Na osnovu člana 9 i stava 3 člana 31 a Pravila doktorskih studija (Bilten Univerziteta Crne Gore broj:513/20 i 561/22), a nakon razmatranja Drugog godišnjeg izvještaja mentora prof. dr Aleksandra J. Ristića i komentora prof. dr Tatjane Pekmezović o napredovanju doktoranda dr med Sanje Gluščević broj:1989 od 17.12.2024.godine, Komisija za doktorske studije na sjednici održanoj dana 21.01.2025. godine je donijela

O D L U K U

1. Predlaže se Vijeću Medicinskog fakulteta da usvoji Drugi godišnji izvještaj mentora prof. dr Aleksandra J. Ristića i komentora prof. dr Tatjane Pekmezović o napredovanju doktoranda dr med Sanje Gluščević broj:1989 od 17.12.2024. godine.

2. Predlog komisije i Izvještaj mentora i komentora sa objavljenim radom iz tačke jedan ove Odluke, dostavljaju se Vijeću Medicinskog fakulteta, na dalje izjašnjenje.

Obrazloženje

U skladu sa stavom 1 člana 31a Pravila doktorskih studija, mentor prof. dr Aleksandar J. Ristić i komentor prof. dr tatjana Pekmezović, blagovremeno su dostavili izvještaj o napredovanju doktoranda dr med Sanje Gluščević, broj: 1989 od 17.12.2024. godine.

Na osnovu stava 3 člana 31 a Pravila doktorskih studija, Komisija za doktorske studije na sjednici održanoj dana 21.01.2025. godine, nakon razmatranja navedenog izvještaja mentora i komentora, konstatovala da izvještaj sadrži sve elemente, da je pravilno popunjen i na osnovu njega se stiče konkretan uvid o ostvarenom napretku kandidatkinje. Mentor i komentor su visokim ocjenama okarakterisali dosadašnji istraživački rad doktorantkinje i dostavili objavljeni rad kao rezultat doktorskih istraživanja. Priloženi podaci u IM obrascu ukazuju na posvećenost kandidatkinje.

Na osnovu navedenog Komisija je odlučila kao u dispozitivu ove Odluke.

DOSTAVLJENO
-Vijeću Medicinskog fakulteta
-Studentskoj službi

KOMISIJA ZA DOKTORSKE STUDIJE
PREDSJEDNIK

Prof. dr Filip Vukmirović

DRUGI GODIŠNJI IZVJEŠTAJ MENTORA O NAPREDOVANJU DOKTORANDA

Akademska godina za koju se podnosi izvještaj			
OPŠTI PODACI O DOKTORANDU			
Titula, ime, ime roditelja, prezime	dr med Sanja (Vukajlo) Gluščević		
Fakultet	Medicinski fakultet u Podgorici, Univerzitet Crne Gore		
Studijski program	Medicina		
Broj indeksa	24/10		
MENTOR/MENTORI			
Mentor	Prof.dr Aleksandar J. Ristić	Klinika za neurologiju, Medicinski fakultet u Beogradu, Univeriztet u Beogradu, Srbija	Neurologija
Ko-mentor	Prof. dr Tatjana Pekmezović	Katedra za epidemiologiju, Medicinski fakultet u Beogradu, Univerzitet u Beogradu, Srbija	Epidemiologija

EVALUACIJA DOKTORANDA*					
Koliko ste zadovoljni kvalitetom održanih susreta sa doktorandom?	☐1	☐2	☐3	☐4	✓5
(Ako je prethodni odgovor „1" ili „2" dati obrazloženje i prijedloge za poboljšanje)					
Da li je definisan plan rada sa doktorandom?	✓ DA	☐NE			
Da li je doktorand ostvario napredak prema predvidenom planu rada?	✓ DA	☐NE			
(Ako je prethodni odgovor „ne" dati obrazloženje i prijedloge za poboljšanje)					
Kvalitet napretka doktorandovog istraživačkog rada u periodu za koji se podnosi zvještaj je:	☐1	☐2	☐3	☐4	✓ 5
(Ako je prethodni odgovor „1" ili „2" dati obrazloženje i prijedloge za poboljšanje)					
Ocjena doktorandove spremnosti za konsultacije.	☐1	☐2	☐3	☐4	✓ 5
Ocjena planiranja i izvršavanja godišnjih istraživačkih aktivnosti i stručnog usavršavanja doktoranda.	☐1	☐2	☐3	☐4	✓ 5
Ocjena napretka u savladavanju metodologije naučno-istraživačkog rada.	☐1	☐2	☐3	☐4	✓ 5

*Ocjene su: 1 – nedovoljan, 2 – dovoljan, 3 – dobar, 4 – vrlo dobar, 5 – odličan

Ocjena doktorandovog generalnog odnosa prema studijama.	☐1	☐2	☐3	☐4	✓ 5
Ocjenu ukupnog kvaliteta doktorandovog rada.	☐1	☐2	☐3	☐4	✓ 5

(Ako je prethodni odgovor „1" ili „2" dati obrazloženje i prijedloge za poboljšanje)

ISPUNJENOST USLOVA DOKTORANDA

Spisak radova doktoranda iz oblasti doktorskih studija koje je publikovao doktorand

Rezultati sprovedenog istraživanja su uspješno i u potpunosti privedeni kraju. Nakon sistematizacije podataka, sprovedena je statistička obrada podataka a dobijeni rezultati su iskorišćeni za objavljivanje originalnog naučnog rada, na kojem je kandidat prvi autor.

