAE 2017 criteria	DS: 11 Total: 169 500 live births	Included children <4 years of age presenting with epilepsy Jan 1, 2014–Dec 31, 2017	6.5 (95% CI = 3.2–10.0)
Asia						
Ishii et al. (2017)[28]	Japan	Based on hospital medical records	• ILAE criteria (date not specified)	DS: 285 Total: NR	Study carried out Sep 2014–Sep 2015; incidence based on those born 2009–2012	2.18

(Continues)

TABLE 1 Continued

Study	Location	Identification of DS	Case definition for DS (all required unless specified)	Population, *n*	Study timing information	Estimate
Prevalence per 100 000 individuals[b]						
North America						
Hollenack et al. (2019)[41]	USA	Based on health care insurance claims databases (Medicaid and commercial databases)	• ≥1 AED (including clobazam or rufinamide), ≥1 diagnosis of refractory epilepsy, ≥1 diagnosis of ID/developmental delay, ≥2 AEDs or a diagnosis of febrile seizures, <91 cumulative days of AEDs that exacerbate DS, and no diagnosis codes for either LGS or abnormal brain imaging	DS: 724 (210 commercial, 514 Medicaid) Total: 25 293 634 (17 427 685 commercial, 7 865 949 Medicaid)	Identification of cases Jan 4, 2016–Dec 3, 2017 (commercial) and Jan 1, 2016–Dec 12, 2016 (Medicaid)	Commercial database: 1.2[c] Medicaid database: 6.5[c]
Europe						
Bjurulf et al. (2022)[55]	Sweden	Based on DS register, pediatric neurologists, and the Dravet Syndrome Association Sweden	• Normal EEG and no pre-existing cerebral lesion • Normal development until the first seizure occurring <1 year of age • Refractory clonic or tonic–clonic seizures affecting one or both sides simultaneously or alternately • Exclusion of other identified epilepsy syndromes, including negative *PCDH19* analysis in *SCN1A*-negative participants	Total individuals with DS: 55 (prevalence calculation: 48) Total: all live births (NR)	Included individuals born 2000–2018	2.22 (95% CI = 1.59–2.86)
Rosander & Hallböök (2015)[30]	Sweden (Gothenburg)	Based on hospital medical records	• ICD-10 codes and ILAE 1989 criteria	DS: 42 Total: 1 919 206	Included children with DS diagnosed 2007–2012 (1–17 years of age)	2.19 (95% CI = 1.58–2.96)
Schubert-Bast et al. (2022)[39]	Germany	Based on health care insurance claims database (Vilua Healthcare)	• ICD-10 diagnosis of epilepsy/SE and use of stiripentol or potassium bromide, or valproate and clobazam with other AEDs • No evidence of sodium-channel blockers, abnormal brain development, or competing etiologies	DS: 64 in 2016 Total: NR	Study completed Jan 1, 2007–Dec 31, 2016	4.7 in 2016 (age- and sex-standardized)

Abbreviations: AED, antiepileptic drug; ASM, antiseizure medication; CI, confidence interval; DS, Dravet syndrome; EEG, electroencephalogram; HCP, health care professional; ICD-9/10, International Classification of Diseases, Ninth Revision/Tenth Revision; ID, intellectual disability; ILAE, International League Against Epilepsy; LGS, Lennox–Gastaut syndrome; NR, not reported; *PCDH19*, gene encoding protocadherin 19; *SCN1A*, gene encoding the voltage-gated sodium channel α subunit 1; SE, status epilepticus.

[a]Number of newly diagnosed cases divided by number of live births.

[b]Number of existing cases divided by resident population at risk.

[c]Estimates based on total population of 1 million-member IBM MarketScan commercial or Medicaid plan.

TABLE 2 Incidence and prevalence of LGS.

Study	Location	Identification of LGS	Case definition for LGS (all required unless specified)	Population, *n*	Study timing information	Estimate
Incidence proportion per 100 000 live births[a]						
Europe						
Rantala & Putkonen (1999)[43]	Finland (Oulu)	Based on hospital medical records	• Clinical diagnosis relevant to LGS (i.e., related to epilepsy) and fitting both criteria • ≥2 of the most common seizure types (tonic axial, atonic, and absence seizures) • Slow spike-waves • <3 Hz on EEG	LGS: 25 Total: mean 4960 live births/year	Study completed Jan 1, 1976–Dec 31, 1993	28 (95% CI = 18–41)
Stödberg et al. (2020)[22]	Sweden (northern Stockholm)	Based on SIRE (registry of hospital records of EEG referrals, epilepsy ICD-10 codes, and neuropediatric emergency room visits)	• ILAE 2017 criteria for LGS confirmed by review of hospital medical records by 2 of the authors • First seizure <2 years of age	LGS: 10 Total: NR	Included individuals with first seizure Sep 1, 2001–Dec 31, 2006 (≥7 years of age)	14.49 (95% CI = 8–29)[b]
Annual incidence per 100 000 individuals[c]						
Europe						
Heiskala (1997)[44]	Finland (Helsinki)	Based on hospital medical records	• Classificatio Morborum 1969 as epilepsia motorica minoris or epilepsia alia definita and fitting one of the following criteria • Stringent version of Gastaut's LGS definition, including: ≥2 types of seizure, mental deficiency, and bursts of diffuse slow spike-waves on EEG • Doose's MAE definition (i.e., overlapping LGS and MAE): specific seizures (myoclonic astatic, myoclonic, or atonic absences, tonic–clonic and frequent status), seizure onset 7 months–6 years, and 4–7-Hz rhythms on EEG followed by irregular fast spike-waves and polyspike-waves and 2–3-Hz spike-waves during status	LGS: 75 Total: all residents 0–14 years of age (140 000 individuals in Helsinki, 80 000 in Uusimaa)	Included all individuals treated in a hospital ward 1975–1985 (0–14 years of age)	Helsinki: 2.1 Uusimaa (excluding Helsinki): 1.9
Rantala & Putkonen (1999)[43]	Finland (Oulu)	Based on hospital medical records	• Diagnosis relevant to LGS and fitting both criteria below • ≥2 of the most common seizure types (tonic axial, atonic, and absence seizures) • Slow spike-waves • <3 Hz on EEG	LGS: 25 Total: average 71 973 children <15 years of age per year	Study completed Jan 1, 1976–Dec 31, 1993	1.93 (95% CI = 1.25–2.85)

