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Epilepsia®

FULL-LENGTH ORIGINAL RESEARCH

Exploring the prevalence and profile of epilepsy across Europe using a standard retrospective chart review: Challenges and opportunities

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Summary

Objective: This study aimed to determine the prevalence of epilepsy in four European countries (Austria, Denmark, Ireland, and Romania) employing a standard methodology. The study was conducted under the auspices of ESBACE (European Study on the Burden and Care of Epilepsy).

Methods: All hospitals and general practitioners serving a region of at least 50 000 persons in each country were asked to identify patients living in the region who had a diagnosis of epilepsy or experienced a single unprovoked seizure. Medical records were accessed, where available, to complete a standardized case report form. Data were sought on seizure frequency, seizure type, investigations, etiology, comorbidities, and use of antiseizure medication. Cases were validated in each country, and the degree of certainty was graded as definite, probable, or suspect cases.

Results: From a total population of 237 757 in the four countries, 1988 (.8%) patients were identified as potential cases of epilepsy. Due to legal and ethical issues in the individual countries, medical records were available for only 1208 patients, and among these, 113 had insufficient clinical information. The remaining 1095 cases were classified as either definite ($n = 706$, 64.5%), probable ($n = 191$, 17.4%), suspect ($n = 153$, 14.0%), or not epilepsy ($n = 45$, 4.1%).

Significance: Although a precise prevalence estimate could not be generated from these data, the study found a high validity of epilepsy classification among evaluated cases (95.9%). More generally, this study highlights the significant challenges facing epidemiological research methodologies that are reliant on patient consent and retrospective chart review, largely due to the introduction of data protection legislation during the study period. Documentation of the epilepsy diagnosis was, in some cases, relatively low, indicating a need for improved guidelines for assessment, follow-up, and documentation. This study highlights the need to address the concerns and requirements of recruitment sites to engage in epidemiological research.

KEYWORDS
burden of disease, data protection, epidemiology, GDPR, general data protection regulation, medical records

1 | INTRODUCTION

In the past decade, global health policy has recognized epilepsy as a leading cause of disability. With approximately 50 million persons worldwide estimated to have epilepsy,[1] the Seventy-Third World Health Assembly of the World Health Organization (WHO) recently identified epilepsy as one of the most common neurological disorders, with a high level of global disability and mortality burden.[2] Within Europe, the European Union (EU) Declaration on Epilepsy called on the EU Commission and Council to prioritize epilepsy as a major disease that imposes a significant burden across Europe.[3] The EU Declaration on Epilepsy estimates that 6 million people have epilepsy in Europe.[3] This estimate is taken from the Atlas of Epilepsy, which applied a prevalence estimate of 8.23 per 1000

Key Points

- This epidemiological study of epilepsy, in four European countries with a total population of 237 757 persons, identified 1988 (.8%) potential epilepsy cases
- Medical records were reviewed and validated in 1095 cases, including 1050 (95.9%) classified as suspected, probable, or definite epilepsy
- Large variability in the degree of certainty of the epilepsy diagnosis indicates a need for standardized criteria for documenting diagnosis
- Challenges accessing medical records due to data protection and resource issues highlight a need for standardized approaches to European-wide research

persons with "current" epilepsy across 53 countries comprising the European Region of the WHO.[4] The 6 million figure remains widely cited despite being based on information from key informants in each participating country, not robust epidemiological methodologies.[5,6]

A markedly lower prevalence estimate in Europe (defined as comprising the EU, Iceland, Norway, and Switzerland) of 5.78 per 1000 persons was determined by the European Brain Council[7] from a systematic review that revealed highly varying within- and between-country estimates.[8,9] This variation was also observed in a Global Burden of Disease Study reporting a prevalence of 6.22 per 1000 persons,[10] and in a global systematic review citing the prevalence of active epilepsy at 6.38 per 1000 persons,[11] with one study determining a prevalence of active epilepsy of 104.97 per 1000 persons.[12]

Despite this variation, it has been argued that there is "little justification for further cross-sectional studies of prevalence."[13] This argument is challenged by studies indicating an increase in prevalence among older individuals, who comprise a rapidly growing population.[14] Similarly, the introduction of International League Against Epilepsy (ILAE)'s new clinical definition of epilepsy[15] will, by definition, increase prevalence estimates, as case ascertainment is now expanded to include cases with one unprovoked seizure with a predicted recurrence rate of >60%. Finally, recently identified sources of heterogeneity, such as the developmental level of countries, sample size of study population, and age of participants, have yet to be applied within pan-European epidemiological research.[1]

This paper reports on findings from the European Study on the Burden and Care of Epilepsy (ESBACE), which aimed to explore the burden of epilepsy across Europe. Funded by the European Commission, the primary objective of ESBACE was to develop and apply a common case ascertainment methodology to determine the prevalence of epilepsy using the new ILAE definition and terminology. A secondary objective of ESBACE was to assess the quality of life and cost for persons with epilepsy identified in the study using matched controls in a 12-month prospective case–control study. This paper reports solely on efforts to address the first objective, although the methodologies outlined below were developed to simultaneously address both objectives.

2 | MATERIALS AND METHODS

2.1 | Study design

A retrospective chart review of patients with epilepsy and unprovoked single seizures was conducted in four European countries to enumerate and profile this population. In a subset of patients, information from patient interviews supplemented information from the chart review.

