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Incidence of epilepsy and associated factors in elderly patients in Germany

Louis Jacob [a], Jens Bohlken [b], Bettina Schmitz [c], Karel Kostev [d,*]

[a] Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux 78180, France
[b] Praxis für Neurologie und Psychiatrie, Berlin, Germany
[c] Department of Neurology, Vivantes Humboldt-Klinikum, Berlin, Germany
[d] Epidemiology, IQVIA, Frankfurt, Germany

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ABSTRACT

Aims: Little is known about the recent epidemiology of epilepsy in the elderly in Germany. Therefore, the goal of this study was to analyze the incidence of epilepsy and associated factors in elderly patients followed in general practices in this country.
Methods: The incidence of epilepsy was estimated using data from all patients aged ≥60 years who were followed in 1203 general practices in Germany in 2017 (IQVIA Disease Analyzer database). The association between predefined variables and epilepsy was further studied using a case–control design (n = 4690 matched pairs). Cases were patients aged ≥60 years who had received a first diagnosis of epilepsy in general practices between 2015 and 2017 (index date). Controls without epilepsy were matched (1:1) to cases by age, gender, index year, and physician.
Results: The incidence of epilepsy was 157 per 100,000 elderly persons. This incidence increased with age (92 per 100,000 persons in patients aged 60–65 years versus 311 in those aged >90 years) and was higher in men (166) than in women (150). The three disorders that had the strongest association with epilepsy were subarachnoid, intracerebral or intracranial hemorrhage (odds ratio [OR] = 3.31), stroke, including transient ischemic attack (OR = 2.32), and mental and behavioral disorders due to use of alcohol (OR = 2.20). In addition, there was a positive association between atypical neuroleptics and epilepsy (OR = 2.40).
Conclusions: The incidence of epilepsy was high and increased with age in elderly patients followed in general practices in Germany. Addressing identified risk factors may help reduce the risk of developing epilepsy.

1. Introduction

Epilepsy is a common neurological condition with a lifetime prevalence of around 8 per 1000 persons worldwide [1]. The prevalence is the highest for epilepsies with generalized seizures and epilepsies of unknown etiology. A recent study in Germany found that the prevalence of unspecified epilepsy and focal epilepsy was around 2.0% and 0.7% respectively [2]. Since epilepsy has a major impact on quality of life [3], comorbidity [4], and mortality [5], new research is needed to improve the diagnosis, management, and treatment of people affected by this disorder.

In recent decades, there has been a growing interest in epilepsy in elderly patients [6–13]. Aura, automatisms, and secondary generalization are less frequent, and postictal confusion lasts longer in the elderly than in young adults [10,14,15]. In addition, previous studies have found that epilepsy tends to occur more frequently in older than in younger populations [6,7,13]. For example, in 2006, Hussain and colleagues observed that the age-specific incidence was 10.6 per 100,000 person-years between the ages of 45 and 59 years, 25.8 between the ages of 60 and 74 years, and 101.1 between the ages of 75 and 89 years among 1919 community-dwelling volunteers from the U.S. [7]. These findings were corroborated in 2018, when researchers from Canada found that the incidence of epilepsy increased with age, from approximatively 40 per 100,000 person-years in individuals aged 10–14 years to 120 per 100,000 person-years in those aged between 85 and 89 years [13]. Interestingly, the increase in the incidence of epilepsy was more pronounced after the age of 60, and this trend was similar in men and women. Although these previous works are of great interest, little is known about the recent epidemiology of epilepsy in elderly patients in Germany. Since epilepsy is associated with a considerable economic burden in older adults in this country [16], this lack of data is of particular concern.

Therefore, the goal of this study was to analyze the incidence of epilepsy and associated factors in elderly patients in Germany.

* Corresponding author at: Epidemiology, IQVIA, Commercial GmbH & Co OHG, Unterschweinstiege 2-14, 60549 Frankfurt am Main, Germany.
E-mail address: kkostev@de.imshealth.com (K. Kostev).

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2. Methods

2.1. Database

This study is based on data from the Disease Analyzer database (IQVIA), which compiles drug prescriptions, diagnoses, basic medical, and demographic data obtained directly and in anonymous format from computer systems used in the practices of general practitioners and specialists [17]. Diagnoses (International Classification of Diseases, 10th revision [ICD-10]), prescriptions (Anatomical Therapeutic Chemical [ATC] Classification system), and the quality of reported data are being monitored by IQVIA based on a number of criteria (e.g., completeness of documentation and linkage between diagnoses and prescriptions).