(Continues)

TABLE 2 Continued

Study	Location	Identification of LGS	Case definition for LGS (all required unless specified)	Population, *n*	Study timing information	Estimate
Incidence per 100 000 person-years[d]						
Europe						
Stödberg et al. (2020)[22]	Sweden (northern Stockholm)	Based on SIRE (registry of hospital records of EEG referrals, epilepsy ICD-10 codes, and neuropediatric emergency room visits)	• ILAE 2017 criteria for LGS confirmed by review of hospital medical records by 2 of the authors • First seizure <2 years of age	LGS: 10 Population data retrieved from Statistics Sweden	Included individuals with first seizure Sep 1, 2001–Dec 31, 2006 (≥7 years of age)	16 (95% CI = 8–29)
Prevalence per 100 000 individuals[e]						
North America						
Hollenack et al. (2019)[41]	USA	Based on health care insurance claims databases (Medicaid and commercial databases)	• ≥1 AED claim (including clobazam or rufinamide) • Diagnosis code for LGS or all of the following • ≥1 diagnosis for refractory epilepsy, ≥1 diagnosis for ID/developmental delay, and no diagnosis that precludes LGS	LGS: 7059 (2273 commercial, 4786 Medicaid) Total: 25 293 634 (17 427 685 commercial, 7 865 949 Medicaid)	Identification period Jan 4, 2016–Dec 3, 2017 (commercial) and Jan 1, 2016–Dec 12, 2016 (Medicaid)	Commercial: 13[f] Medicaid: 60.8[f]
Trevathan et al. (1997)[45]	USA (Atlanta)	Based on Metropolitan Atlanta Developmental Disabilities Study (data from schools including SEPs, hospitals, physicians, and EEG laboratories)	• Identified as having epilepsy and all of the following criteria) • ≥2 seizure types including tonic, atonic, atypical absence, and/or myoclonic seizures that resulted in multiple falls • Interictal EEG with slow (≤2.5 Hz) SWD • ID was not included as a diagnostic criterion	LGS: 23 Total: 89 534	Follow-up at age 10 years Jan 1, 1975–Dec 31, 1977	26 (95% CI = 16–39)
Europe						
Beilmann et al. (1999)[15]	Estonia (south/ northeast)	Based on hospital medical records and physician identification with visits to confirm diagnosis	• Based on ILAE 1989 criteria for LGS	LGS: NR Total: 576 042	Study completed Jan 1, 1995–Dec 31, 1997 (participants 1 month–19 years of age)	10
Chin et al. (2021)[49]	UK	Based on CPRD data (primary care data)	• Confirmed case: Read codes for LGS • Probable case: ICD-10 or Read code for epilepsy and rufinamide prescription	LGS: 256 total; 110 confirmed, 146 probable Total number enrolled and alive in 2017: 180 total; 74 confirmed, 106 probable	Included individuals enrolled in database Jan 1, 1987–Oct 31, 2018	Overall: 5.78 • Confirmed cases: 2.89 • Probable cases: 4.20

TABLE 2 Continued

Study	Location	Identification of LGS	Case definition for LGS (all required unless specified)	Population, *n*	Study timing information	Estimate
Endziniene et al. (1997)[24]	Lithuania (Kaunas)	Based on medical records from specific neurological clinic (including hospitalization), outpatient clinics, and institutions for children with disability	• Epilepsy diagnosis (≥2 unprovoked epileptic seizures) and ILAE 1989 and ICE criteria for LGS based on medical records and follow-up interviews with individuals and parents when required	LGS: NR Total: 88 871	Prevalence estimated on Jan 1, 1995, for those aged 0–15 years	18
Sidenvall et al. (1996)[31]	Sweden (Vasterbottenan)	Based on pediatrician identification, hospital medical records, and a register of children with mental disability	• Epilepsy diagnosis (≥2 unprovoked epileptic seizures) and ILAE 1989 criteria for LGS based on medical records and questionnaires for individuals and parents	LGS: 9 Total: 36 523	Study completed Oct 1985–Dec 1986 (included those aged 0–16 years)	20

Strzelczyk et al. (2021)[50]	Germany	Based on health care insurance claims database (Vilua Healthcare)	• Identification algorithm based on any of the following criteria
			  • ≥1 ICD-10 diagnosis of G40 (epilepsy)/G41 (status epilepticus) and ≥1 claim of either rufinamide or felbamate
			  • If no claim of rufinamide or felbamate, ≥2 different AEDs in combination with ≥1 developmental delay diagnosis
			  • Individuals with narrowly defined LGS had ≥1 documented G40/G41 claim before their 6th birthday; individuals ≥6 years of age on the first day of the study were not included in the narrowly defined LGS population
				LGS: 545 (broad definition) and 102 (narrow definition; diagnosis of epilepsy <6 years of age)
				Total population data retrieved from Vilua Healthcare research database
					Study completed Jan 1, 2007–Dec 31, 2016; prevalence estimated using 2016 data only	Broad definition: 39.2
						Narrow definition: 6.5

Abbreviations: AED, antiepileptic drug; CI, confidence interval; CPRD, Clinical Practice Research Datalink; EEG, electroencephalogram; ICD-10, International Classification of Diseases, Tenth Revision; ICE, International Classification of the Epilepsies and Epileptic Syndromes; ID, intellectual disability; ILAE, International League Against Epilepsy; LGS, Lennox–Gastaut syndrome; MAE, myoclonic astatic epilepsy; NR, not reported; SEP, special education program; SIRE, Stockholm Incidence Registry of Epilepsy; SWD, spike-wave discharge.

[a]Number of newly diagnosed cases divided by number of live births.

[b]Described as birth prevalence but appears equivalent to incidence proportion calculation.

[c]Number of new cases per year divided by resident population per year.

[d]Number of new cases divided by total person-years at risk.

[e]Number of existing cases divided by resident population.