2.2 | Settings

Four European countries, each of which was classified as having either an upper-middle- or high-income economy by the World Bank,[16] were selected for participation in ESBACE and represented northern (Denmark), central (Austria), eastern (Romania), and western (Ireland) Europe.

2.3 | Study size

Within each country, research teams identified eligible cases in a region of at least 50 000 inhabitants. Regions were considered by teams as representative of the country. Across the four regions, the study population totaled 237 757 persons, specifically: Austria, $n = 59\ 543$; Denmark, $n = 62\ 342$; Ireland, $n = 61\ 845$; and Romania, $n = 54\ 027$.

2.4 | Participating cases

A harmonized case ascertainment approach required research teams to recruit all general practitioners (GPs) and all pediatric and adult hospitals with neurology units serving the four regions. Ethical approval was obtained by each research team and by each local site as required. Each site was invited to identify all patients who were (1) living in the study region and either (2) had a current or previous diagnosis of epilepsy or (3) had experienced a single unprovoked seizure. To encourage participation, GPs received information on electronic and paper-based search strategies, including International Classification of Diseases (ICD) codes (G40.1–G40.9, G41.0–G41.9, F80.3, and R56.8) and listings of antiseizure medications, and where local policies permitted, a discretionary nominal payment. Although GPs were asked to identify all eligible patients on their current patient list, for practical purposes a timeframe was provided for participating hospitals limiting their search to patients who presented in the previous 10 years (i.e., between January 1, 2006 and December 31, 2016).

2.5 | Participating case ascertainment sites

In total, 16 hospitals and 142 GPs were identified as providing services to the catchment areas of the four study

regions. All identified sites received a letter from the lead partner in each country inviting them to participate, with follow-up phone calls, outlining the study and requesting information on whether ethical approval was necessary beyond that already obtained by each research team. The interpretation of data protection regulations by some ethical committees and institutions, notably in Denmark and Ireland, was that research teams were prohibited from directly accessing patients' medical records without their prior informed consent. A consequence of this interpretation was that informed consent had to be considered within all four countries in light of the study aim of employing a standardized methodology across all participating countries. Case ascertainment sites were therefore requested to issue written invitations to all eligible patients to consent to their participation in the full ESBACE study, which involved granting access to their medical records and enrollment in a prospective 12-month quality of life and costs online survey. These invitations were prepared by the research team and signed by the issuing individual GPs and hospital staff. In cases where eligible patients did not respond to the written invitation, and where local governance codes permitted, research teams requested individual sites to provide nonconsented access to medical records in formats adhering to local governance structures. It is important to note that data collection was ongoing during the introduction of the Europe-wide General Data Protection Regulation (GDPR), and a number of sites reported being unclear at that time on their capacity to provide data from medical records without patient consent.

2.6 | Data collection

A team of two researchers from the research team in each country completed chart reviews by accessing medical records and extracting data using a standardized case report form (CRF). The CRF is available in Appendix S1. CRFs collected information on seizure frequency, types of seizures (e.g., generalized, focal, and unclassifiable seizures), status epilepticus, electroencephalography (EEG), imaging investigations, etiology, epilepsy syndromes, psychiatric and somatic comorbidities, use of antiseizure medication, date of most recent update of medical record, and validation of the epilepsy diagnosis, and a summary of the level of supporting evidence for the epilepsy diagnosis. These data were entered in nonidentifiable format by research teams on a secure server using REDCap software.[17] A deduplication process ensured that participants who received invitations from more than one case ascertainment site were uniquely enrolled into the study.

Each country's data collection team, comprising two researchers, received face-to-face instruction at two international meetings from epileptologists on how to extract information from patients' medical records to complete CRFs. Intrarater reliability was checked by a coordinating data manager who monitored all data being entered on REDCap. Interrater reliability was assessed by both members of each team independently completing a random sample of 10 CRFs. As not all fields on the CRF were relevant to all cases, teams were asked to report on the number of agreed items per case. Teams were instructed to note any disparities in the completion of CRFs and come to an agreement on the more valid response. If further input was needed, the two researchers were instructed to seek guidance from the neurologist(s) on their team (hereafter termed epileptologists). The average level of agreement for all 10 cases was reported as 82.3% in Austria, 71.1% in Denmark, 94.4% in Ireland, and 96.4% in Romania, with an average of 86.2% across all four countries. Throughout data collection, all teams met monthly via face-to-face online meetings to discuss progress. Following data entry, all CRFs were formally validated by each team's epileptologist(s), who was/were required to review each CRF. Epileptologists were asked specifically to validate the research team's classification of each patient's epilepsy diagnosis in accordance with the new ILAE clinical definition of epilepsy, as a case of (1) at least two unprovoked (or reflex) seizures occurring >24 h apart; (2) a diagnosis of an epilepsy syndrome; or (3) a diagnosis of a single seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years. They were also asked to make a determination on whether the case was "definite," "probable," "suspect," or "not epilepsy" according to agreed operational definitions. These operational definitions, and others used throughout the case report form, are available in Appendix S2.

3 | RESULTS

In total, half of all invited hospitals (8/16, 50%) and just over one third of all invited GPs (48/142, 34%) agreed to participate. There was large intercountry variation in participation (Table 1).

