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The Incidence and Prevalence of Epilepsy in the United Kingdom 2013-2018: a retrospective cohort study of primary care disease registers.

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Highlights

- In the UK, the estimated overall point prevalence for epilepsy was 9.37 per 1,000 persons
- The overall estimated incidence rate was 42.68 per 100,000 person-years
- In England, the estimated incidence, 37.41 per 100,000 person-years and prevalence, 8.85 per 1,000 persons was lower compared to figures for Scotland, Wales and Northern Ireland

Abstract

295 words

Purpose
The aim of this study was to update overall incidence and prevalence calculations for epilepsy of the United Kingdom (UK) and its constituent nations (England, Northern Ireland, Scotland, and Wales).

Methods
We used data from primary care practices contributing to the Clinical Practice Research Datalink (CRPD), based on the electronic health records of 14 million patients, representing approximately 20% of the population. CPRD contains data from two different health record systems: the Vision clinical system (CPRD GOLD database) and the EMIS Web® clinical system (CPRD Aurum database). We calculated incidence and prevalence rates with 95% confidence intervals (CIs). Data were stratified by age, gender, deprivation, country (England, Scotland, Wales and Northern Ireland) and region (England only).

Results
In the UK, the estimated overall point prevalence for epilepsy was 9.37 per 1000 persons / year (95% CI 9.34-9.40) and the overall estimated incidence rate was 42.68 per 100,000 person-years (95% 42.18-43.18) using the CPRD GOLD database. In England, the estimated incidence (37.41 (95% CI 36.96-37.83)) and prevalence (8.85 (95% CI 8.83-8.87)) was lower (combined databases) compared to figures for Scotland (incidence 47.76 (95% CI 46.15-49.42)); prevalence 10.13 (95% CI 10.06-10.20)) (CPRD GOLD only), Wales (incidence 54.84 (95% CI 52.79-56.95); prevalence 11.40 (95% CI 11.31-11.49)) (CPRD GOLD only) and Northern Ireland (incidence 46.18 (95% CI 43.13-49.90); prevalence 12.08 (95% CI 11.93-12.23))(combined databases). Prevalence and incidence were higher in more deprived regions.

Conclusion
The prevalence and incidence of epilepsy in the UK is broadly in line with other high income studies, showing the usual pattern of high incidence in the young and the old, with a nadir in middle age. The prevalence of epilepsy has fallen slightly since 2011. There is significant geographical variation (between countries and between regions), and a suggestion of a relationship between deprivation and epilepsy which needs further investigation.

Introduction

The estimated incidence (50-80 per 100,000 person-years) and prevalence rates (5-10 per 1000 person / year) for epilepsy have been found to be relatively consistent across high income countries [1-3]. Nevertheless, changes in demographics and risk factors mean that the epidemiology of epilepsy may change over time. For instance, in countries with an aging population, the increasing prevalence of diseases of old age such as stroke or dementia could increase the prevalence of epilepsy. Conversely, improved General Practitioner (GP) and specialist training, improved guidance for clinicians, better obstetric care and more accurate differential diagnosis could be leading to a reduction in the number of people with epilepsy. Reductions in relevant pathologies (such as mesial temporal sclerosis) have been reported in high income countries [4], with a resultant fall in epilepsy surgeries, a phenomenon that has also been seen in the United Kingdom (UK) [5]. Given how important incidence and prevalence rates are for many aspects of health service planning, and that estimates of these parameters for the UK were most recently published over a decade ago, it seemed timely to re-examine the epidemiology of epilepsy and to explore temporal changes in this country (UK) [6].

The aim of this study was to update the epidemiology of epilepsy in the UK specifically

- To estimate the incidence and prevalence of epilepsy by year, age group, gender, country (England, Scotland, Wales and Northern Ireland) and region (England).
- To estimate the incidence and prevalence of epilepsy by practice-level 2015 Index of Multiple Deprivation (IMD) decile.
- To characterise changes in prevalence and incidence rates since 2011.