[f]Estimate based on a total population of 1 million-member IBM MarketScan commercial or Medicaid plan.

individuals (two articles),[22,43] annual incidence ranged from 1.93 to 2.1 per 100 000 individuals (two articles),[43,44] incidence per 100 000 person-years was reported as 16 (one article),[22] and prevalence was reported as 5.78–60.8 per 100 000 individuals (seven articles)[15,24,31,41,45,49,50] (Table 2). As with DS, the numbers of individuals with LGS used to calculate LGS incidence and prevalence estimates were highly variable, with those used to calculate LGS incidence ranging from 10 to 75 individuals and for LGS prevalence ranging from nine to 7059 individuals.

A potential source of variation in estimates was the study population source. For example, in one US-based study that used different sources of insurance claims data, the highest LGS prevalence estimate of 60.8 per 100 000 individuals was calculated based on a 1 million-member Medicaid plan, whereas the same study also reported a considerably lower prevalence estimate of 13 per 100 000 individuals when based on a 1 million-member IBM MarketScan commercial plan.[41] The highest prevalence estimate for LGS reported in a population-based study that did not use insurance claims data was 26 individuals per 100 000.[45]

Another source of heterogeneity in estimates was the variation in case definitions. For example, a study based on German health insurance claims data[50] reported a six-fold difference in prevalence estimates between broad and narrow case definitions for LGS (data obtained from the Vilua Healthcare research database, representing approximately 5% of the German population covered by statutory health insurance). In this study, prevalence of broadly defined LGS (all individuals with probable LGS based on ICD-10 diagnostic codes and medication records, $n = 545$) was estimated to be 39.2 per 100 000 individuals. However, when using a narrow definition of LGS (individuals with broadly defined LGS [based on ICD-10 diagnostic codes and medication records] who had received ≥1 ICD-10 diagnoses of epilepsy or status epilepticus before their sixth birthday, $n = 102$), prevalence was estimated as 6.5 per 100 000 individuals.

Study size, length of follow-up, and age at which incidence and prevalence were estimated varied, but no notable trends in estimates were observed. There were no clear geographical patterns identified, although studies were limited to Europe (eight articles)[15,22,24,31,43,44,49,50] and North America (two articles).[41,45] Studies were published between 1996 and 2021, with no apparent trend in estimates over time.

3.3 | Diagnostic data

Overall, 35 studies included information on diagnosis; 29 reported outcomes specific to DS, and six reported outcomes specific to LGS. Studies reporting on DS were mainly limited to Europe (15 articles)[29,30,42,55,57–67] and Asia (nine articles),[14,33,35,38,68–72] with minimal representation from North America (one article),[73] South America (one article),[74] Africa (one article),[75] and Oceania (one article).[34] The setting of one study was not reported.[76] Studies reporting information on LGS diagnosis were limited to North America (four articles),[16,17,48,77] Asia (one article),[46] and Europe (one article).[22] Full details of diagnostic outcome data are listed in Table S6.

Across the included studies, average age at diagnosis (mean/median) for individuals with DS ranged from 1.6 to 9.2 years (five articles),[30,55,65,67,73] with a decrease in age at diagnosis over time reported in one study based in Sweden (comparing children born during 2000–2009 vs. 2010–2018)[55] and one based in Norway (reporting a decrease in time from seizure onset to DS diagnosis in children born after 2003 compared with before 2003).[67] The authors of the study in Sweden attributed this decrease to increased awareness of rare epilepsies such as DS, increased use of genetic screening, discovery of mutations in *SCN1A* as a biomarker for DS (in 2001),[9] and increased availability of gene panels to allow comprehensive genetic screening.[55]

Two studies reported that diagnostic delay and misdiagnosis were more common in adults with DS than in children with DS. Both studies used online surveys of individuals with DS (surveys were completed by caregivers who were predominantly based in Europe) and reported that 80%–83% of adults experienced a diagnostic delay of more than 4 years,[57,60] whereas 20% or fewer of children waited more than 2–4 years for a diagnosis.[57,60] One of these studies, based in Spain, noted that although misdiagnosis was common at the first physician visit, the diagnosis rate of DS had improved from 2016 to 2020. This improvement in making a correct final diagnosis of DS was suggested to be owing to investigations conducted following the first physician visit (e.g., genetic testing).[57] Overall, these findings suggest that improvements in diagnostic tools have contributed to a decrease in age at diagnosis for individuals with DS, although there were insufficient data to determine whether age at diagnosis has decreased over time in regions other than Europe.

Age at diagnosis for individuals with LGS was reported by two studies and overall ranged from 2 to 15 years,[16,46] with one study reporting LGS diagnosis being made most frequently at 5 years old.[46] Fewer studies reported diagnostic data for LGS (six articles)[16,17,22,46,48,77] than for DS (29 articles),[14,29,30,33–35,38,42,55,57–76] which may reflect difficulties associated with diagnosing LGS and/or the evolution of LGS from another condition, in the setting of a heterogeneous group of etiologies and lack of a single causative genetic variant. For example, one US-based retrospective chart review reported that 80% of individuals

(28/35) who satisfied LGS diagnostic criteria did not have a documented diagnosis.[77] A US-based prospective longitudinal study over a 20-year follow-up period reported that 19 of 22 children in whom LGS was diagnosed by the end of follow-up did not receive the diagnosis until a median of 1.9 years after an initial epilepsy diagnosis.[16] In another US prospective cohort study, the number of individuals diagnosed with LGS increased from four to 19 over the 2-year study period owing to initial misdiagnosis in three individuals and evolution of another condition to LGS in 13 individuals; incorrect initial diagnosis of LGS was only reported in one individual, who had symptomatic generalized epilepsy.[17]

3.4 | Genotype

Genotype outcomes were reported in 63 studies. Of these, 57 studies included only individuals with DS,[18–21,23,25–30,32,34,35,40,42,54–56,58,59,62,63,65,67–70,72,74–76,78–102] five included individuals with DS or LGS,[14,33,37,38,71] and one included only individuals with LGS.[52] Studies were predominantly limited to Europe (30 articles) and Asia (20 articles), with considerably fewer studies based in North America (three articles), South America (two articles), Oceania (four articles), and Africa (two articles). Setting was not reported in two included articles. When reported, the most commonly used screening method was Sanger sequencing (15 articles),[14,25,28,29,32,37,54,56,72,78,82,84,85,92,93] followed by whole exome sequencing (four articles)[20,72,76,80] and targeted gene panels (four articles).[28,37,69,79]