From a total population of 237 757 individuals in the four participating regions, 1988 (.8%) individuals were identified as being potentially eligible from patient lists of hospitals and GPs who agreed to participate. To determine whether these identified cases were in fact cases of epilepsy, access to the individuals' medical records was required. Access to medical records was possible for 1208 (60.7%) of the 1988 individuals identified, inclusive of

TABLE 1 Number of identified and recruited case ascertainment sites by each of the four participating countries

	Country				
	Austria	Denmark	Ireland	Romania	Total
Hospitals identified, *n*	2	2	2	10	16
Hospitals recruited, *n* (%)	2	2	2	2	8 (50%)
GPs identified, *n*	32	60	26	24	142
GPs recruited, *n* (%)	11	1	19	17	48 (34%)

Abbreviation: GP, general practitioner.

TABLE 2 Number of identified and recruited cases with CRF data in each of the four participating countries

	Country				
	Austria	Denmark	Ireland	Romania	Total
Total population	59 543	62 342	61 845	54 027	237 757
Total patients identified by case ascertainment sites, *n*	616	482	476	414	1988
Total patients with partial or completed CRF, *n*	486	113	318[a]	291	1208
Patients for whom a CRF was partially or fully completed, %	78.9	23.4	66.8	70.3	60.8

Abbreviation: CRF, case report form.

[a]Four pilot cases from Ireland were included in the final dataset.

cases where patients provided consent and cases where medical facilities provided access without explicit consent. Between-country variation in access to medical records was marked, with Austria converting 79% of those identified to a completed CRF, whereas Denmark converted 23% (Table 2). In Denmark, access to medical records was only permitted for those patients who had provided informed consent. Reasons for the variation in access were largely related to issues of data protection where researchers sought access to medical records in the absence of explicit consent. Challenges were also experienced in the conversion of recruited GPs to recruited participants; in Austria, for example, whereas 11 GPs issued invitations to eligible patients to participate, none of these patients responded with explicit consent to have their medical records included in the study.

Of the 1208 individuals for whom a partial or completed CRF was available, 113 cases (9.3%) were deemed to have insufficient clinical data to determine whether they could reliably be classified as cases of epilepsy. The remaining 1095 cases were validated by the epileptologist(s) on each team as "definite cases" ($n = 706$, 64.5%), "probable cases" ($n = 191$, 17.4%), "suspected cases" ($n = 153$, 14.0%), and "not epilepsy" ($n = 45$, 4.1%). Thus, 95.9% of cases where sufficient clinical data were available in medical records to make a determination were classified as epilepsy and 81.9% were classified as either definite or probable cases of epilepsy. Prevalence estimates of validated definite and probable individuals, extrapolated to all cases inclusive of both validated and unvalidated cases, are presented in Table 3.

The tables and commentary below are confined to those cases validated by epileptologists in each country as being either definite or probable cases ($n = 897$). It should be noted that tables do not report data on fewer than five individuals. Table 4 presents the demographic and epilepsy diagnosis status of these patients.

3.1 | Demographics and seizure type

Whereas gender distribution was comparable across the four regions, differences were observed in age distribution, where Ireland and Romania observed higher numbers of patients younger than 19 years and Ireland observed lower numbers within the older age categories. In all countries, epilepsy diagnosis was most often reported (>80%) as a patient having two or more unprovoked seizures. Epilepsy diagnosis based on a single seizure, including single seizures within an epilepsy syndrome, accounted for 15.2% of patients, with the lowest reporting from Denmark and Ireland. Denmark is distinguished by reporting both the highest percentage of definitive epilepsy cases at 95.4% and the highest rates of seizure freedom at 58.3%.

TABLE 3 Prevalence estimates of (1) individuals with completed case report form validated as definite or probable epilepsy, (2) cases adjusted to European standard population, and (3) extrapolations to identified but unvalidated cases

	Country				
	Austria	Denmark	Ireland	Romania	Total
Crude cases per 1000 with 95% CI of individuals validated with definite or probable epilepsy	6.9 (6.3–7.6)	1.7 (1.4–2.1)	2.8 (2.4–3.2)	3.8 (3.2–4.3)	3.8 (3.5–4.0)
Adjusted[a] cases per 1000 with 95% CI of individuals validated with definite or probable epilepsy	7.1 (6.6–7.6)	1.8 (1.5–2.0)	3.1 (2.8–3.5)	4.5 (4.1–4.9)	4.1 (3.7–4.5)
Adjusted[a] cases per 1000 with 95% CI extrapolating proportions of validated definite/probable cases to identified but unvalidated cases	9.0 (8.4–9.6)	7.7 (7.2–8.2)	4.6 (4.2–5.0)	6.4 (5.9–6.9)	6.7 (6.1–7.2)

Abbreviation: CI, confidence interval.

[a]Adjusted to EU27 + European Free Trade Association standard population 2013.

Generalized seizures ranged from 22.2% of patients in Denmark to 43.8% of patients in Romania, with tonic–clonic, typical absence, and myoclonic seizures dominating the seizure subtypes. Focal seizures were identified as ranging from 44.8% of patients in Romania to 75.7% of patients in Ireland, with focal evolving to bilateral tonic–clonic seizures being most commonly reported. Reporting of unclassified seizures was low across countries (8.4%), as was reporting of lifetime status epilepticus (14.3%), except in Austria, where it was observed for 21.3% of patients.