Methods

Source Data

General practitioners (GP) play a key role in the UK health care system, as they are responsible for most primary health care, maintaining national disease registers, making specialist referrals and monitoring long term treatment. The Quality and Outcomes Framework (QOF) requires GPs to keep a register of patients with important long-term conditions including epilepsy [7]. QOF is mainly a tool for UK health policy makers to ensure that agreed treatment standards for the conditions included are met, but it also provides important and high quality statistical information. Different practices use different electronic clinical records systems. Two of the most widely used are EMIS Web® and Vision® [8]. Clinical Practice Research Datalink (CPRD) is a collaboration which collects data from consenting GP practices using these two clinical systems to create two separate and non-overlapping databases (CPRD Aurum = EMIS Web®, CPRD GOLD = Vision®). The data recorded in both databases include diagnoses, demographics, prescriptions, clinical events, preventive care, specialist referrals, hospital admissions and their major outcomes. While the structure and the content of the CPRD Aurum and CPRD GOLD databases are very similar, they are not identical. Combined, the two databases include data for over 60

million patients since 1987, with 16 million currently contributing patients. This is the best source of epilepsy diagnostic data in the UK representing approximately 20% of the population.

The United Kingdom (UK) has four constituent nations (England, Wales, Scotland, Northern Ireland). Although the overall framework of the National Health Service (NHS) covers the whole of the UK, the system is not completely uniform with different health care bodies governing its constituent nations. The coverage of the two CPRD databases differs regionally and between the constituent nations of the UK, so both CPRD databases, CPRD GOLD and CPRD Aurum were used for this study. The study period for the current analysis was 1st January 2013 to 31st December 2018. In order to meet our case definition for active epilepsy patients, the available records of individual patients of all ages had to meet two criteria: 1) a diagnosis of Epilepsy on or before 31/12/2018, and 2) use of an anti-seizure medication (ASM) on or before 31/12/2018 and after the first recording of an epilepsy diagnosis (to ensure that the indication for the use of ASM was indeed for epilepsy).

Case Definition

The first criterion was met when patients' records included a Read or SNOMED CT code for Epilepsy within their clinical or referral records. Read codes and SNOMED CT codes are alphanumeric codes that are associated with a Read term such as epilepsy or asthma [9]. They provide a standard vocabulary for clinicians to record patient findings and procedures, in health and social care. Out of a total of 115,984 diagnostic Read codes in CPRD GOLD (Vision® practices) and in excess of 1 million SNOMED CT codes in CPRD Aurum (EMIS Web® practices), 253 CPRD Aurum medical codes and 162 CPRD GOLD medical codes were used to select people with epilepsy. These were selected by the authors as the best chance to capture as many people with epilepsy as possible, including those for whom no specific epilepsy type was found in their record. There is no published consensus on exactly which codes should be used for the identification of epilepsy, and so they were determined by the authors. In addition to directly epilepsy-related diagnostic terms themselves, terms intrinsically related to a diagnosis of epilepsy were included in the search criteria. This included terms such as "epilepsy prevents employment", "petit-mal epilepsy", "Pregnancy advice for patients with epilepsy". These terms, along with a confirmed prescription of an ASM were sufficient to conclude the patient had an active diagnosis of epilepsy.

In order to meet the second inclusion criterion, an ASM prescription, as identified by the authors, had to be recorded within 12 months of the recording of the epilepsy diagnosis. The presence of a diagnostic record and a subsequent ASM prescription was concluded as indicative of active epilepsy. The index date for epilepsy was defined as the date of the first ASM record meeting this criterion. Patients with an index date on or before 31/12/2018 were included. Patients were excluded from the study as cases if their follow-up within the CPRD data ended before the beginning of the study period.

The denominator data was defined as the sum of the person years of follow-up of patients who were alive and registered at a CPRD contributing practice during each calendar year of interest.

The full list of Read and SNOMED CT codes considered as indicative of a diagnosis of epilepsy and the Read codes for the ASMs is provided in Supplement 1, along with full details of the study design.

Incident Cases

Patients were defined as incident if their index date as defined above, occurred 12 months or more after the patient's registration date with the practice and during the patient follow-up period, with the assumption therein that the diagnosis was a new one made in the previous twelve months. The numerator was defined as the total number of patients who met the definition of an incident case of epilepsy during each calendar year of interest. Age was calculated as the difference between the patient year of birth and the calendar year of the index date.