Rad pod naslovom „ Nationwide epidemiological study of epilepsy in Montenegro", objavljen je u časopisu Epilepsy&Behavior (Impact factor 2.3 (2023))

Obrazloženje mentora o korišćenju sprovedenih istraživanja u publikovanim radovima

Odlukom Senata Univerziteta Crne Gore a na predlog Vijeća medicinskog fakulteta i Centra za doktorske studije, imenovana je Komisija za ocjenu podobnosti doktorske teze pod nazivom „ Prevalencija epilepsije u Crnoj Gori – epidemiološki i klinički aspekti".
Kandidatkinja je javno obrazlagala ciljeve i očekivane rezultate 11.04.2023. godine, pred Komisijom u sastavu: prof. dr Aneta Bošković, redovni profesor Medicinskog fakulteta Univerziteta Crne Gore (predsjednik Komisije), doc. dr Aleksandar J. Ristić, docent na Medicinskom fakultetu u Beogradu, Univerziteta u Beogradu (mentor), prof.dr Tatjana Pekmezović, redovni profesor Medicinskog fakulteta u Beogradu, Univerzitet u Beogradu (komentor), prof. dr Dragan Laušević, redovni profesor Medicinskog fakulteta Univerziteta Crne Gore, (član Komisije), prof. dr Slavica Vujisić, redovni profesor Medicinskog fakulteta Univerziteta Crne Gore (član Komisije).
Komisije). Nakon obrazlaganja teme i usvajanja izvještaja Komisije za ocjenu podobnosti doktorske teze, Vijeće Medicinskog fakulteta je predložilo Senatu Univerziteta Crne Gore da se prihvati kao podobna doktorska teza pod nazivom „Prevalencija epilepsije u Crnoj Gori – epidemiološki i klinički aspekti". Odlukom Senata Univerziteta Crne Gore (broj odluke 03-1237/4) od 23.06.2023, prihvaćena je kao podobna doktorska teza pod naslovom „ Prevalencija epilepsije u Crnoj Gori – epidemiološki i klinički aspekti".

Planirano istraživanje je bilo veoma obimno i podrazumijevalo je pretraživanje kompletne medicinske dokumentacije svih pacijenta u Crnoj Gori starijih od 18 godina, koji se liječe od epilepsije (korišćenjem prethodno konstruisanog algortima pretraživanja: dijagnoza G40-G40.9, odrađen makar jedan EEG, odrađen makar jedna MR ili CT mozga, propisan makar jedan antiepileptički lijek) uz dodatno ispitivanje pacijenata od strane kandidatkinje za sve one varijable koje nisu navedene u medicinskoj dokumentaciji, a koje su od značaja za istraživanje. Od sociodemografskih varijabli unosili se podaci o polu, starosti, obrazovanju, zaposlenosti, bračnom statusu, a od kliničkih starost na početku bolesti, trajanje bolesti, učestalost napada, vrijeme javljanja napada, tip napada, tip epilepsije, epileptički sindrom, etiologija, upotreba antiepileptika, broj antiepileptika, komplijansa, prisustvo psihijatrijskih i nepsihijatrijskih komorbiditeta, prisustvo epileptičkog statusa, faktora rizika, pozitivne porodične anamneze, nalaz na EEG-u i nalaz na neuroimidžingu.

Država je bila podijeljena u tri regiona - sjeverni (Pljevlja, Bijelo Polje, Berane, Rožaje, Plužine, Žabljak, Mojkovac, Plav, Andrijevica, Kolašin, Šavnik, Petnjicu i Gusinje) centralni (Podgorica, Zeta, Tuzi, Danilovgrad, Cetinje, Nikšić) i južni (Bar, Budva, Tivat, Kotor, Herceg Novi i Ulcinj). S obzirom na to da u sjevernom i južnom regionu postoji bar po jedna opšta bolnica ka kojoj gravitira stanovništvo iz navedenih gradova, medicinska dokumentacija je pretraživana primarno u tim bolnicama, prema prethodno navedenom algoritmu.

Nakon sistematizacije podataka sprovedena je statistička obrada podataka. Obrada podataka je vrš□ena u programu SPSS verzija 16.0 (SPSS Inc, C□ikago, Ilinois, SAD). U analizi podataka koris□ćene su metode deskriptivne statistike radi prikazivanja podataka (apsolutni i relativni brojevi), mjere centralne tendencije i mjere disperzije. Od analitic□kih statistic□kih metoda u evaluaciji neparametarskih obilježja između dvije grupe ispitanika primijenjeni su hi kvadrat (χ^2), Fis□erov test tac□ne vjerovatnoce (Fisher's exact test) i Kruskal-Wallis-ov test analize varijanse, a za statistic□ku evaluaciju parametarskih obiljez□ja između dvije grupe ispitanika Man-Vitnijev-ov test (Mann-Whitney). Ispitivane varijable su smatrane statistic□ki znac□ajnim ukoliko je vjerovatnoća rizika za sluc□ajnu razliku između empirijskih i teorijskih vrijednosti manja od 0,05 ($p<0,05$), a visoko statistic□ki znac□ajnim ukoliko je ta vjerovatnoća manja od 0,01 ($p<0,01$). Korelacije dvaju varijabli su ispitivane Spearmanovim koeficijentom korelacije ranga. Dobijeni rezultati su korišćeni za pripremanje I objavljivanje originalnog naučnog rada na kom je kandidatkinja prvi autor.

Kandidatkinja dr Sanja Gluščević je u svom istraživačkom radu pokazala veliku posvećenost, motivisanost i predanost. Učestvovala je u svim fazama istraživanja i izrade rada: osmišljavanju istraživanja, prikupljanju podataka, statsističkoj obradi dobijenih rezultata, uz pomoć mentora kao i pisanju publikacije i odabiru časopisa u koji je publikacija poslata. Ostvarila je veliki napredak u savladavanju vještina neophodnih za adekvatno sprovodenje naučno-istraživačkog rada. Kandidatkinja je u potpunosti ovladala vještinom jasnog, preciznog, ali i strukturiranog i infomativnog saopštavanja naučnih rezultata.