3.2 | Investigations and etiology

Table 5 presents data on investigations and the etiology of epilepsy as reported in patient medical records across all four countries.

Whereas >90% of patients in Austria and Denmark had an EEG, figures were lower for patients in Ireland and Romania, where more than one quarter of cases in both countries were returned "unknown." EEG results typically reported abnormal results (approximately 70%), with focal abnormalities being the most commonly reported abnormality in all countries bar Austria, where "abnormality but not epileptiform" was recorded for 46.1% of those with an abnormal EEG.

Imaging was reported at >85% in all countries except Ireland (66.3%). Both magnetic resonance imaging (MRI) and computed tomography (CT) are commonly used in Austria and Denmark, but different patterns are observed in Ireland (93.2%) and Romania (75.7%), where MRI and CT dominate, respectively.

Etiology of epilepsy was most often reported as structural/metabolic in all regions. Cerebral infarction and traumatic brain injury were among the most commonly reported structural/metabolic etiologies.

3.3 | Comorbidities

Table 6 presents the reporting of developmental disability, mental health conditions, and somatic disorder among the four sites. On average, one in two patients (53.1%) reported a developmental or mental health disorder, ranging from 40.9% in Romania to 66.5% in Ireland. Intellectual disability and mood disorders were the most common conditions across all sites, bar Romania, where intellectual disability and alcohol- and drug-related conditions dominated. Comorbid somatic disorders ranged from 25.0% in Denmark to 32.4% in Ireland, with cardiovascular disease, stroke, and brain injury in general being more commonly reported.

3.4 | Treatment

All sites reported high proportions of patients currently on antiseizure medication, ranging from 83.5% in Austria to 94.8% in Ireland. Levetiracetam, lamotrigine, and valproic acid were reported as the most commonly prescribed antiseizure medication in all countries with the exception of lamotrigine, which did not appear among the top five reported antiseizure medications in Romania (Table 7).

4 | DISCUSSION

The primary objective of ESBACE was to develop and apply a common case ascertainment methodology to determine the prevalence of epilepsy in four countries in Europe using the new ILAE definition and terminology of epilepsy.[15,18,19] Methodological challenges during the study period significantly hampered this endeavor, and although the dataset provides an interesting glimpse of the

TABLE 4 Demographics and epilepsy diagnosis for 897 patients classified with definite and probable epilepsy in each of the four participating countries

	Country								Total	
	Austria		Denmark		Ireland		Romania			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Total patients validated with a definite or probable diagnosis of epilepsy	413		108		173		203		897	
Age of patients, years										
0–9	20	4.8	5	4.6	17	9.8	18	8.9	60	6.7
10–19	40	9.7	6	5.6	25	14.5	31	15.3	102	11.4
20–29	39	9.4	7	6.5	25	14.5	18	8.9	89	9.9
30–39	41	9.9	5	4.6	31	17.9	14	6.9	91	10.1
40–49	45	10.9	18	16.7	28	16.2	23	11.3	114	12.7
50–59	55	13.3	26	24.1	18	10.4	22	10.8	121	13.5
60–69	50	12.1	20	18.5	12	6.9	28	13.8	110	12.3
70+	123	29.8	21	19.4	17	9.8	49	24.1	210	15.5
Gender of participants										
Male	205	49.6	53	49.1	82	47.4	120	59.1	460	51.3
Female	208	50.4	55	50.9	91	52.6	83	40.9	437	48.7
Epilepsy diagnosis										
At least two unprovoked seizures	332	80.4	<105	–	<165	–	165	81.3	761	84.8
Epilepsy syndrome	17	4.1	0	.0	11	6.4	12	5.9	40	4.5
Single seizure	64	15.5	<5	–	<5	–	26	12.8	96	10.7
Level of diagnosis										
Definite epilepsy	347	84.0	103	95.4	112	64.7	144	70.9	706	78.7
Probable epilepsy	66	16.0	5	4.6	61	35.3	59	29.1	191	21.3
Seizure frequency										
Seizure-free latest year	137	33.2	63	58.3	57	32.9	37	18.2	294	32.8
1–3 seizures latest year	152	36.8	19	17.6	30	17.3	77	37.9	278	31.0
Less than monthly (4–11 latest year)	46	11.1	11	10.2	29	16.8	19	9.4	105	11.7
Less than weekly (12–51 latest year)	18	4.4	8	7.4	17	9.8	22	10.8	65	7.2
Daily or weekly seizures	27	6.6	7	6.5	28	16.2	12	5.9	74	8.3

(Continues)

TABLE 4 (Continued)