Incidence rates were calculated by dividing the number of incident cases by the calculated person-time at risk for that year. Incidence rates were expressed as the number of newly diagnosed cases per 100,000 person-years. Incidence rates were stratified separately by year, gender, age categories in 5-year age groups, UK country, region/strategic health authority and 2015 IMD practice-level deciles.

A figure was calculated for each area for each of the 6 years. These were then averaged to give the mean annual incidence across the six year period.

Prevalent Cases

All patients meeting the case inclusion criteria were defined as prevalent cases. Patients had to have their index date before the end of patient follow-up. Patient follow-up end was defined as the earliest of that practice last collection date, the patient transfer out date, the CPRD date of death and the end of the study period: 31/12/2018. There was no requirement for prior registration time before index date for prevalent cases.

Point prevalence rates were calculated at the mid-point of each year within the study period. The prevalence rate was calculated as the total number of cases occurring on or before the 01 July of the calendar year of interest (numerator) divided by the total number of unique individuals in the denominator population. Prevalence was expressed as the number of cases affected by the condition per 1,000 patients. As with incidence, prevalence rates were stratified separately by year, gender, 5-year age categories, UK country, 2015 IMD practice-level deciles, and region/SHA.

A figure was calculated for each area for the mid-point for each of the 6 years. These were then averaged to give the mean prevalence across the six-year period at the mid-point.

Statistical Analysis

95% confidence intervals (CI) for the incidence estimate were calculated using a Poisson distribution. 95% confidence intervals (CI) for the prevalence estimate were calculated using a binomial distribution. This analysis was undertaken using the April 2020 static version of the CPRD GOLD and CPRD Aurum databases. Population-weighted estimates using the

two databases were calculated for the incidence and prevalence rates in England and Northern Ireland. The UK GOLD incidence and prevalence figure were calculated by applying the individual incidence and prevalence rates to each country's population and adding these together to give a UK figure. This means the different relative contributions to the base data (more samples as a percentage of the country population for some than others) should not skew the prevalence rate.

Results

In 2020 the source population used from the CPRD GOLD database included 3,138,215 individuals, registered with 83 GP practices in England, 179 practices in Scotland, 101 practices in Wales and 35 practices in Northern Ireland (accessed 09/11/2020). In the same year the source population from the CPRD Aurum database included 11,802,119 individuals, registered with 1,233 GP practices in England and 11 practices in Northern Ireland (accessed 09/11/2020).

Prevalence

The overall estimated prevalence rate (Table 1) for epilepsy in the UK using the CPRD GOLD database was 9.37 per 1,000 persons/year (95% CI 9.34-9.37). In England the prevalence was 9.08 per 1,000 (95% CI 9.02-9.15), in Scotland 10.13 per 1,000 (95% CI 10.06-10.20), in Wales 11.40 per 1,000 (95% CI 11.31-11.49) and in Northern Ireland 12.33 per 1,000 (95% CI 12.16 -12.51). Prevalence estimates for epilepsy in England and Northern Ireland using the CPRD Aurum database were slightly lower, with an estimated prevalence of 8.82 per 1,000 (95% CI 8.80-8.85) in England and 10.92 per 1,000 (95% CI 10.78-11.07) in Northern Ireland. The overall prevalence by country and gender are shown in e-Table 1. The combined estimate for the prevalence of epilepsy in England was 8.85 (95% CI 8.83-8.87) and the prevalence in Northern Ireland was 12.08 (95% CI 11.93-12.23).

Prevalence by country and age group is shown in e-Table 2 and e-Charts 1, 2, 3, 4 and 5 with a trend of increasing prevalence for each 5-year grouping seen in each country until at least the 75-79 age group. Prevalence data by age groups for Northern Ireland using the CPRD AURUM database was not presented due to small numbers and resultant wide confidence intervals,

Prevalence by English regions (using the CPRD AURUM database) is reported in e-Table 3 and e-Chart 6 with the lowest reported prevalence being in London (6.96 per 1,000; 95% CI 6.92-7.01) and the highest prevalence rate being in the North East (11.03 per 1,000; 10.90-11.17).