S obzirom na to da je kandidatkinja obavila najveći dio istraživačkog rada i svoje obaveze uspješno obavlja, uprkos upisanoj užoj specijalizaciji iz oblasti kliničke neurofiziologije sa epileptologijom, smatramo da dr Sanja Gluščević uspješno napreduje ka odbrani doktorske disertacije i predlažemo da joj se omogući nastavak i završetak doktorskih studija.

Ocjena o aktivnostima sprovedenim na pisanju i objavljivanju naučnih radova.	☐1 ☐2 ☐3 ☐4 ✓5
SAGLASNOST ZA NASTAVAK STUDIJA	
Može li doktorand nastaviti studije?	✓ **Da** ☐Da, uz određene uslove ☐Ne
(Ako je prethodno dat odgovor pod „Da, uz odredjene uslove“ ili „Ne“ dati obrazloženje i prijedloge za poboljšanje)	
Napomene	
(Popuniti po potrebi)	

U Beogradu,
02.12.2024.

Ime i prezime mentora
Prof.dr Aleksandar J. Ristić

Ime i prezime komentora
Prof.dr Tatjana Pekmezović

MP

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Research Paper

Nationwide epidemiological study of epilepsy in Montenegro

Sanja Gluscevic [a], Slavica Vujsic [b], Aleksandar Ristic [c,d,1,*], Tatjana Pekmezovic [e,1,*]

[a] Clinic of Neurology, Clinical Center of Montenegro, Ljubljanska bb, 81000 Podgorica, Montenegro
[b] Faculty of Medicine, University of Montenegro, Krusevac bb, 81000 Podgorica, Montenegro
[c] Clinic of Neurology, University Clinical Center of Serbia, Dr Subotica 6, 11000 Belgrade, Serbia
[d] Faculty of Medicine, University of Belgrade, Dr Subotica 8, 11000 Belgrade, Serbia
[e] Institute of Epidemiology, Faculty of Medicine, University of Belgrade, Visegradska 26A, 11000 Belgrade, Serbia

ARTICLE INFO

Keywords:
Epilepsy
Incidence
Prevalence
Montenegro

ABSTRACT

The aim of this study was to estimate the incidence and prevalence of epilepsy in Montenegro over the period 2011–2022 using hospital case records. The main sources for this study were hospital case records in every outpatient and inpatient neurological department in Montenegro, including the Clinical Center of Montenegro in the capital, a primary referral national center for epilepsy. For every patient, aged 18 and above, two neurologists reviewed all data collected to verify the validity of the diagnosis and to establish the date of clinical onset of the disease. Information on age and sex, EEG, CT scan, and MRI were included. Prevalent cases were selected in 2022 population. Incident cases of epilepsy were identified in 2011 and the incidence trend was followed up for the next 12 years. Crude and standardized incidence and prevalence were calculated. Average crude incidence rate of epilepsy for study period was 56.0 per 100,000 individuals (men 58.1; women 54.2). The age-specific incidence was lowest in the 30 s, and early 40 s and highest after 65 years. Over the 12-year period, increasing trend of standardized epilepsy incidence rates was observed for the total population and for females ($p = 0.024$ and $p = 0.020$ respectively). The crude overall prevalence of epilepsy on December 31, 2022 was 13.0 per 1000 individuals (men 13.5; women 12.6). The highest prevalence was in patients in their early 20 s and in the seventh decade. In conclusion, the incidence of epilepsy in this study was similar to those of other industrialized countries, with increasing trend during study period. Prevalence was higher compared to European countries.

1. Introduction

Epilepsy ranks as a third most prevalent neurological disorder globally. It is defined as a chronic multifactorial brain disease characterized by recurring seizures and associated neurobiological, cognitive, psychological, and social consequences of seizure recurrence [1,2]. It is estimated to affect around 70 million people worldwide and it generates a significant social and economic burden [3,4].

The epidemiology of epilepsy varies considerably among countries and regions.

Studies around the world in developed countries report the overall incidence of epilepsy to be about 50 per 100,000/person-years (range 40–70/100,000 person-years) [3,5]. The recent study by Ngugi et al. suggests that the incidence of epilepsy in low- and middle-income countries, approximately 81.7 per 100,000 person-years (ranging from 28.0 to 239.5 per 100,000 person-years), is nearly double that observed in high-income countries [3]. This discrepancy may be partly attributed to certain risk factors, such as perinatal injury, CNS infections, and head trauma which are more common in developing regions. In terms of age-specific occurrence, previous studies have shown a high incidence of epilepsy during the first year of life and early childhood in both developing and developed countries [6]. On the other hand, there has been an observed increase in the incidence of epilepsy among older individuals in developed countries [7–9]. Epilepsy therefore tends to have its onset at the two extremes of life following a U-shape distribution. However, some studies have shown a substantial decline in the incidence of epilepsy in children and adults over time, coupled with an accompanying increase in frequency among the elderly [10].