All studies screened for mutations in *SCN1A*, with 14 studies also including screening for other genes associated with DEEs, such as the gene encoding protocadherin 19 (*PCDH19*; Table 3). For DS, *SCN1A* mutations were identified in 70% or more of individuals in 42 articles, with the remaining 20 articles reporting lower prevalence. The majority of studies that reported lower prevalence screened individuals with various types of epilepsy or DEEs (with subgroup analyses of individuals with DS). The most commonly reported types of *SCN1A* mutations were missense and truncations. Other possible pathogenic variants were identified in 12 articles, including *PCDH19*, sodium voltage-gated channel beta subunit 1 (*SCN1B*), gamma-aminobutyric acid type A receptor subunit alpha 1 (*GABRA1*), syntaxin 1B (*STX1B*), chromodomain helicase DNA binding protein 2 (*CHD2*), and sodium voltage-gated channel alpha subunit 8 (*SCN8A*).[18,33,35,69,70,72,75,78–80,84,85] For LGS, genetic mutations were reported by three articles. In a study of 22 individuals with clinical features of LGS, one individual had a de novo heterozygous point mutation in *SCN1A*.[52] Two other studies identified possible pathogenic variants in aldehyde dehydrogenase 7 family member A1 (*ALDH7A1*), syntaxin binding protein 1 (*STXBP1*), *CHD2*, and *SCN8A*.[14,37]

TABLE 3 Number of articles screening genetic mutations implicated in DS or LGS.

Gene	Number of articles	
	DS	LGS
SCN1A	62	1
PCDH19	9	0
ALDH7A1	1	1
CHD2	2	1
STXBP1	0	1
SCN1B	3	0
STX1B	1	0
SCN8A	4	1
GABRA1	1	0

Note: Articles may have screened for mutations in multiple genes.

Abbreviations: *ALDH7A1*, gene encoding aldehyde dehydrogenase 7 family member A1; *CHD2*, gene encoding chromodomain helicase DNA binding protein 2; DS, Dravet syndrome; *GABRA1*, gene encoding gamma-aminobutyric acid type A receptor subunit alpha 1; LGS, Lennox–Gastaut syndrome; *PCDH19*, gene encoding protocadherin 19; *SCN1A*, gene encoding sodium voltage-gated channel alpha subunit 1; *SCN1B*, gene encoding sodium voltage-gated channel beta subunit 1; *SCN8A*, gene encoding sodium voltage-gated channel alpha subunit 8; *STX1B*, gene encoding syntaxin 1B; *STXBP1*, gene encoding syntaxin binding protein 1.

3.5 | Mortality and SUDEP

Overall, 21 articles reported on mortality and SUDEP outcomes (Tables 4 and 5, respectively). The majority (17 articles) reported information for DS, with 16 reporting on mortality and 11 reporting on SUDEP; 10 articles reported on both outcomes. Only four articles provided mortality information for LGS, none of which reported SUDEP data. Twelve studies[18,39,43,49,50,54,55,58,59,65,90,103] were based in Europe, specifically Finland, France, Germany, Sweden, and the UK. The remaining nine studies were based in Australia, Canada, China (Hong Kong), Japan, and the USA[19,20,23,34,81,83,94,104]; one study did not report a location.[105]

Mortality in individuals with DS over study follow-up periods of 2–26 years ranged from 4% to 20.8%.[19,23,34,39,54,55,58,81,83,90,94,103,105] Reported mortality in individuals with LGS was similar, ranging from 4% to 35.3% over study follow-up periods of 10–25 years.[43,49,104] In general, studies with shorter follow-up periods reported lower mortality than those with longer follow-up periods. In one retrospective population-based study conducted in Germany, mortality over the 10-year study period was 11.88% in individuals with probable DS compared with

TABLE 4 Mortality findings for DS and LGS.

Study	Location	Study details	Findings
DS			

Akiyama et al. (2010)[94]	Japan	• Observational cohort study
		• Included 31 individuals with DS (14 "typical" DS and 17 "borderline" DS) followed up from childhood until ≥18 years of age
		• Initial cohort was 37 individuals, but 6 died before study completion
			• Mortality: 6/37 (16.2%) individuals died before the end of the study (4 had typical DS, 2 had borderline DS)
			• Age at death: ranged from 5 years 1 month to 12 years 7 months
			• Causes of death, *n*:
			  • SE/clustering seizures, 3
			  • Pneumonia, 2
			  • SUDEP, 1

Bjurulf et al. (2022)[55]	Sweden	• Population-based study using medical records and clinical assessments • Included 55 children (≤19 years of age at time of assessment) with DS born Jan 2000–Dec 2018 with data collected up to Apr 2020 • 2 individuals were excluded from the mortality analyses because they were not born in Sweden	• Mortality: 7/53 children (13%) died • Age at death: median = 4.7 years (range = 3.3–11.0 years) • Cause of death, *n*: • Pneumonia (SUDEP excluded), 2 • Definite SUDEP, 1 • Probable SUDEP with pneumonia, 1 • Possible SUDEP with pneumonitis, 1 • Acute anoxic brain injury after seizure-induced aspiration, 1 • Pneumonitis (SUDEP excluded), 1

Brunklaus et al. (2012)[54]	UK	• Retrospective cohort study using clinical data
		• Mortality was reported for a subgroup of 88 children aged 3–7 years and born 2003–2007 (of 241 individuals in the study) with *SCN1A*-positive DS
			• Mortality: 5/88 children (6%) died
			• Age at death: median, 5 years
			• Causes of death, *n*:
			  • SUDEP, 3
			  • SE, 2

Brunklaus et al. (2012)[102]	UK	• Prospective cohort study using clinical data
		• 207 individuals with *SCN1A*-positive DS
		• Data were collected over 5 years
			• Mortality: 8/207 individuals (4%) died
			• Causes of death, *n*:
			  • SUDEP, 5
			  • SE, 3