The sampling methods used for the selection of physicians' practices are consistent with a representative database of general and specialized practices in Germany [17]. Prescription statistics for several drugs were very similar to data available from pharmaceutical prescription reports [17]. The age groups for given diagnoses in the Disease Analyzer database also corresponded to those in relevant disease registries. Finally, this database has already been used in studies focusing on epilepsy [18–20].

2.2. Study population

The incidence of epilepsy was estimated using data from all patients aged ≥60 years who were followed in 1203 general practices in Germany in 2017 (IQVIA Disease Analyzer database). The association between predefined variables and epilepsy was further studied using a case–control design (n = 4690 matched pairs). Cases were patients aged ≥60 years who had received a first diagnosis of epilepsy (ICD-10: G40, G41) between 2015 and 2017 in general practices (index date). They were included only if they were followed for at least 365 days prior to the index date. After applying similar inclusion criteria, controls without epilepsy were matched (1:1) to cases by age, gender, index year, and physician. The index date was a randomly selected visit date during the study period (Fig. 1).

2.3. Study outcomes and variables

The first outcome of the study was the incidence of epilepsy in individuals aged ≥60 years in 2017. The incidence was calculated based on the number of incident epilepsy cases and the total number of patients visiting general practices during this year. The second outcome was the association between predefined variables and epilepsy in previously selected cases and controls. The predefined variables were the patients' diagnosed disorders and the therapies they had been prescribed within 365 days prior to the index date that are known to be potentially associated with epilepsy. Disorders were syncope and collapse (ICD-10: R55) [21], intracranial injury (S06) [22], mental and behavioral disorders due to use of alcohol (F10) [23], stroke, including transient ischemic attack (I63, I64, G45) [24], mild cognitive impairment (F06.7) [25], subarachnoid, intracerebral or intracranial hemorrhage (I60–62)

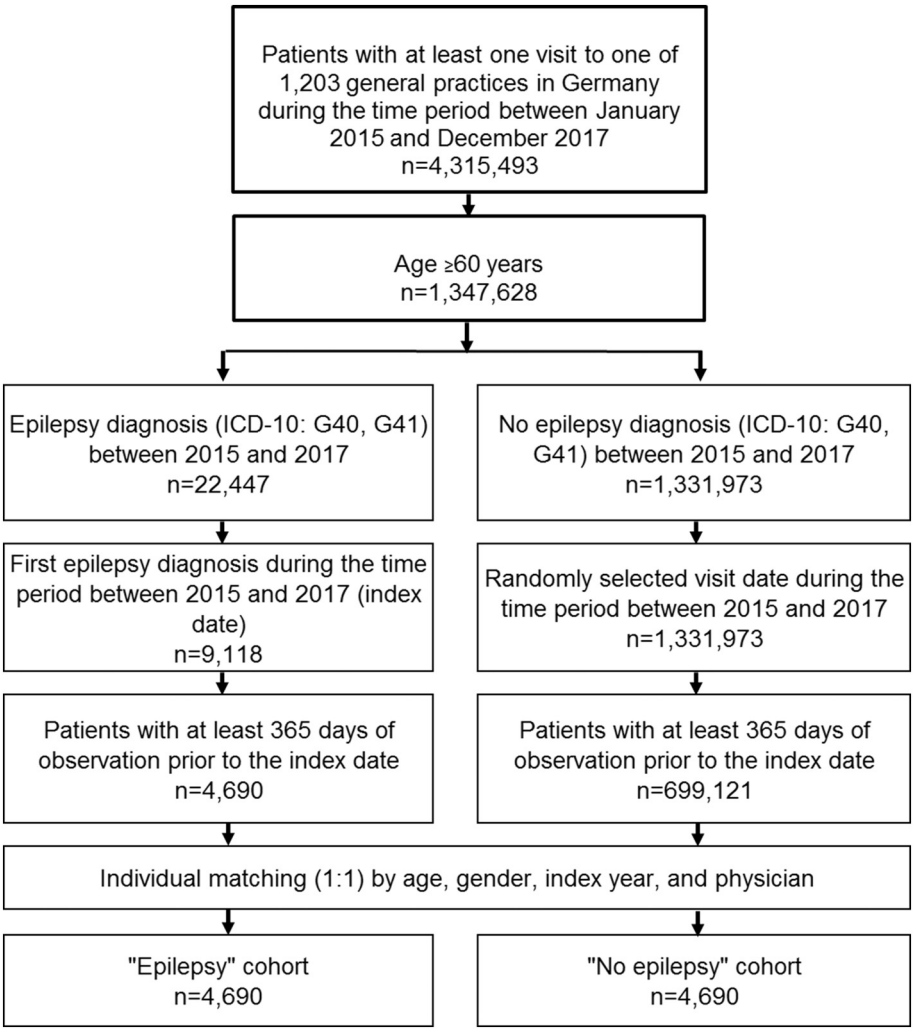

Fig. 1. Selection of study patients.