Prevalence by practice level IMD decile is reported in e-Table 4 and e-Charts 7 and 8, with a clear trend of increasing prevalence with successive levels of deprivation, increasing from a prevalence of 7.86 per 1,000 (95% CI 7.74-7.99) in the lowest IMD decile (1) to a prevalence of 12.07 per 1,000 (95% CI 11.93-12.20) in the highest IMD decile (10 – most deprived) in the CPRD GOLD database (all UK) with a similar picture seen in the CPRD AURUM database (England and Northern Ireland only).

Incidence

The calculated incidence rates by country and gender are shown in Table 2. The overall estimated incidence for the UK using the CPRD GOLD database was 42.68 per 100,000 person-years (95% CI 42.18-43.18), the estimated incidence rate for England was 41.41 (95% CI 39.99-42.87), for Scotland 47.76 (95% CI 46.15-49.42), for Wales 54.84 per 100,000 (95% CI 52.79-56.95) and for Northern Ireland 45.48 (95% CI 42.13-49.01).

As with the prevalence rates, incidence rates in England and Northern Ireland using the CPRD AURUM database were slightly lower with an estimated incidence rate of 36.93 per 100,000 person-years (95% CI 36.46-37.39) in England and 49.38 (95% CI 42.14-57.52) in Northern Ireland. The combined estimates for the incidence of epilepsy in England was 37.41 (95% CI 36.93-37.83) and the incidence in Northern Ireland was 46.18 (95% CI 43.13-49.90) respectively.

Incidence by country by age group is reported in e-Table 6 and e-Charts 9, 10, 11, 12 and 13, with a pattern of a high incidence rate in the early age groups (0-4, 5-9), with the incidence steadily increasing from the 60-64 age group upwards, with the highest incidence rate seen in the 85-89 age group in all 4 countries.

Incidence by English region is reported in e-Table 7 and e-Chart 14, mirroring the prevalence figures with the lowest incidence rate being in London 28.5 per 100,000 person-years (95% CI 27.56-29.46) and the highest incidence rate in the North East 41.69 (95% CI 39.07-44.44).

Incidence by practice level IMD decile is reported in Tables 3 and e-Table 8 and e-Charts 15 and 16, with the results mirroring that seen for prevalence with incidence rates increasing from the least deprived (IMD decile level 1) 35.6 per 100,000 persons-years (95% CI 32.88-38.48) to the most deprived (IMD decile 10) 58.35 (95% CI 55.32-61.50) in the CPRD GOLD database (all UK) with a similar picture seen in the CPRD AURUM database (England and Northern Ireland). Increasing levels of social deprivation appear to be highly correlated to epilepsy incidence (r=0.68) and prevalence (GOLD: r=0.97); ARUM: r=0.93) rates.

Discussion

The principal aim of this study was to provide updated estimates for the incidence and prevalence of epilepsy in the United Kingdom (UK). Our analysis revealed an overall estimated prevalence rate of 9.37 per 1000 using the CPRD GOLD database, with slightly lower estimates for the prevalence in England and Northern Ireland respectively. This suggests that the overall prevalence has fallen slightly since 2011. The trends seen in the prevalence figures were mirrored in the incidence figures with an estimated overall incidence of 42.68 per 100,000 person-years using the CPRD GOLD database, with slightly lower estimates (for England and Northern Ireland) using the CPRD AURUM database.

These figures indicate that the reported incidence and prevalence of epilepsy in the UK is broadly in line with that of other high-income countries, with an overall estimate of the annual incidence of epilepsy of 45 per 100,000 (IQR 30.3-66.7) calculated in a systematic review [1], with increasingly higher estimates for Scotland, Wales and Northern Ireland. A more recent meta-analysis of 48 studies suggesting a slightly higher incidence rate of 61.44 per 100,000 person-years (95% CI 50.75-74.38), although not limited to higher income countries [3]. Looking at the age distributions for the incidence of epilepsy, it is clear that epilepsy is increasingly becoming a condition of the elderly, both in terms of a new diagnosis (for example we found the highest age-related incidence rate of 102.16 among those aged 85-90 in England) but also in terms of prevalence, a finding that was replicated in all four constituent nations of the United Kingdom.

Other key findings in this study are the significant regional variations (in England) in the incidence and prevalence of epilepsy, with the highest incidence (and prevalence) seen in the North East, which according to a recent workforce survey by the Association of British Neurologists (ABN), has the lowest concentration of neurologists, whilst the lowest prevalence figures were seen in London, which has the highest concentration of neurologists [10].