Brunklaus et al. (2019)[105]	NR (abstract only)	• Individual reported outcomes study • 130 previous study participants were contactable and sent 4 questionnaires • 70 individuals with *SCN1A*-positive DS responded and were included in the study • Data collection period not reported, although it states that mortality was evaluated over 10 years	• Mortality: 7/130 individuals (5%) with *SCN1A*-positive DS died in the 10-year period

Brunklaus et al. (2019)[90]	UK, Ireland, and Australia	• Prospective cohort study
		• 103 individuals with DS
		• Data were collected over 9 years
			• Mortality: 7/103 individuals (7%) died
			• Causes of death, *n* (%):
			  • SUDEP, 4 (57)
			  • SE, 1 (14)
			  • Acute respiratory distress syndrome due to influenza infection, 1 (14)
			  • Unknown, 1 (14)

Catarino et al. (2011)[59]	UK[a]	• Observational cohort study
		• 26 individuals with DS (22 adults and 4 pediatric postmortem cases)
		• Data collection period not reported
			• Causes of death (adult series), *n*:
			  • Bronchopneumonia, 3
			  • SUDEP, 1
			• Causes of death (pediatric DS group), *n*:
			  • SUDEP, 3
			  • Ischemic brain injury, 1

Cooper et al. (2016)[81]	Australia and overseas[b]	• Consecutive cohort study • 100 individuals with DS (87% with an *SCN1A* mutation) • Data collected either Feb 2001–Feb 2015 or from when the child turned 1 year until date of death or last date the individual was confirmed alive • Living individuals had a median follow-up of 10 years	• Mortality: 17/100 individuals (17%) died • Mortality: 15.84 (98% CI = 9.01–27.85) per 1000 person-years • Age at death: median, 7 years (IQR = 3–11 years)

TABLE 4 (Continued)

Study	Location	Study details	Findings
Gaily et al. (2016)[18]	Finland	• Retrospective population-based study • 6 individuals with DS of a total cohort of 158 individuals born 1997–2006 • 92% of the total cohort ($n = 158$) were followed up until 2 years of age or death	• Mortality: 0 individuals with DS died before 2 years of age

Genton et al. (2011)[103]	France	• Cohort study; no further details specified
		• 24 individuals with DS first referred between 1970 and 1992
			• Mortality: 5/24 individuals (20.8%) died
			• Age at death: mean = 24.8 years
			• Causes of death, *n*:
			  • SUDEP, 3
			  • SE and complications of SE, 1
			  • Unknown, 1

Gertler et al. (2020)[19]	USA	• Single-center retrospective chart review • 137 individuals with DS • Data collected 2007–Apr 2016	• Mortality: 7/137 individuals (5.1%) died • Cause of death: 4/7 deaths (57.1%) were due to SUDEP
Howell et al. (2021)[20]	Australia	• Population-based cohort study • 4 individuals with DS of a total cohort of 114 individuals, all born 2011–2013	• Mortality: no individuals with DS died <2 years of age
Kwong et al. (2012)[23]	China (Hong Kong)	• Genetic screening with retrospective evaluation of clinical data • 18 individuals with DS of a total cohort of 100 • Data collection period was not reported	• Mortality: 1/18 individuals (5.6%) died • Age at death: 3 years ($n = 1$)

Li et al. (2021)[34]	Australia	• Prospective cohort study
		• 205 individuals with *SCN1A*-positive DS
		• Data were collected between 1995 and 2020
			• Mortality: 25/205 individuals (12%) died
			• Age at death: median = 6.5 years (range = 11 months–39 years)
			• Causes of death, *n* (%):
			  • SUDEP, 13 (52)
			  • Cerebral edema, 5 (20)
			  • Accidental drowning, 4 (16)
			  • SE, 2 (8)
			  • Asphyxia due to aspiration of gastric contents, 1 (4)

Sakauchi et al. (2011)[83]	Japan	• Questionnaire survey
		• 623 individuals with DS
		• Questionnaires sent out Jul 2009; no further details reported
			• Mortality: 63/623 individuals (10.1%) died
			• Age at death: prevalence of sudden death reached a first peak at 1–3 years of age and a second peak at ≥18 years of age
			• Causes of death (only available for 59/63 individuals), *n* (%):
			  • Sudden death, 31 (53)
			  • Acute encephalopathy with SE, 21 (36)
			  • Drowning, 6 (10)
			  • Other causes, 1 (1)

Schubert-Bast et al. (2022)[39]	Germany	• Retrospective population-based study
		• 160 individuals with probable DS
		• 10-year study period (2007–2016)
			• Mortality ($p < .001$ between groups), *n* (%)
			  • Probable DS: 19 (11.88)
			  • Matched controls: 172 (1.19)
			• Mortality was similar in male (11 deaths, 12.79% of all male patients with DS) and female (8 deaths, 10.81% of all female patients with DS) individuals

(Continues)

TABLE 4 (Continued)

Study	Location	Study details	Findings
LGS			

Autry et al. (2010)[104]	USA	• Retrospective population-based cohort study
		• 34 individuals with LGS born 1975–1977
		• Total study cohort comprised 688 children with epilepsy
		• Follow-up period 1975–2001
			• Mortality: 12/34 individuals (35.3%) with LGS died
			• Mortality ratios (population of interest vs. general population):
			  • LGS, 13.92 (95% CI = 7.19–24.31)
			  • LGS with infantile spasms, 15.24 (95% CI = 4.15–39.02)
			  • LGS without infantile spasms, 13.34 (95% CI = 5.75–26.27)
			  • Total children with epilepsy, 3.11 (95% CI = 2.39–3.98)

Chin et al. (2021)[49]	UK	• Retrospective linkage cohort study
		• 256 individuals with LGS enrolled 1987–2018; 110 individuals (43%) with confirmed LGS and 146 (57%) with probable LGS
		• Mortality was only calculated for individuals with CPRD linkage to ONS ($n = 122$)
		• Follow-up period Jan 1998–Feb 2018
			• Mortality: 18/122 individuals (14.8%) died during follow-up
			  • Confirmed LGS, 11
			  • Probable LGS, 7
			• Age at death, median (min.; max.)
			  • Confirmed LGS, 26 (11; 46) years
			  • Probable LGS, 16 (4; 64) years
			• Crude mortality (deaths per 1000 person-years)
			  • Confirmed LGS, 6.12
			  • Probable LGS, 4.17