	Country								Total	
	Austria		Denmark		Ireland		Romania			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Missing	33	8.0	0	.0	12	6.9	36	17.7	81	9.0
Generalized seizures										
Yes	139	33.7	24	22.2	44	25.4	89	43.8	296	33.0
No or missing	274	66.3	84	77.8	129	74.6	114	56.1	601	67
Generalized seizure type (multiple)[a]										
Typical absence	25	18.0	<15	–	13	29.5	<5	–	49	16.6
Myoclonic	13	9.4	<10	–	11	25.0	<5	–	33	11.2
Tonic–clonic	112	80.6	24	100.0	37	84.1	78	87.6	251	84.8
Other generalized seizure types	13	9.4	<5	–	<10	–	13	14.6	32	10.8
Focal seizures										
Yes	253	61.3	80	74.1	131	75.7	91	44.8	555	61.9
No or missing	160	38.8	28	26.0	42	24.2	112	55.2	342	38.2
Focal seizure type (multiple)[a]										
Evolving to bilateral tonic–clonic	166	65.6	66	82.5	102	77.9	41	45.1	375	67.6
Without impairment of awareness	89	35.2	29	36.2	46	35.1	18	19.8	182	32.8
With impairment of awareness	107	42.3	42	52.5	86	65.6	50	54.9	285	51.4
Status epilepticus										
Yes	88	21.3	6	5.6	21	12.1	13	6.4	128	14.3
No or missing	325	78.7	102	94.4	152	87.8	190	93.6	769	85.7
Status epilepticus types (multiple)[a]										
With prominent motor symptom	59	67.0	<10	–	<20	–	<15	–	95	74.2
Without prominent motor symptom	30	34.1	<5	–	<5	–	<5	–	34	26.6
Unclassified seizure										
Yes	17	4.1	5	4.6	26	15.0	27	13.3	75	8.4
No or missing	396	95.9	103	95.4	147	84.9	176	86.7	822	396

Note: In cells with fewer than five persons, we have used "<5." In rows and columns where it was possible to deduct the number of individuals in cells with fewer than five persons, we revised the number in the rows/columns; for 5–9 persons we used "<10" and for 10–14 persons we used "<15" to prevent the deduction of number of the individual cells with fewer than five persons.

[a]Multiple answers can be recorded for these items; hence, totals may exceed 100%.

TABLE 5 Investigations and etiology for 897 patients classified with definite and probable epilepsy in each of the four participating countries

	Country								Total	
	Austria		Denmark		Ireland		Romania			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Total patients with definite or probable epilepsy	413		108		173		203		897	
EEG performed										
Yes	388	93.9	101	93.5	118	68.2	145	71.4	752	83.8
No, unknown, or missing	25	6.1	7	6.5	55	31.7	58	28.6	145	16.2
EEG result										
Abnormal	330	85.0	73	72.3	77	65.3	132	91.0	612	81.4
Normal or missing	58	15.0	28	27.7	41	34.7	13	9.0	140	18.6
EEG result in detail										
Generalized abnormality	36	10.9	12	16.4	16	20.8	25	18.9	89	14.5
Focal abnormality or multifocal	142	43.0	42	57.5	47	61.0	100	75.8	331	54.1
Abnormal but not epileptiform	152	46.1	19	26.0	14	18.2	7	5.3	192	31.4
Imaging investigation										
Yes	363	86.8	101	91.8	118	66.3	181	85.8	763	83.2
No, unknown, or missing	55	13.2	9	8.2	60	33.7	30	14.2	154	16.8
Imaging types (multiple)[a]										
MRI	254	70.0	85	84.2	110	93.2	49	27.1	498	65.3
CT	268	73.8	57	56.4	8	6.8	137	75.7	470	61.6
Others	39	10.7	<5	–	<5	–	<5	–	40	5.2
Imaging results overall										
Normal	95	26.5	42	42.4	50	44.2	53	30.6	240	32.3
Abnormal	263	73.5	57	57.6	63	55.8	120	69.4	503	67.7
Imaging results in detail										
Cerebral hemorrhage or infarction	89	33.8	22	38.6	11	17.4	56	46.7	178	35.4
Cerebral tumor/neoplasm[b]	–	–	–	–	–	–	–	–	67	13.3
Traumatic brain injury[b]	–	–	–	–	–	–	–	–	41	8.2
Cerebral infection	–	–	–	–	–	–	–	–	9	1.8
Mesial temporal sclerosis	–	–	–	–	–	–	–	–	32	6.4
Perinatal insults	–	–	–	–	–	–	–	–	11	2.2
Malformation of cortical/ brain development	–	–	–	–	–	–	–	–	29	5.8
Neurocutaneous syndromes	–	–	–	–	–	–	–	–	5	1.0
Other	128	48.7	30	52.6	33	52.4	34	28.3	225	44.7
Etiology										
Genetic	27	6.5	25	23.1	44	25.4	32	15.8	128	14.3
Structural/metabolic	241	58.4	49	45.4	68	39.3	103	50.7	461	51.4
Unknown or missing	145	35.1	34	31.5	61	35.2	68	33.5	308	34.3
Genetic etiology[a]										

(Continues)

TABLE 5 (Continued)