Table 1
Incidence of epilepsy in cases per 100,000 people in patients aged ≥60 years who were followed in 1203 general practices in Germany in 2017.

Cohort	Incidence in 2017 (95% CI)*
Age 60–65	92 [81–103]
Age 66–70	117 [99–135]
Age 71–75	149 [128–170]
Age 76–80	180 [161–199]
Age 81–85	227 [199–254]
Age 86–90	248 [211–285]
Age > 90	311 [252–371]
Males	166 [150–182]
Females	150 [141–159]
Total	157 [148–166]

[26], dementia (F01, F03, G30) [27], Parkinson's disease (G20) [28], diabetes (E10–14) [29], hypertension (I10) [30], coronary heart disease (I24, I25) [31], insomnia (F510) [32], and depression (F32, F33) [33]. Therapies included in the study were selective serotonin reuptake inhibitors (SSRIs; Ephmra ATC: N06A4) [34], serotonin–norepinephrine reuptake inhibitors (SNRIs; N06A5) [35], other antidepressants (N06A9) [35], atypical neuroleptics (N05A1) [36], other neuroleptics (N05A9) [37], antidementia agents (N07D1) [38], opioids (N02A) [39], and benzodiazepines (N05C) [40]. Finally, demographic variables included age and gender.

2.4. Statistical analyses

The incidence of epilepsy was studied in the overall population and in different age and gender subgroups. A multivariate logistic regression analysis was further conducted to investigate the association between predefined variables and epilepsy. This model was adjusted for all disorders and therapies included in this study. A P-value of <0.05 was considered statistically significant. All analyses were carried out using SAS 9.4 (SAS Institute, Cary, USA).

3. Results

The incidence of epilepsy was 157 per 100,000 persons in individuals aged ≥60 years who were followed in general practices in Germany in 2017 (Table 1). This incidence increased from 92 per 100,000 persons in patients aged 60–65 years to 311 per 100,000 persons in those aged >90 years and was higher in men (166 per 100,000 persons) than in women (150 per 100,000 persons). The results of the multivariate logistic regression model are displayed in Table 2. Eight disorders were significantly associated with epilepsy: subarachnoid, intracerebral or intracranial hemorrhage (odds ratio [OR] = 3.31), stroke, including transient ischemic attack (OR = 2.32), mental and behavioral disorders due to use of alcohol (OR = 2.20), dementia (OR = 2.08), intracranial injury (OR = 1.82), mild cognitive impairment (OR = 1.70), Parkinson's disease (OR = 1.53), and syncope and collapse (OR = 1.49). In addition, six families of drugs increased the risk of developing epilepsy: atypical neuroleptics (OR = 2.40), other neuroleptics (OR = 1.53), SSRIs (OR = 1.45), opioids (OR = 1.44), antidementia agents (OR = 1.38), and SNRIs (OR = 1.33).

4. Discussion

We found that the incidence of epilepsy was 157 per 100,000 elderly patients followed in general practices in Germany in 2017. Furthermore, this incidence increased with age and was higher in men than in women. Finally, it was observed that the risk of developing epilepsy was positively associated with several disorders and families of drugs such as subarachnoid, intracerebral or intracranial hemorrhage, stroke, including transient ischemic attack, mental and behavioral disorders due to use of alcohol, and atypical neuroleptics.

Several studies have recently investigated the incidence of epilepsy in the elderly [6–13], and it has been revealed that epilepsy is more common among older adults [8,41]. For example, a prospective study conducted in Iceland found that the age-specific incidence of epilepsy was highest in children (130 per 100,000 person-years) and in participants aged ≥65 years (110.5 per 100,000 person-years) [41]. Thus, epilepsy is considered as a disorder of old age and is often a symptom of an underlying brain condition. The most frequent etiologies of epilepsy in the elderly are stroke (36%), atherosclerosis (15%), neurodegenerative disorders (12%), and trauma (7%) [8].