Rantala & Putkonen (1999)[43]	Finland	• Retrospective review of 25 individuals with LGS • Data collected 1976–1993 • Mean follow-up period: 10.2 years (range = 5.3–15.6 years)	• Mortality: 1/25 individuals (4%) died • Cause of death: pneumonia due to aspiration during SE ($n = 1$)
Strzelczyk et al. (2021)[50]	Germany	• Retrospective study over 10 years from 2007 to 2016 • 1571 individuals with broadly defined probable LGS; 208 individuals with narrowly defined probable LGS • Follow-up period: 10 years	• Narrowly defined probable LGS mortality was higher than that observed in control population (2.88% [6 events] vs. .01% [1 event], $p < .001$) • Broadly defined probable LGS mortality greater than narrowly defined probable LGS population (10.01% [157 events] vs. 2.88% [6 events], $p < .001$)

Abbreviations: CI, confidence interval; CPRD, Clinical Practice Research Datalink; DS, Dravet syndrome; IQR, interquartile range; LGS, Lennox–Gastaut syndrome; max., maximum; min., minimum; NR, not reported; ONS, Office for National Statistics; *SCN1A*, gene encoding the voltage-gated sodium channel alpha subunit 1; SE, status epilepticus; SUDEP, sudden unexpected death in epilepsy.

[a]Location not reported, but majority of authors based in the UK.

[b]61 individuals from Australia; 39 from overseas with no further details.

1.19% in age- and sex-matched controls ($p < .001$).[39] This elevated mortality was also reported for individuals with LGS by two studies. One retrospective study based in the USA with a follow-up period from 1975 to 2001 reported a higher observed-to-expected mortality ratio for individuals with LGS (13.92) than for all children with epilepsy (3.11),[104] and another retrospective study in Germany with a follow-up period from 2007 to 2016 reported a mortality of 2.88% for individuals with narrowly defined LGS (patients had ≥1 documented epilepsy or status epilepticus diagnosis based on ICD-10 diagnostic codes before 6 years of age) compared with .01% for the age- and sex-matched control population ($p < .001$).[50] Mortality rates were reported in one study for each condition, with estimated rates for DS and LGS of 15.84 deaths[81] and 6.12 deaths[49] per 1000 person-years, respectively. Median age at death ranged from 4.7 to 7 years for individuals with DS across four articles,[34,54,55,81] compared with 26 years in individuals with confirmed LGS or 16 years in those with probable LGS based on one article.[49] SUDEP was the most frequently reported cause of death for individuals with DS (10/21 articles reporting mortality outcomes) and, when reported, was the cause of death in 17%–63% of total deaths for individuals with DS. Cause of death, which was unrelated to SUDEP, was only reported for one individual with LGS in one study.[43]

TABLE 5 SUDEP findings for DS.

Study	Location	Study details	Deaths reported due to SUDEP
Bjurulf et al. (2022)[55]	Sweden	• Population-based study using medical records and clinical assessments • 55 children (≤18 years of age) with DS (born Jan 2000–Dec 2018) were included with data collected up to Apr 2020	• 3/7 deaths (42.9%) were due to definite/probable/possible SUDEP
Brunklaus et al. (2012)[54]	UK	• Retrospective cohort study using clinical data • Mortality was reported for a subgroup of 88 children aged 3–7 years and born 2003–2007 (from 241 individuals in the study) with *SCN1A*-positive DS	• 3/5 deaths (60%) were due to SUDEP
Brunklaus et al. (2012)[102]	UK	• Prospective cohort study using clinical data • 207 individuals with *SCN1A*-positive DS • Data collected over 5 years	• 5/8 deaths (62.5%) were due to SUDEP
Brunklaus et al. (2019)[90]	UK, Ireland, and Australia	• Prospective cohort study • 103 individuals with DS • Data collected over 9 years	• 4/7 deaths (57%) were due to SUDEP • SUDEP rate for DS was 4.4 per 1000 person-years
Catarino et al. (2011)[59]	UK[a]	• Observational cohort study • 26 individuals with DS (22 adult individuals and 4 pediatric postmortem cases) • Data collection period not reported	• 1/4 adult deaths (25%) were due to SUDEP • 3/4 pediatric deaths (75%) were due to SUDEP
Cooper et al. (2016)[81]	Australia and overseas[b]	• Cohort study; no further details specified • 100 individuals with DS (87% had an *SCN1A* mutation) • Data collected either Feb 2001–Feb 2015 or when the child turned 1 year old until date of death or last date the individual was confirmed alive	• 10/17 deaths (59%) were due to SUDEP • SUDEP classifications were definite ($n=3$), definite plus ($n=1$), and probable ($n=6$) • SUDEP rate for DS was 9.32 per 1000 person-years (98% CI = 4.46–19.45)
Genton et al. (2011)[103]	France	• Cohort study; no further details specified • 24 individuals with DS first referred between 1970 and 1992	• 3/5 deaths (60%) were due to SUDEP
Gertler et al. (2020)[19]	USA	• Single-center retrospective chart review • 137 individuals with DS, data collected 2007– Apr 2016	• 4/7 deaths (57.1%) were due to SUDEP
Li et al. (2021)[34]	Australia	• Prospective cohort study • 205 individuals with *SCN1A*-positive DS, data collected between 1995 and 2020	• 13/25 deaths (52%) were due to SUDEP or probable SUDEP
Sakauchi et al. (2011)[83]	Japan	• Questionnaire survey • 623 individuals with DS • Questionnaires sent out Jul 2009; no further details reported • 63/623 individuals with DS had died; data analysis was conducted on 59 of these	• 31/59 deaths (53%) were due to SUDEP
Villeneuve et al. (2014)[65]	France	• Prospective cohort study • 21 individuals with DS 6–10 years old • Data collected between 2003 and 2012	• 4 individuals were excluded from the study owing to deaths due to SUDEP before the study began (of 27 individuals eligible at the beginning of the study)

Abbreviations: CI, confidence interval; DS, Dravet syndrome; *SCN1A*, gene encoding the voltage-gated sodium channel alpha subunit 1; SUDEP, sudden unexpected death in epilepsy.