A recent *meta*-analysis revealed the lifetime prevalence of epilepsy to be 7.6 per 1000 persons, with lower numbers in developed (5.8/1000

* Corresponding authors.
E-mail addresses: alexaristic@gmail.com (A. Ristic), pekmezovic@sezampro.rs (T. Pekmezovic).
[1] These authors contributed equally to this work and share the last authorship.

https://doi.org/10.1016/j.yebeh.2024.110065
Received 3 June 2024; Received in revised form 26 August 2024; Accepted 19 September 2024
Available online 10 October 2024

persons) compared to developing countries (10.3/1000 persons) [3,11]. The same pattern was observed in the point prevalence of active epilepsy, with lower figures in developed countries (6.4/1000 persons) as opposed to developing ones (12.7/1000 persons) [3,11]. Possible explanations for these discrepancies include different methodological approaches, dissimilar clinical classification of etiology and type of seizures, and varying definitions in epidemiological studies.

Trends regarding incidence and prevalence have been reviewed in several studies, with conflicting results so far. In a study from Korea, both incidence and prevalence increased during respective follow-up period, primarily due to aging and improved survival rates in people with chronic central nervous system illnesses [12]. Conversely, a recent study from Canada, demonstrated a stabile decline over a 5-year period time, attributed to better perinatal and neonatal care, universal vaccination, and improved method of ascertainment for diagnosis of epilepsy through different databases [13].

Epidemiological research on epilepsy in the Balkan countries is relatively scarce, with only a few studies conducted in the region [6–9]. Specifically, epidemiological data on epilepsy in Montenegro are limited. This study represents the first population-based, cross-sectional survey in Montenegro. The main aim of this survey was to estimate the incidence and prevalence of epilepsy and to evaluate the basic sociodemographic and clinical characteristics of people with epilepsy aged 18 years and older in Montenegro.

2. Material and Method

2.1. Area of investigation

This retrospective study was conducted from January to December 2022 in Montenegro, a country in Southeastern Europe. It has a coast on the Adriatic Sea to the southwest and is bordered by Croatia to the west, Bosnia and Herzegovina to the northwest, Serbia to the northeast, and Albania to the southeast. According to the 2011 national census, 620,029 inhabitants live in Montenegro (48.7 % male and 50.3 % female), with an average age of 35.7 years [18].

2.2. Cases collection

The primary data sources for this study were hospital case records from both outpatient and inpatient neurological departments across all 11 hospitals in Montenegro. They also included also the Clinical Center of Montenegro in Podgorica, which serves as the primary referral national center for epilepsy. Since there is no electronic/paper database of all patients with epilepsy in Montenegro, data were collected by retrospective analysis of hospital records from the period 2011–2022. As data were collected based on medical documentation, an algorithm for search was constructed as follows: diagnosis (codes for search according to ICD: G40-G40.9), presence of at least one standard EEG, at least one neuroimaging scan (brain MRI or brain CT), and prescription of at least one antiepileptic drug. After a detailed examination of each medical record, only those patients aged 18 and more and with complete clinical documentation and confirmed diagnosis of epilepsy were included in the study (inclusion criteria). From 2022 onwards, we have been collecting data continuously and the epilepsy electronic database on a national level, located at the Clinic of Neurology, Clinical Center of Montenegro in Podgorica, was established. To ensure the accuracy of the data, each patient's record was reviewed by two neurologists, one from the Clinical Center of Montenegro and one from the local hospital. This review process was to verify the validity of the diagnosis and to establish the clinical onset date of the disease.

In Montenegro, epilepsy is diagnosed exclusively by a neurologist. The neurological services are organized in all 11 hospitals in the country. All patients who visit a general physician, emergency medical service, or emergency center under suspicion of a crisis of consciousness are referred to a neurologist. Neurologists are the ones who establish the diagnosis of the disease, prescribe therapy, and follow patients.

The classification and diagnosis of epileptic seizures were based on the 2017 International league against epilepsy (ILAE) classification of epilepsies [19], and in addition to the neurological examination, every referred participant underwent additional diagnostics: electroencephalography (EEG), CT, and brain MRI (1.5 T or 3 T). EEG recording consisted of a standard 30-minute recording, and in insufficiently conclusive patients, prolonged EEG recording and/or EEG after sleep deprivation was performed.

Patients identified as having symptomatic seizures (only one seizure as part of an acute event, without the spontaneous occurrence of seizures during a follow-up of at least one year, and without other factors increasing the likelihood of seizure recurrence) and pregnant women who experienced a seizure as part of eclampsia (which did not recur after successful treatment and had no additional risk factors increasing the likelihood of seizure relapse) were excluded from further analysis. Additionally, we excluded patients if it was found that their seizures induced by substance abuse, occurred after cessation of alcohol and/or narcotics use, or if they had acute psychiatric illnesses. Additionally, those patients whose documentation was incomplete were also excluded from the study. Out of 6265 screened patients, 6186 were included, while 79 (51 males and 28 females) were excluded due to the reasons mentioned above.

Prevalent cases were selected in the 2022 population. Incident cases of epilepsy were identified in 2011 and the incidence trend was followed up for the next 12 years.

The study was approved by the Ethics Committee of the Medical Faculty, University of Montenegro.

2.3. Statistical analysis

The prevalence of epilepsy, as a proportion of subjects affected by the disease, in the population of Montenegro, was calculated on December 31st, 2022. The incidence rates were calculated according to the year of epilepsy diagnosis. Population denominator data for the calculation of both incidence and prevalence was obtained from the 2011 national census by interpolation [18]. The 95 % confidence intervals (CI) for incidence and prevalence are based on Poisson's frequency distribution for rarely occurring events [19].

The crude incidence and prevalence were adjusted for age using the method of direct standardization according to the European standard population and the WHO standard population [20,21].

Differences between mean values of continuous variables were tested using analysis of variance, while the proportions were compared using χ^2 test and the Fisher exact test, as appropriate.