In this study, we found that subarachnoid, intracerebral, and intracranial hemorrhages were associated with a 3.3-fold increase in the epilepsy risk. In 2012, Woo and colleagues estimated that 8.4% of 263 consecutive patients with spontaneous intracerebral hemorrhage developed either early or late seizures [26]. Cortical involvement and young age had a significant impact on early seizures, while cortical involvement and communicating hydrocephalus favored the occurrence of late seizures. The fact that cortical involvement was a risk factor

Table 2
Association between defined chronic conditions and prescribed drugs and epilepsy in elderly patients in general practices in Germany.

Variable	Proportion among patients with epilepsy (%)	Proportion among patients without epilepsy (%)	Odds ratio (95% CI)	P-value
Diagnoses (ICD-10 codes) within 365 days prior to the index date				
Syncope and collapse (R55)	11.5	7.4	1.49 (1.28–1.74)	<0.001
Intracranial injury (S06)	3.4	1.5	1.82 (1.35–2.46)	<0.001
Mental and behavioral disorders due to use of alcohol (F10)	5.0	2.1	2.20 (1.72–2.83)	<0.001
Stroke, including TIA (I63, I64, G45)	24.4	11.9	2.32 (2.06–2.61)	<0.001
Mild cognitive impairment (F06.7)	1.4	0.7	1.70 (1.08–2.61)	0.023
Subarachnoid, intracerebral or intracranial hemorrhage (I60–62)	4.2	1.0	3.31 (2.39–4.58)	<0.001
Dementia (F01, F03, G30)	24.9	10.8	2.08 (1.83–2.36)	<0.001
Parkinson's disease (G20)	6.1	2.9	1.53 (1.22–1.91)	<0.001
Drugs prescribed (ATC codes) within 365 days prior to the index date				
SSRIs (N06A4)	16.4	9.3	1.45 (1.26–1.67)	<0.001
SNRIs (N06A5)	5.4	2.4	1.33 (1.02–1.74)	0.032
Atypical neuroleptics (N05A1)	10.2	2.6	2.40 (1.93–3.00)	<0.001
Other neuroleptics (N05A9)	24.7	11.3	1.53 (1.35–1.74)	0.002
Antidementia agents (N07D1)	6.0	1.9	1.38 (1.06–1.82)	0.005
Opioids (N02A)	13.5	8.5	1.44 (1.25–1.66)	<0.001

Abbreviations: ICD-10 — International Classification of Diseases, 10th revision; ATC — Anatomical Therapeutic Chemical; TIA — Transient ischemic attack; SSRIs — Selective serotonin reuptake inhibitors; SNRIs — Serotonin and norepinephrine reuptake inhibitors.
There was no significant effect for diabetes (E10–14), hypertension (I10), coronary heart disease (I24, I25), insomnia (F510), depression (F32, F33), other antidepressants (N06A9), and benzodiazepines (N05C).

may be explained by the fact that it irritates the cortex, leading to its overactivation [26]. We further observed a strong relationship between stroke and epilepsy. In 2016, Bryndziar et al. showed that 7.2% of a sample of 489 participants presented with new-onset seizures in the years following the first ischemic stroke [42]. In addition, poststroke seizures worsened the functional outcome and increased the risk of mortality. Seizures following ischemic strokes may be related to an increase in intracellular Ca^{2+} and Na^{+} resulting in a lower threshold for depolarization, glutamate excitotoxicity, hypoxia, metabolic dysfunction, global hypoperfusion, and hyperperfusion injury [24]. By contrast, previous research has found that seizures following hemorrhagic strokes are attributable to blood products that irritate the brain.