Finally this study suggests a correlation between social deprivation and epilepsy, with the incidence and prevalence in England and Wales increasing from the lowest to the highest IMD decile with an over 40% increase, replicating more broadly a finding that had previously been demonstrated more locally in London [11] and in Wales [12].

We had postulated that the prevalence of epilepsy in the UK may be increasing given the increasing proportion of the UK population, yet our findings suggest a slight decrease relative to the 2011 estimates [6]. This figure is nevertheless over 20% higher than the prevalence currently quoted by Public Health England for people aged 18 and which this body with key responsibilities for health service planning uses for decision-making purposes (8 per 1000 for people aged 18 and over in England) [13].

There are likely to be a number of reasons for the difference between the prevalence and incidence figures calculated in this study and those cited by PHE. One possible reason for the higher figures calculated in this study may be the difference in case definition – with PHE defining epilepsy cases as having 'recurrent unprovoked seizures' whereas this study required patients only to be receiving at least one ASM prescription after their diagnosis. The fact that the PHE numbers refer to adults only cannot explain the lower prevalence and incidence figures because these figures are, on average, higher in those under the age of 18 than across the adult age range. The fact that PHE uses Read code data from the whole

country might suggest that its figures are more reliable, but extensive epidemiological work with the CPRD database has previously documented that the data it contains is representative of the whole population of the UK [14] [15].

To some extent the lower prevalence and incidence rate generated by PHE's analysis of QOF data may be explained by differences in case definition i.e. the Read codes used. NHS Digital (email correspondence) have confirmed that the original code list for including people with epilepsy was based on age criteria and therefore excluded some "juvenile" forms of epilepsy such as juvenile absence and myoclonic epilepsies amongst other, which is likely to reduce prevalence figures in those above age 17. In particular Juvenile Myoclonic Epilepsy (accounting for 5% - 11% of all epilepsies) and Juvenile Absence Epilepsy (accounting for 2%-3% of the total epilepsy prevalence in adults in previous studies) [16] [17] are likely to be particularly relevant omissions. This study highlights the need for a consensus method for defining epilepsy in the UK using primary care data.

The major limitation of this study, and one inherent in all large database studies, is the accuracy of the coding and the inevitable variation seen, a fact seen in the slight different figures estimates given by the CPRD Aurum and CPRD GOLD databases. One of the major concerns with the use of the CRPD database, is that individual practices can opt in or out, representing a potential source of bias. Nevertheless the CRPD has previously been demonstrated to be representative of the UK population [18-20]. Moreover we employed wider diagnostic criteria than just epilepsy type to capture those with a current active diagnosis or a new diagnosis of epilepsy. In addition there was insufficient data available to report prevalence and incidence by English region from CPRD GOLD database. A further limitation of the data relates to the relationship between social deprivation and the incidence and prevalence of epilepsy. Whilst the data suggests a strong relationship, the nature of the data does not allow to establish correlation between the two. In order to accurately establish a correlation would require prospective cohort data to see if social deprivation changed over time in those with a new (incident cases) and pre-existing (prevalent cases) over time.

In summary, this study provides updated estimates for the incidence and prevalence of epilepsy in the UK and the constituent nations of the UK, as well as estimates by gender, age group and regional variations. Although our figures indicate that the prevalence of epilepsy has fallen slightly relative to the 2011 the estimates generated by our analysis are significantly higher than pre prevalence figures used by Public Health England for national healthcare planning purposes. Our findings provide further support for the correlation between the incidence (and prevalence) and social deprivation with an almost 40% increase in the incidence (and prevalence) from the lowest to the highest deprivation decile. Finally as a result of this study and the highlighted variation in coding employed, NHS Digital have confirmed, going forward, that they will include all missing epilepsy codes, allowing for more accurate estimates for the incidence and prevalence of epilepsy.

Author contributions

SW, MR, JD and AN were involved in the study design.
EY and TA undertook the database analysis and produced the initial results and statistical analysis.
SW and AN undertook the analysis and wrote the first draft.

AN undertook additional statistical analysis.
SW, MR, JD and AN were involved in interpretation of data.
All authors were involved in the critical revision of the manuscript.

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Supplement 3 = Release Notes: CPRD AURUM April 2020

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