A time trend analysis of epilepsy incidence as a function of time was performed using a linear regression model. A linear regression equation ($y = a + bx$) was used to estimate incidence trends over time while an F test was performed to estimate the significance of changes in annual incidence rates observed during the study period. The linear regression coefficient was tested using the Fisher's exact test.

3. Results

Clinical characteristics of patients with epilepsy in Montenegro during the period investigated are presented in Table 1.

From 2011 to 2022, 6186 patients, 3125 males (50.5 %) and 3061 females (49.5 %), living in Montenegro were suffering from epilepsy.

The average crude incidence rate of epilepsy for a 12-year period was 56.0/100,000 individuals; incidence rates between both genders were similar, just slightly higher in males (58.1/100,000 vs. 54.2/100,000, respectively). When adjusted by the European and WHO standard population, similar values of incidence rates were observed (52.4/100,000 and 49.6/100,000, respectively). A similar pattern of standardized incidence rates according to gender was shown, with a slightly lower incidence among females (57.2/100,000 vs. 47.5/100,000, using the

Table 1
Clinical characteristics of patients with epilepsy in Montenegro.

Clinical characteristic	Number of patients (%)
The classification of epileptic seizures*	
– focal onset	4521 (73.1)
– generalized onset	1480 (23.9)
– unknown	185 (3.0)
Diagnostic methods	
– Neurological examination	6186 (100)
– Electroencephalogram (EEG)	
– standard**	6186 (100)
– prolonged	613 (9.9)
– sleep deprived	1422 (23.0)
– Brain magnetic resonance imaging (MRI)	
– standard	3946 (63.8)
– according to the Protocol for epilepsy	878 (14.2)
– Computed Tomography (CT) scan	1362 (22.0)
Types of epilepsy	
– focal epilepsy	4492 (72.6)
– generalized epilepsy	1480 (23.9)
– focal and generalized epilepsy	29 (0.5)
– unknown	185 (3.0)
Etiology of epilepsy	
– genetic	1113 (18.0)
– structural	2719 (44.0)
– unknown	2354 (38.0)
Risk factors for epilepsy	
– febrile convulsion	91 (1.5)
– head trauma	583 (9.4)
– neuroinfection	181 (2.9)
– perinatal brain injury	150 (2.4)

* 2017 ILAE classification;
** at least once during the study period.

European standard population and 54.7/100,000 vs. 44.6/100,000, using WHO standard population, respectively) (Table 2).

The age-specific incidence for a 12-year period, showed a J-shaped curve, being lowest in the fourth and first half of the fifth decade of life (the 30 s, and early 40 s), and increasing thereafter, with an explosive increasing trend between the ages of 65 and 75 + years. A similar pattern was observed among both genders, with higher incidence rates in males in most age groups. The only age group with higher female incidence was observed in the 75 + group (Table 3). The incidence was higher than 180/100,000 persons in both genders in this age group.

The number of people with epilepsy and the corresponding population in each age group/gender/total and incidence rates during the period 2011–2022 are presented in the Supplementary file.

During the period studied (2011–2022), a statistically significant increasing trend of standardized epilepsy incidence rates (according to the European standard population) in Montenegro, was observed for the total population ($y = 62.977 + 1.326x$, $p = 0.024$), and for females ($y = 34.856 + 0.871x$, $p = 0.020$); upward trend registered for males also, but without statistical significance ($y = 35.206 + 0.729x$, $p = 0.156$) (Fig. 1a, 1b, and 1c). Similar relationships were obtained with adjustment according to the WHO standard population.

Table 2
Average crude and age-adjusted (/100,000) incidence rates of epilepsy in Montenegro, 2011–2022.

	Crude incidence rates (95 % CI)	Age-adjusted incidence rates (European standard population) (95 % CI)	Age-adjusted incidence rates (WHO standard population) (95 % CI)
Males	58.1 (56.5–59.7)	57.2 (55.8–58.6)	54.7 (53.2–56.2)
Females	54.2 (52.3–56.1)	47.5 (45.8—9.2)	44.6 (43.4–45.9)
Both genders	56.0 (54.4–57.6)	52.4 (51.3–53.5)	49.7 (48.5–50.7)

95% CI – confidence interval.

The crude overall prevalence of epilepsy on December 31, 2022, was 13.0 per 1000 individuals (95 % confidence interval 12.7–13.3), with the value of 13.5/1000 in males and 12.6/1000 in females. When adjusted by the European and WHO standard populations, a slight decline in prevalence rates was observed (12.8/1000 and 12.6/1000, respectively). A similar trend was noted among genders individually (13.4/1000 for males and 12.2/1000 for females using the European standard population, and 13.2/1000 in males and 12.1/1000 in females, using the WHO standard population, respectively) (Table 4).

The age-specific prevalence of epilepsy was highest in the early 20 s 15.0/1000, 11.4/1000 in the fourth decade, and afterward the rate steadily decreased; however, the highest age-specific prevalence of 20.0/1000 was observed in the seventh decade (Table 5). In men, prevalence decreases gradually from 16.4/1000 to 9.0/1000 at 45–54 years and then more steeply, especially after 65 years, reaching 21.5/1000 at 75 + years. In women, the initial tendency is similar, with slightly lower values than in men before reaching the lowest prevalence of 9.3/1000 between 45–54 years and then rising steeply as in men, with the highest prevalence reaching 18.9/1000 inhabitants in the age group above 75 years.

The number of people with epilepsy and the corresponding population in each age group/gender/total and prevalence on December 31, 2022 are presented in the Supplementary file.

4. Discussion

To our best knowledge, this is the first study to provide both the incidence and prevalence estimates of epilepsy at the Montenegrin national level. This retrospective, longitudinal study was based on healthcare records of all patients in the country. To improve diagnostic certainty, both patients and their records were reassessed and only those with confirmed diagnosis were included, as previously stated.