[a]Location not reported, but majority of authors based in the UK.

[b]61 individuals from Australia and 39 from overseas with no further details given.

4 | DISCUSSION

Despite DEEs such as DS and LGS receiving an increasing amount of research interest in recent years,[106–109] significant knowledge gaps remain in understanding the associated global epidemiological factors associated with these conditions. To this end, this systematic review presents a comprehensive summary and evaluation of the published literature describing the epidemiology of DS and LGS. Analysis of the 91 articles identified revealed

high levels of interstudy variability in methods and results, and a clear skew of research attention toward DS. A paucity of studies focusing on LGS was observed despite this condition having been recognized for longer than DS.[110,111] These issues, identified in the present analysis, make it difficult to draw reliable conclusions about the epidemiology of DS and LGS.

Strzelczyk et al.[112] recently conducted a systematic literature review on the burden of illness of LGS, which included analysis of incidence, prevalence, and mortality outcomes. In general, there was a high degree of similarity between the Strzelczyk et al.'s systematic review and the findings on LGS presented here. Our systematic review included all of the same studies reporting epidemiological outcomes except one review article,[113] which was excluded from our study based on the inclusion criteria of the present analysis.

Overall, our findings for LGS incidence and prevalence outcomes were similar to the Strzelczyk review findings, although the number of included studies varied slightly (seven studies vs. 10 studies in this review). Our reported incidence estimates have a wider range of 1.93–28 cases per 100 000 individuals (three studies), compared with 1.9 per 100 000 children younger than 15 years (reported by two different studies). Reported prevalence estimates also differed slightly (5.78–60.8 per 100 000 individuals in our review vs. 4.2–60.8 [probable LGS] or 2.9–28 [confirmed LGS] per 100 000 individuals reported by Strzelczyk et al.). This is because we did not stratify between probable and confirmed LGS throughout our review and because we included the overall prevalence of LGS reported by Chin et al. (5.78 per 100 000 individuals), rather than reporting the prevalence for probable LGS (4.20 per 100 000 individuals) or confirmed LGS (2.89 per 100 000 individuals) individually from the same publication.[49] Additionally, we have reported one estimate of 28 per 100 000 individuals from one study as an incidence proportion,[43] whereas Strzelczyk et al. reported the same value as a prevalence estimate. We included this value as an incidence proportion because this was how we consistently reported all included study estimates (10 articles) that were calculated as the number of newly diagnosed cases divided by the number of live births reported.[18,22,26,28,30,40,43,54–56] Mortality findings for LGS were also in alignment with those reported by Strzelczyk et al., with a higher mortality for individuals with LGS than for the general population and epilepsy population.

No clear geographical patterns were identified across any of the outcomes; however, this may have been due to the lack of comparable studies across multiple countries. For each outcome category, there was an underrepresentation of studies in low-income countries and of studies in Africa, Oceania, and South America. As a result, the findings described in this review may not be generalizable to these populations, preventing the identification of epidemiological trends across different races and ethnicities. Given the high prevalence of epilepsy in developing countries,[114] the true incidence and prevalence of DS and LGS globally may be underestimated. Additionally, there is a clear lack of global information available on the mortality of patients with DS and LGS, meaning the true impact of these conditions is also likely to be underestimated, and hinders comparison with other types of epilepsy.

Scientific advances in diagnostic methods and treatment have driven changes in diagnostic criteria and definitions for DS and LGS over time.[2,115] These changes were reflected in the results of this review by a wide variation in diagnostic criteria used across studies, with some (mainly older) studies likely to have included individuals who would perhaps not receive a diagnosis of DS or LGS today. Most study case definitions were based on existing diagnoses of DS or LGS, which will likely underestimate the true population incidence and prevalence, because DS and LGS are believed to be underdiagnosed.[116–118]

The development of genetic screening for *SCN1A* variants in individuals with DS has facilitated earlier detection and accurate diagnosis, thereby reducing unnecessary investigations and improving access to appropriate therapies and care (e.g., discontinuation of contraindicated medications), resulting in improved seizure control.[38,58] The ubiquitous use of genetic testing to screen for *SCN1A* variants observed in this review may explain the large discrepancy in the number of studies identified for DS compared with LGS. *SCN1A* screening has simplified DS diagnosis, but overreliance on this method could potentially lead to an overemphasis on individuals with *SCN1A* variants in the literature, and, although common in individuals with DS, they are not always present.[119] Use of *SCN1A* screening to define DS in two studies[34,42] could have led to underreporting of the incidence and prevalence of DS.

Clear additional difficulties exist in diagnosing LGS compared with DS. The later onset of seizures (≥2 years of age) in LGS creates challenges in distinguishing between late onset LGS and cases of diagnostic delay,[16] and may result in underestimation of prevalence estimates. Although beneficial for future studies, updates to diagnostic criteria over time, for example the ILAE-recommended diagnostic age, may also influence the variability in prevalence estimates.[4,120] The potential evolution from other epilepsy syndromes (e.g., infantile epileptic spasms syndrome) also makes distinguishing between LGS and other conditions difficult, particularly with a current lack of stringent, consistent diagnostic criteria in studies to date. Given the degree of heterogeneity observed in the LGS electroclinical phenotype, LGS diagnoses may encompass multiple separate conditions that each have different etiologies,

genotypes, risk of mortality/SUDEP, and treatment requirements, which might partly explain the variation in findings identified in this review. Although there is still uncertainty in terms of identifying a definitive LGS diagnosis in the existing published literature, updated and more robust diagnostic criteria will aid in re-evaluating the reliability of current estimates, and ensure consistent reporting in future studies.[4]

Unlike DS, LGS has variable presentation and etiology, with no specific associated genetic variant. Therefore, no definitive method of diagnostic verification exists, as highlighted by only six articles reporting genotype information for individuals with LGS. As a result, the accuracy of LGS diagnosis will depend on the degree to which diagnostic criteria are adhered to, and thus will affect estimates of incidence and prevalence. Case definitions used for LGS were highly heterogeneous across the included studies (e.g., some studies included a definition of "probable LGS" for individuals with unconfirmed LGS diagnoses), which, combined with the lack of a disease biomarker and heterogeneity of presentation, could have reduced the reliability of study findings and inflated incidence and prevalence estimates.