Moreover, there is a positive relationship between epilepsy and mental and behavioral disorders due to use of alcohol. A 2010 meta-analysis that included six studies reported that alcohol consumption was strongly associated with epilepsy and unprovoked seizures and that the risk of developing epilepsy steadily increased with the amount of alcohol consumed [23]. For example, individuals consuming an average of eight drinks every day exhibited 3-fold increased odds of developing epilepsy. The chronic alcohol consumption–epilepsy relationship is likely mediated by multiple factors such as brain traumas, hypoxia, and long-term changes in neuronal excitability [23]. It is very likely that mental and behavioral disorders due to use of alcohol in our study were an indirect marker of the chronic consumption of alcohol, although several psychiatric conditions have been previously associated with epilepsy and seizures [33]. Mild cognitive impairment and dementia were found to be additional risk factors for epilepsy in this retrospective study conducted in Germany. A recent meta-analysis of 19 studies showed that the prevalence of epilepsy was around 4–5% in people affected by dementia [27]. There is growing evidence that Alzheimer's disease and other types of dementia favor pathological excitability and neuronal changes, leading in turn to seizures and epilepsy [43]. For example, there is a decreased number of neurons in the entorhinal cortex and the hippocampal field CA1 in very mild Alzheimer's disease [44], while cell loss and reorganization of neuronal circuitry in these regions are common in temporal lobe epilepsy [43].

Regarding intracranial injury, it was found that this condition led to a 1.8-fold increase in the risk of developing epilepsy. In 2000, Annegers and Coan discovered that the severity of the injury in victims of traumatic brain injury was positively associated with epilepsy (mild: relative risk [RR] = 1.5; moderate: 2.9; and severe: 17.2) [22]. Identified risk factors were brain contusion with subdural hematoma, skull fracture, loss of consciousness or amnesia lasting one day or more, and age over 65 years. Taken together, these findings underline the major impact of traumatic brain injury on the activity and the excitability of cortical neurons. Another interesting result of our study is that it reveals a significant and positive relationship between Parkinson's disease and epilepsy. In 2018, Gruntz et al. observed in a nested case–control study including 23,086 patients with incident Parkinson's disease and 92,343 controls that the crude incidence rate of epilepsy was 267 and 112 per 100,000 person-years in cases and controls respectively [28]. This research clearly shows that, although Parkinson's disease is a subcortical disorder, it can involve the cortex even in the early stages of the disease [45]. The last condition found to be a risk factor for epilepsy in this study was syncope. Although it is difficult to differentiate these two conditions, researchers from Ireland recently reported a case series of 12 patients who presented with generalized tonic–clonic seizures after a clear syncopal phase, suggesting that syncope may be an underrecognized trigger for convulsive seizures [21].

Finally, we observed that epilepsy was positively associated with the use of SSRIs, SNRIs, atypical neuroleptics, other neuroleptics, antidementia agents, and opioids. In 2015, Hill and colleagues found that the use of antidepressant drugs increased the risk of developing epilepsy in a cohort study using a primary care database from the United Kingdom [35]. The highest hazard ratios (HR) were found for trazodone, lofepramine, venlafaxine, and combined antidepressant treatments. Two years later, Chou et al. estimated that the cumulative incidence of poststroke epilepsy was higher in SSRI users than in SSRI nonusers participating in a population-based nationwide study [34]. Moreover, SSRIs were positively associated with epilepsy (HR = 2.45), and this association increased with the daily dose of SSRIs. As for its association with antipsychotic drugs, it was shown in a cohort of 60,121 patients with schizophrenia, affective disorders, or dementia that the incidence rate of seizures was higher in users of these molecules (24 to 59 per 10,000 person-years) than in nonusers (12 per 10,000 person-years) [46]. The association between these various drugs and epilepsy may be explained by the fact that they have a significant impact on seizure threshold [36,38,47]. Regarding anti-dementia drugs and opioids, the findings of this study must be interpreted with great caution and need to be corroborated by further analyses.

This study is subject to several limitations that should be mentioned at this point. Firstly, we included only elderly patients followed in general practices. Since an important proportion of these older adults may have been followed in neurological practices and other settings, this may have biased the present findings. Secondly, the definition of incidence was based on the number of patients followed in general practices in 2017. Since a small proportion of the elderly population may have not seen any general practitioner during this year, we may have overestimated the incidence of epilepsy in older adults. Thirdly, because of the design of the study, it was not possible to determine causality or temporality in the association between defined variables and epilepsy. Moreover, further variables that could be associated with epilepsy – including smoking behavior, physical activity, patterns of alcohol consumption, other social factors – are not available in the database used. Finally, only drug classes and no drugs were analyzed separately. On the other hand, the strength of this study is the fact that it is based on a nationwide database that includes a large number of patients, doctors, and variables.

Overall, the incidence of epilepsy was high and increased with age in elderly patients followed in general practices in Germany. Several factors were found to be significantly associated with epilepsy, and addressing these factors may help reduce the risk of developing epilepsy in the future.

Declaration of conflicts of interest

The authors declare that they have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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