The average crude and age-standardized incidence rates of epilepsy in Montenegro during a 12-year period are estimated to be 56/100,000 and 52.4/100,000, respectively. These estimates align with those from other countries as reported in various studies [5], and recent *meta*-analysis in developed countries [3,11]. However, they are higher than rates reported in several studies from the United States and Europe, which ranged from 43/100,000 to 47/100,000 [22,23,8,9]. The incidence rates between both genders were similar, though slightly higher in males (58.1/100,000 vs. 54.2/100,000, respectively). Similar gender variations have also been reported in other studies [24,25]. The reasons behind these gender differences are various and possible reasons are the higher rate of traumatic brain injury [26,27] and higher prevalence of all developmental disabilities [28] in males compared to females. There are other studies, like that from Giussani et al. which reported lower incidence rates in the oldest age group, but under-ascertainment of cases was the probable reason for their finding [29].

Over a nine-year period, the incidence of epilepsy was lowest in the fourth decade and the first half of the fifth decade of life (the 30 s and early 40 s), increasing thereafter with a marked rise between the ages of 65 and 75 + years, where rates exceeded 180/100,000 in both genders. This trend formed a J-shaped curve, consistent in females, but with generally higher incidence rates in males across most age groups. Only slightly, the incidence rates were higher in females in the youngest age (18–24) and oldest age group in the study (75 +). This increase in epilepsy incidence could be attributed to factors such as the prevalence of certain epilepsy syndromes like juvenile myoclonic epilepsy, which is more common in women, and a longer life expectancy. These age-dependent incidence trends were similar to previously reported studies [8,9,30].

This study found a statistically significant increasing trend of standardized epilepsy incidence rates for both the total population and for females (according to both European and WHO standard populations). In our population, it was difficult to attribute the increase of epilepsy to a single cause. An especially intriguing aspect was the notion of a

Table 3
Age- and gender-specific incidence rates of epilepsy in Montenegro, 2011–2022.

Age groups (years)	Males		Females		Both genders	
	Inc/100,000	95 %CI	Inc/100,000	95 %CI	Inc/100,000	95 %CI
18–24	42.6	39.2—46.1	42.7	40.3—45.1	42.6	40.0—45.3
25–34	45.9	41.7—50.0	26.7	24.3—29.1	36.5	34.0—38.9
35–44	40.4	38.2—42.6	26.4	24.8—28.0	33.3	31.8—34.9
45–54	41.8	38.4—45.3	28.2	25.3—31.1	34.9	32.4—37.4
55–64	53.5	50.6—56.4	50.9	45.6—56.3	52.1	48.2—56.1
65–74	94.7	92.2—97.2	93.5	90.0—96.9	93.8	91.0—96.6
75+	180.2	172.8—187.6	184.1	181.4—186.9	181.4	177.3—185.4

Inc – incidence, 95% CI – confidence interval.