	Country								Total	
	Austria		Denmark		Ireland		Romania			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Genetic syndrome	18	66.7	22	.0	16	36.4	25	78.1	81	63.3
Genetic chromosomal encephalopathy	<10	–	<5	–	<5	–	<10	–	14	10.9
Other or missing	<5	–	<5	–	27	63.6	<5	–	33	25.8
Structural/metabolic[a]										
Cerebral hemorrhage	23	9.5	11	22.4	<5	–	<5	–	40	8.7
Cerebral infarction	64	26.6	11	22.4	9	13.2	52	50.5	136	29.5
Cerebral tumor/neoplasm	11	4.6	<5	–	<10	–	8	7.8	28	6.1
Traumatic brain injury	31	12.9	10	20.4	21	30.9	12	11.7	74	16.1
Cerebral infection	<5	–	<5	–	5	7.4	<5	–	12	2.6
Mesial temporal sclerosis	13	5.4	7	14.3	17	25.0	0	.0	37	8.0
Perinatal insults	<5	–	6	12.2	5	7.4	<5	–	16	3.5
Malformations cortical/ brain development	11	4.6	<5	–	<10	–	8	7.8	28	6.1
Neurocutaneous syndromes	<5	–	<5	–	<5	–	<5	–	5	1.1
Degenerative neurologic disease	17	–	<5	–	<5	–	<5	–	19	4.1
Metabolic or toxic insult to brain	8	3.3	0	.0	0	.0	0	.0	8	1.7
Inborn errors of metabolism	<5	–	<5	–	<5	–	<5	–	<5	–
Inflammation	12	5.0	<5	–	0	.0	<5	–	15	3.2
Vascular malformation	7	2.9	<5	–	5	7.4	<5	–	18	3.9
Other	49	20.3	11	22.4	<5	–	<10	–	70	15.2

Note: In cells with fewer than five persons, we have used "<5." In rows and columns where it was possible to deduct the number of individuals in cells with fewer than five persons, we revised the number in the rows/columns; for 5–9 persons we used "<10" and for 10–14 persons we used "<15" to prevent the deduction of number of the individual cells with fewer than five persons.

Abbreviations: CT, computed tomography; EEG, electroencephalography; MRI, magnetic resonance imaging.

[a]Multiple answers can be recorded for these items; hence, totals may exceed 100%.

[b]Too few cases to provide details by country.

profile of patients with epilepsy and disparities in epilepsy health care across Europe, it was not possible to determine an accurate estimate of prevalence from validated cases.

There were two main challenges comprising firstly, confusion surrounding the introduction of new data protection regulations in Europe and secondly, a lack of resources in case ascertainment sites to support participation. Europe's GDPR came into force on May 25, 2018, when data collection was underway. Case ascertainment sites reported both uncertainty and conflicting views on their obligations under GDPR. Feedback from research ethics committees and other approval bodies varied both within and between participating countries. In Denmark, for example, 482 individuals were identified as potential cases of epilepsy. Of these, medical chart reviews of just 113 (23.4%) were approved for inclusion in this study. The low conversion rate from identification to completed CRFs was primarily due to a decision by regional officials that accessing medical records where patients had not returned consent would contravene GDPR. Challenges also arose in Ireland, where the research team was restricted to accessing pseudonymized data drawn from medical records, a process that resulted in high levels of missing data. It may be that the call by the funding body, which required that individuals who were identified as cases in the present study would then be enrolled into a quality and costs outcomes study, exacerbated the concerns of case ascertainment sites, notably as participants would be required to provide explicit consent for this second objective of the study.

The variation in GDPR interpretation by stakeholders in this research study has been observed elsewhere.[20] The Health Research Regulations supplementary to GDPR introduced in

TABLE 6 Comorbidities for 897 patients classified with definite and probable epilepsy in each of the four participating countries

	Country								Total	
	Austria		Denmark		Ireland		Romania			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Total patients with definite or probable epilepsy	413		108		173		203		897	
Developmental disabilities and mental health conditions										
No or missing	183	44.3	60	55.6	58	33.5	120	59.1	421	47.0
Yes	230	55.7	48	44.4	115	66.5	83	40.9	476	53.1
Types of developmental disabilities and mental health conditions[a]										
Dementia	34	8.2	<5	–	<5	–	22	10.8	62	6.9
Alcohol and drug-related	27	6.5	<5	–	<5	–	30	14.8	60	6.7
Schizophrenia and psychosis	7	1.7	<5	–	<5	–	<5	–	16	1.8
Mood disorders	66	16.0	38	35.2	14	8.1	17	8.4	135	15.1
Neurotic and somatoform	10	2.4	<5	–	<5	–	23	11.3	35	3.9
Eating disorder	<5	–	6	5.6	<5	–	<5	–	9	1.0
Anxiety disorder	<5	–	19	17.6	<10	–	24	11.8	54	6.0
Personality disorder	6	1.5	<5	–	<5	–	13	6.4	22	2.5
Intellectual disability	40	9.7	21	19.4	24	13.9	31	15.3	116	12.9
Autism spectrum disorder	35	8.5	<5	–	<10	–	6	3.0	49	5.5
Attention-deficit/ hyperactivity disorder	5	1.2	<5	–	<5	–	13	6.4	23	2.6
Other	13	3.1	<10	–	17	9.8	<5	–	39	4.3
Somatic disorder										
No or missing	280	67.8	81	75	117	67.6	144	70.9	622	69.3
Yes	133	32.2	27	25.0	56	32.4	59	29.1	275	30.7
Types of somatic disorder[a]										
Brain tumor	41	9.9	5	4.6	7	4.0	12	5.9	65	7.2
Migraine	5	1.2	19	17.6	7	4.0	14	6.9	45	5.0
Hearing and vision loss	<10	–	20	18.5	<5	–	16	7.9	44	4.9
Stroke	68	16.5	16	14.8	11	6.4	50	24.6	145	16.2
Cardiovascular disease	133	32.2	21	19.4	6	3.5	90	44.3	250	27.9
Respiratory system	33	8.0	11	10.2	14	8.1	13	6.4	71	7.9
Gastrointestinal disorder	37	9.0	<10	–	<5	–	24	11.8	70	7.8
Osteoporosis and osteopenia	25	6.1	15	13.9	12	6.9	14	6.9	66	7.4
Diabetes mellitus	20	4.8	7	6.5	7	4.0	20	9.9	54	6.0
Brain injury	16	3.9	13	12.0	18	10.4	40	19.7	87	9.7
Other	173	41.9	31	28.7	95	54.9	20	9.9	319	35.6