Improvements in the diagnosis of conditions with phenotypes similar to LGS, including other DEEs associated with multiple treatment-resistant seizure types and developmental delay, could indirectly improve the diagnosis of LGS through reducing the number of misdiagnoses. For example, the recent discovery of genetic causes for cyclin-dependent kinase-like 5 (*CDKL5*) deficiency disorder facilitates differentiation of this condition and LGS.[121] Consequently, increasingly accurate diagnoses of DEEs through genetic screening could lead to a reduction in uncertain diagnoses such as "probable LGS."

Both DS and LGS were found to pose a significant risk of premature death in affected individuals. Despite having a lower estimated incidence and prevalence, individuals with DS appear to have a higher mortality and die at a younger age than those with LGS. These findings may be partially explained by the relatively high prevalence of SUDEP observed in individuals with DS, as well as the later onset and difficulties in diagnosis observed for LGS, which may mean that individuals do not receive a correct LGS diagnosis before death.

No cases of SUDEP in individuals with LGS were identified in this systematic review, perhaps reflecting a paucity of available data. It should be noted that during screening, an article that recorded a case of death due to SUDEP in an individual with LGS was identified,[122] but this study did not meet the inclusion criteria for this review (case report).

One long-term prospective outcome study identified in this review reported a DS-specific SUDEP rate of 4.4/1000 person-years,[90] whereas another study reported a higher rate of 9.32 per 1000 person-years (98% confidence interval = 4.46–19.45).[81] In epilepsy overall, the incidence of SUDEP is estimated to be .58 (range = .31–1.08) per 1000 person-years,[123] suggesting that SUDEP is considerably more common in individuals with DS than in those with other types of epilepsy.

Reliability and generalizability of the review findings were limited by quality concerns, inconsistency in case definitions, and poor geographical representation of some regions. The most frequent quality concerns across the studies related to sample representativeness, disease and outcomes measures used, and reporting clarity. Notably, use of Medicaid databases in some of the US-based studies may have skewed estimates of incidence and prevalence, given that Medicaid specifically covers health care costs for children and people with low income or disabilities and is not representative of the US general population. The high prevalence estimates in studies using the Medicaid database compared with other population-based studies may therefore be explained by an overrepresentation of people with DS and LGS in this database.[41] The absence of specific ICD-10 codes for DS and LGS in many countries and the relatively recent introduction of codes in the USA (in 2020 and 2015, respectively) may also prevent reliable identification of individuals from historical claims data for epidemiological analyses.[106,124]

Inconsistency with case definitions, especially for LGS, hindered the ability to make direct comparisons across studies. The harmonization of study methods is needed to facilitate comparisons across epidemiological studies going forward.

Finally, several geographical regions were underrepresented in the included studies, particularly Africa, Oceania, and South America. As a result, a true global understanding of the epidemiology of DS and LGS is not possible, highlighting the need for large multinational studies.

To overcome these quality concerns and limitations, future studies should aim to include representative samples of the DS and LGS individual populations and use clearly described, up-to-date diagnostic criteria that allow accurate identification and diagnosis of individuals with DS and LGS, and reliable interstudy comparison.

5 | CONCLUSIONS

This systematic review highlights the considerable differences in research attention and available diagnostic tools for DS and LGS. The benefits of having a genetic biomarker to aid diagnosis and ultimately to improve patient care are apparent with DS, and likely explain the skew of included

articles toward this condition compared with LGS. Whereas prevalence estimates were higher for LGS compared to DS per 100 000 individuals (LGS, 5.8–60.8; DS, 1.2–6.5), mortality and the risk of SUDEP appear to be higher for DS than for LGS. There was a paucity of existing data on certain outcomes for both conditions, particularly for LGS, and difficulty comparing studies because of variations in methods and case definitions used. These issues emphasize the need for new, systematic epidemiological studies that apply a clear and consistent case definition across multiple countries. Addressing existing evidence gaps would facilitate greater understanding of how many individuals are affected by DS and LGS, and the identification of issues relating to diagnosis and mortality around the globe.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design, interpreted the results, contributed to writing, and approved the final version of the manuscript for submission.

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CONFLICT OF INTEREST STATEMENT

A.B., J.S.A., and D.S. are employees of Takeda Pharmaceutical Company and own stock or stock options. J.R. is a former employee of Takeda Pharmaceutical Company, and is currently an employee of Novo Nordisk Health Care, Zürich, Switzerland. E.B. and A.J. are employees of Oxford PharmaGenesis, Oxford, UK. The following authors have received compensation for serving as consultants or speakers, or they or the institutions they work for have received research support or royalties from the companies or organizations indicated: J.S., BioPharm Solutions, Bright Minds, CAMP4 Therapeutics, Dravet Syndrome Foundation, Encoded Therapeutics, Epilepsy Study Consortium, Epygenix Therapeutics, Greenwich Biosciences, Longboard Pharmaceuticals, Marinus Pharmaceuticals, Neurocrine Biosciences, PCDH19 Alliance, Praxis, Stoke Therapeutics, Takeda, Xenon Pharmaceuticals, and Zogenix; J.H.C., Biocodex, Engineering and Physical Sciences Research Council (UK), Epilepsy Research UK, Great Ormond Street Hospital Children's Charity, GW Pharmaceuticals/Jazz Pharmaceuticals, Marinus Pharmaceuticals, National Institute for Health and Care Research, National Institute of Health Research Biomedical Research Centre at Great Ormond Street Hospital, Nutricia, Ovid Therapeutics, Stoke Therapeutics, UCL Great Ormond Street Institute of Child Health, UltraGenyx, Vitaflo, Waterloo Foundation, and Zogenix/UCB. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

All relevant data from the original articles are included in this review, and citations are provided to indicate the original source for all information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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