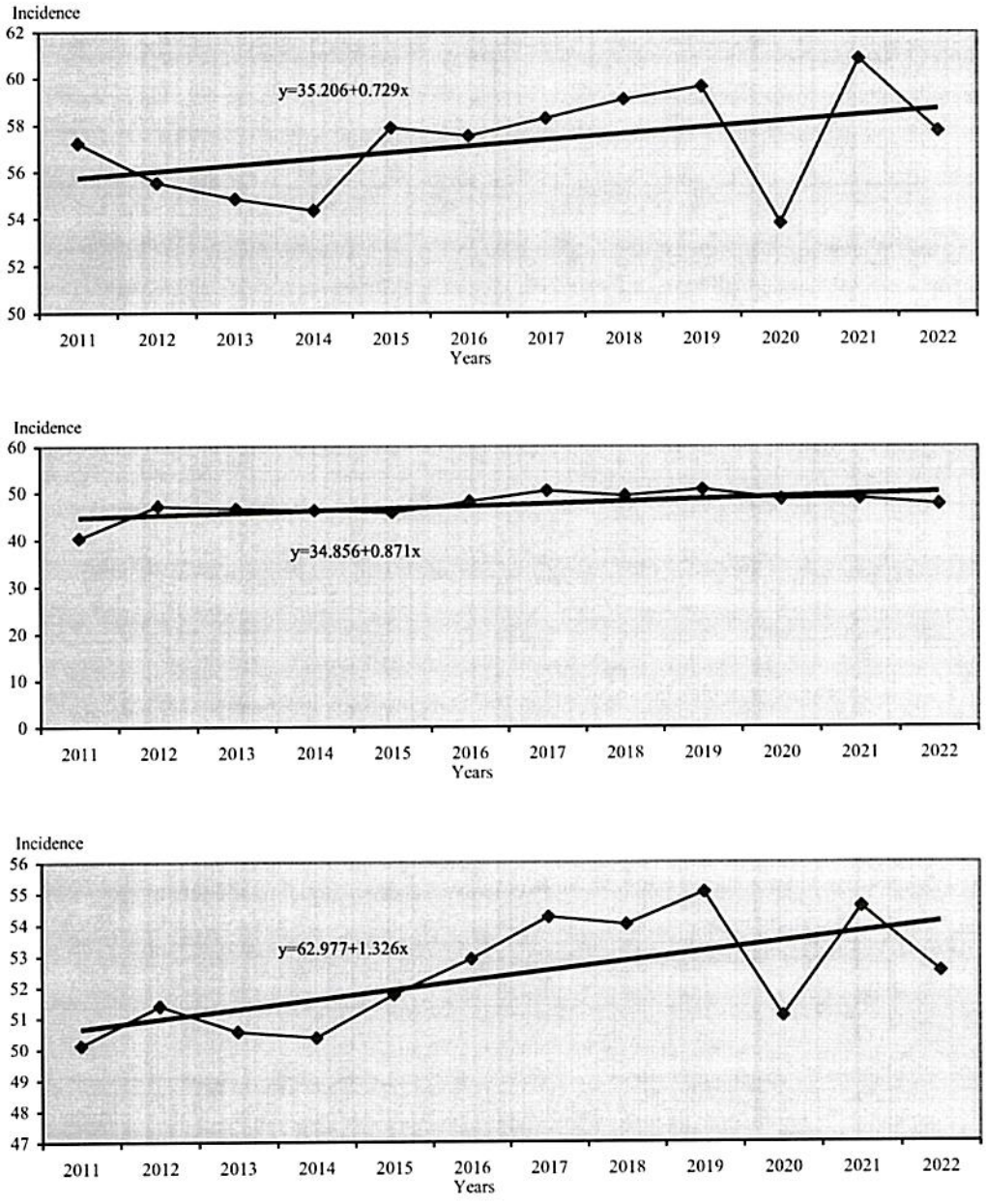

Fig. 1. A trend of standardized epilepsy incidence rates (according european standard population) in males, in montenegro, 2011–2022.

steadily increase in epilepsy among females. Epilepsy is a chronic disorder caused by various possible causes. Anything that disturbs the normal pattern of neuronal activity, such as abnormal brain development, illness (immune-mediated, infectious, metabolic, and genetic disorders) or trauma can lead to seizures. We can only speculate what could have led to new cases of epilepsy in our population:

Table 4
Age-adjusted (/1000) prevalence of epilepsy on December 31, 2022 in Montenegro.

	Crude prevalence (95 % CI)	Age-adjusted prevalence (European standard population) (95 % CI)	Age-adjusted prevalence (WHO standard population) (95 % CI)
Males	13.5 (12.7—14.4)	13.4 (12.6—14.2)	13.2 (12.4—14.1)
Females	12.6 (11.8—13.4)	12.2 (11.5—13.0)	12.1 (11.3—12.8)
Both genders	13.0 (12.2—13.9)	12.8 (12.0—13.6)	12.6 (11.9—13.4)

95% CI – confidence interval.

inadequate prenatal and postnatal care of women from rural areas, an increase of motor vehicle accidents, inadequate management of high blood pressure, poor diet, poor education, and social deprivation, although we did not analyze changes in risk factors profile in our epilepsy patients over time, due to missing data. Variations in the incidence of epilepsy over time are related to the quality of incidence data, which can be limited by various factors in this disease. Continuous and systematic registration of patients certainly has an advantage over retrospective analyses, and the influence of both stigmatization of patients and traditional social norms, on the quality of incidence data in our country, cannot be ruled out. Similar trends were observed in the neighboring country of Macedonia [15]. Increasing trends in both incidence and prevalence were also noted in Korea, where an aging population and a rise in chronic central nervous system illnesses were cited as primary factors. Conversely, there has been a noted increase in the incidence of epilepsy among older individuals in developed countries [7–9], while some studies have reported a significant decline in epilepsy incidence among children and adults, with a concurrent increase among the elderly [10].

Trends regarding incidence and prevalence have been reviewed in several studies. The results so far are conflicting. In a study from Korea, both incidence and prevalence increased during respective follow-up period, primarily due to aging and improved survival rates in people with chronic central nervous system illnesses [12]. Conversely, a recent study from Canada, demonstrated a stabile decline over a five-year period time, due to better perinatal and neonatal care, universal vaccination, and better method of ascertainment for the diagnosis of epilepsy through a drug use database [13].

This study found the crude overall prevalence of epilepsy on December 31, 2022, of 13.0/1000 (95 % CI 12.7–13.3). Even when adjusted by the European and WHO standard populations, only a slight decline in prevalence rates was observed which is higher than figures reported in many European countries [11,2,22,29,31,32]. Our results are therefore also much higher than those detected in the European Union in 2017 by the Global Burden of Disease Study (3.6/1000) [33], Korea in 2009 [34] (3.8/1000), and Japan in 2019 (6.0/1000) [35]. Conversely, our prevalence is lower compared to data coming from Africa and South America (151000 in sub-Saharan Africa and 18/1000 in Latin America) [36]. Studies from our neighboring countries that investigated the epidemiology of epilepsy reported a lower prevalence (4.9/1000, 6.7/1000, and 6.3/1000, respectively) [14,15,17], except for the study from the Croatian County of Sibenik–Knin, which reported significantly higher crude lifetime prevalence of 11.1/1000 [16]. Nevertheless, these studies cannot be directly compared with ours, primarily because of the different methodological approaches used.

Contrary to incidence, which shows a typical J or U shape due to high rates in the first year of life, prevalence might progressively rise or be steady throughout childhood [37,38]. The steep rise in the prevalence of epilepsy in the second half of life, more pronounced in men than in women, was observed not only in ours but in many other studies [31,33,35,39] This result may be explained mainly by cardiovascular comorbidities, in particular stroke, traumatic brain injuries, mainly due to falls or firearms accidents, and an increase of age-related diseases who undoubtedly show epileptogenic potential [11,27,40,41,42]. In our study, the highest prevalence in men was noted in the age group 65 and more 21.6/1000 (95 %CI 19.7—23.7), whereas in women, although the initial tendency was similar, the highest prevalence reached 18.9/1000 (95 %CI 17.0—21.0) in the age group above 75 years. This aligns with the common fact that women have a longer life expectancy and better survival rates compared to men [42,43]. These data suggest that more aggressive treatment of modifiable risk factors should be implemented, although all countries around the globe face this challenge.