Note: In cells with fewer than five persons, we have used "<5". In rows and columns where it was possible to deduct the number of individuals in cells with fewer than five persons, we revised the number in the rows/columns; for 5–9 persons we used "<10" and for 10–14 persons we used "<15" to prevent the deduction of number of the individual cells with fewer than five persons.

[a]Multiple answers can be recorded for these items; hence, totals may exceed 100%.

Ireland, for example, have created significant problems for research, including chart review studies, prompting researchers to argue whether, without intervention, Ireland may face exclusion from European-wide research consortia.[21] Without a broader interpretation of the current regulations of retrospective chart review studies, there is concern that epidemiological studies, of low risk to participants and high public benefit, will be severely hampered.[22]

TABLE 7 AED treatment for 897 patients classified with definite and probable epilepsy in each of the four participating countries

	Country								Total	
	Austria		Denmark		Ireland		Romania			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Total patients with definite or probable epilepsy	413		108		173		203		897	
AED treatment										
Current AED treatment	345	83.5	102	94.4	164	94.8	174	85.7	785	87.5
Previous AED treatment	31	7.5	<10	–	<10	–	7	3.4	51	5.7
No treatment	8	1.9	<5	–	<5	–	14	6.9	24	2.7
Unknown or missing	29	7.1	<5	–	<5	–	8	3.9	37	4.2
Most commonly prescribed AEDs in each country, *n* (%)										
1st	Levetiracetam 203 (58.8)		Lamotrigine 64 (62.7)		Levetiracetam 79 (48.2)		Valproic acid 77 (44.3)			
2nd	Valproic acid 69 (20.0)		Levetiracetam 26 (25.5)		Lamotrigine 49 (29.9)		Carbamazepine 56 (32.2)			
3rd	Lamotrigine 58 (16.8)		Valproic acid 18 (17.6)		Valproic acid 30 (18.3)		Levetiracetam 36 (20.7)			
4th	Carbamazepine 33 (9.6)		Clobazam 9 (8.8)		Clobazam 27 (16.5)		Phenytoin 27 (15.5)			
5th	Lacosamide 21 (6.1)		Carbamazapine 7 (6.9)		Oxcarbazepine 14 (8.5)		Clonazepam 19 (10.9)			
5th (tied)			Oxcarbazepine 7 (6.9)		Zonisamide 14 (8.5)					
5th (tied)			Topiramate 7 (6.9)							

Note: In cells with fewer than five persons, we have used "<5." In rows and columns where it was possible to deduct the number of individuals in cells with fewer than five persons, we revised the number in the rows/columns; for 5–9 persons we used "<10" and for 10–14 persons we used "<15" to prevent the deduction of number of the individual cells with fewer than five persons.

Abbreviation: AED, antiepileptic medication.

Challenges were also experienced in terms of resources required by case ascertainment sites to engage in the study. Both hospitals and GPs approached by the study team commented on the lack of dedicated staff to engage in research projects. Within hospitals, researchers experienced difficulties in accessing time-poor personnel who could advise on participation and champion the study through research ethics committees. It was also challenging to get confirmation on the exact catchment area of some hospitals to determine whether these sites provided care to patients within teams' study regions. Finally, researchers experienced difficulties in identifying personnel who could navigate access to medical records in a manner compliant with local governance structures. Despite these challenges, recruitment from hospitals was successful in all countries except Romania, where just two of 10 hospitals in the surrounding geographical area were recruited. Reasons for nonparticipation were related to a lack of in-house resources.

In contrast, the recruitment of GPs was low across the full study, generating <10% of cases. Recruitment of GPs was particularly low in Denmark and Austria and may reflect that these research teams were unable to use their personal contacts to leverage access in the manner they successfully used within the hospital sector. In Austria, no participants were recruited through primary care despite 11 GPs distributing invitations to their patients to participate. Across all research teams, one key facilitator to the recruitment of GPs may have been absent, that is, the ability to demonstrate that participation in a study confers a direct benefit to their patients.[23] In Austria, for example, GPs do not identify patients by ICD codes, and consequently would need to hand search their registers for cases. It may also be that the condition itself, epilepsy, may have deterred some primary care physicians from taking part. In both Austria and Denmark, for example, people with epilepsy are typically treated at specialist hospital clinics, and it may be that the low rate of engagement

by Danish and Austrian primary care physicians in this study reflects their perception that epilepsy is a condition that is treated elsewhere.[24] Attempts to garner the support of professional associations for GPs in Ireland were unsuccessful, which may again reflect the low priority of epilepsy in primary care. One potential solution to these recruitment challenges is to incentivize the expansion of voluntary surveillance systems within general practice beyond notifiable disease surveillance to include epidemiological research.[25]

Notwithstanding these challenges, the present study has generated a comprehensive dataset of 897 definite and probable cases of epilepsy in four regions in Europe using a harmonized approach inclusive of the new ILAE definition and terminology of epilepsy. It is important to note that operational classifications from ILAE[18] were introduced at the planning phase of this study and that a period of adjustment for research purposes was anticipated in their implementation.[26] In the present study, the adoption of ILAE's new classification system resulted in the identification of 10.7% of cases as meeting the criterion of a single seizure with a recurrence risk of at least 60% occurring over the next 10 years and another 4.5% the criterion of a single seizure within an epilepsy syndrome. The distribution of the single seizure cases across the four countries was, however, highly skewed, with the majority being diagnosed in Austria. These data indicate that although the ILAE's new definition and terminology will, by definition, increase prevalence estimates, this may be observed sooner in more affluent countries, which are likely to be quicker adoptees of these new conventions.

Differences across the four countries undoubtedly reflect the case ascertainment sites from which they were recruited, with high representation of adults and those prescribed antiseizure medication likely reflecting the higher recruitment from tertiary hospital sites. The data also provide an indication of the quality of medical records available for research and of clinical practice in these jurisdictions. Notable here is that some Irish data were provided in a pseudonymized form, resulting in the inability to capture seizure type, which is a cause for concern. Interventions to improve the documentation practices of physicians working in epilepsy have been developed by the American Academy of Neurology and report positive gains that would be beneficial to enhance the quality of these records and related chart review research.[27,28]

Where reporting of seizure types was complete, variations among countries included low numbers of typical absences and myoclonic seizures being reported in Romania, and a high number of cases of status epilepticus in Austria. Austria is also distinguished in the reporting of "abnormality but not epileptiform" EEG results, which were proportionately nine times higher in Austria (46%) than Romania (5%). These variations among countries may reflect the interests of individual clinicians in particular case ascertainment sites but may also reflect broader diagnostic techniques within different settings, and therefore any comparison across countries should be made with caution. The reporting of MRI use during the study period, for example, is lower in Romania than for other countries. Variations in the reporting of etiology are similarly observed; genetic etiology was low in Austria and Denmark, a pattern that may reflect the movement of "idiopathic generalized" seizures to "genetic generalized" seizures in the new ILAE classifications. These findings may suggest important differences in clinical practice and/or differences in the classification of "genetic cases" indicating the need for more support by ILAE in ensuring a harmonized approach across European jurisdictions.

Limitations of this study include the large reliance on cases from hospitals, which have a known bias toward more severe cases, and the lack of certainty regarding whether eligible patients were treated at sites unknown to researchers, notably in Romania, albeit this weakness is observed in similar studies.[29] In contrast, strengths of this study include the development of an operational criterion to identify epilepsy cases using the new ILAE definition and terminology and the validation of all cases by epileptologists in each country, which when combined address known high rates of misdiagnosis in epilepsy.[30,31] The study design incorporated sources of heterogeneity, including the developmental level of countries, sample size of study population, and age of participants, that had yet to be applied within pan-European epidemiological research.[1]

In conclusion, this study points to the need for considerably greater guidance and more uniformity at both European and national levels on the appropriate application of data protection regulations lest patient privacy come at the cost of epidemiological research. To have impact, all stakeholders must be involved, such as researchers, research ethics committees, and data controllers. Pressure from ILAE Europe and Epilepsy Alliance Europe could raise this issue within the epilepsy field. In the absence of a coordinated approach, understandable caution leads to a risk-averse culture where data are withheld. National datasets, such as the Danish National Patient Register,[32] permit the enumeration of individuals with medical conditions and are ideally suited to epidemiological research; unfortunately, such databases are rare outside of Nordic countries.

Despite the inability to precisely determine epilepsy prevalence, this study highlights variation in the quality of epilepsy medical reports throughout Europe that may reflect true differences in clinical practice and access to medical care. Further exploration of these differences may

ameliorate some of the health inequities experienced by persons with epilepsy throughout Europe.

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CONFLICT OF INTEREST

E.T. reports personal fees from EVER Pharma, Marinus, Argenix, Arvelle, Medtronic, Bial–Portela & C[a], NewBridge, GL Pharma, GlaxoSmithKline, Hikma, Boehringer Ingelheim, LivaNova, Eisai, UCB, Biogen, Genzyme Sanofi, GW Pharmaceuticals, and Actavis outside the submitted work; his institution has received grants from Biogen, UCB Pharma, Eisai, Red Bull, Merck, Bayer, the European Union, FWF Osterreichischer Fond zur Wissenschaftsforderung, Bundesministerium für Wissenschaft und Forschung, and Jubilaumsfond der Österreichischen Nationalbank outside the submitted work. J.C. reports honoraria from serving on the scientific advisory board of UCB Nordic and Eisai, has received honoraria for giving lectures from UCB Nordic and Eisai, and has received funding for a trip from UCB Nordic. A.M. reports a research grant from UCB Pharma paid to University of Liverpool. T.T. reports grants from Eisai, GSK, UCB, Bial, Stockholm County Council, and CURE and personal fees from Eisai, Sanofi, Sun Pharma, and UCB outside the submitted work. None of the other authors has any conflict of interest to disclose. 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.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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APPENDIX 1

European Study on the Burden and Care of Epilepsy (ESBACE) consortium

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