As suggested by Bell et al., the estimated prevalence of epilepsy may be broadly similar worldwide. However, comparisons are limited by the scarcity of door-to-door studies in high-income economies and variations in the definitions of several clinical determinants of epilepsy [32].

This study has certain limitations; they primarily relate to the method of establishing cases and collecting data. Retrospective design could be a source of selection bias and potentially lead to an underestimation of the incidence and prevalence of epilepsy. Retrospective data collection is associated with a large number of missing variables, which affects their completeness and accuracy. Additionally, we limited the research only to health institutions, and thus not be able to include cases of epilepsy that never came to a health facility and were not treated. However, we assume that these cases are almost rare and that the degree of under ascertainment is low. Therefore, a direct population survey is the most important way to acquire epidemiological data [44].

5. Conclusion

The incidence of epilepsy in Montenegro is similar to those registered in other European countries, with an increasing trend during the period 2011–2022, while epilepsy prevalence was higher compared to the other studies. Although our findings are based on an examination of hospital records and therefore should be interpreted with caution, these results could be of importance for future health care and services planning.

CRediT authorship contribution statement

Sanja Gluscevic: Writing – review & editing, Writing – original

Table 5
Age- and gender-specific prevalence of epilepsy on December 31, 2022 in Montenegro.

Age groups (years)	Males		Females		Both genders	
	Prev/1000	95 %CI	Prev/1000	95 %CI	Prev/1000	95 %CI
18–24	16.4	15.0—17.9	13.5	12.3—14.7	15.0	14.1 – 15.9
25–34	11.3	10.3—12.3	11.6	10.6 – 12.7	11.4	10.7—12.2
35–44	11.5	10.6—12.6	10.3	9.3—11.3	10.9	10.2—11.6
45–54	9.0	8.2 – 9.9	9.2	8.3 – 10.1	9.1	8.5—9.7
55–64	14.2	12.9—15.6	12.0	11.0—13.2	13.1	12.3—13.9
65–74	21.6	19.7—23.7	18.5	16.9—20.2	19.9	18.6—21.1
75+	21.5	19.2—24.1	18.9	17.0—21.0	20.0	18.4—21.6

Prev – Prevalence, 95% CI – confidence interval.

draft, Investigation, Formal analysis, Data curation. **Slavica Vujsic:** Writing – review & editing, Supervision, Conceptualization. **Aleksandar Ristic:** Writing – review & editing, Investigation, Conceptualization. **Tatjana Pekmezovic:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This study was supported by the Ministry of Science, Technological development and Innovation of the Republic of Serbia (grant no. 200110).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2024.110065.

References

[1] Fisher RS, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005;46(4):470–2. https://doi.org/10.1111/j.0013-9580.2005.66104.x.
[2] Beghi E. The epidemiology of epilepsy. Neuroepidemiology 2020;54:185–91. https://doi.org/10.1159/000503831.
[3] Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia 2010; 51(5):883–90. https://doi.org/10.1111/j.1528-1167.2009.02481.x.
[4] World Health organization Fact sheet no 999. In: Epilepsy, http://www.who.int/mediacentre/factsheets/fs999/en/; [Accessed on January 14, 2023].
[5] Kotsopoulos IAW, Van Merode T, Kessels FGH, De Krom MCTFM, Knottnerus JA. Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures. Epilepsia 2002;43:1402–9. https://doi.org/10.1046/j.1528-1157.2002.t01-1-26901.x.
[6] Banerjee PN, Filippi D, Allen HW. The descriptive of epilepsy-a review. Epilepsy Res 2009;85:31–45. https://doi.org/10.1016/j.eplepsyres.2009.03.003.
[7] Lavados J, Germain L, Morales A, Campero M, Lavados P. A descriptive study of epilepsy in the district of El Salvador, Chile, 1984–1988. Acta Neurol Scand 1992; 85:249–56. https://doi.org/10.1111/j.1600-0404.1992.tb04040.x.
[8] Olafsson E, Hauser WA, Ludvigsson P, Gudmundsson G. Incidence of epilepsy in rural Iceland: a population-based study. Epilepsia 1996;37:951–95. https://doi.org/10.1111/j.1528-1157.1996.tb00532.x.
[9] Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in rochester, minnesota: 1935–1984. Epilepsia 1993;34:453–68. https://doi.org/10.1111/j.1528-1157.1993.tb02586.x.
[10] Sillanpää M, Kälviäinen R, Klaukka T, Helenius H, Shinnar S. Temporal changes in the incidence of epilepsy in Finland: nationwide study. Epilepsy Res 2006;71: 206–15. https://doi.org/10.1016/j.eplepsyres.2006.06.017.
[11] Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon CS, Dykeman J, et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology 2017;88(3):296–303. https://doi.org/10.1212/WNL.0000000000003509.
[12] Jeon JY, Lee H, Shin JY, Moon HJ, Lee SY, Kim JM. Epidemiology committee of korean epilepsy society increasing trends in the incidence and prevalence of epilepsy in korea. J Clin Neurol. 2021;17(3):393–9. https://doi.org/10.3988/jcn.2021.17.3.393.
[13] Hernández-Ronquillo L, Thorpe L, Pahwa P, Téllez-Zenteno JF. Secular trends and population differences in the incidence of epilepsy. A population-based study from Saskatchewan, Canada. Seizure 2018;60:8-15. doi: 10.1016/j.seizure.2018.05.018.
[14] Bielen I, Cvitanovic-Sojat L, Bergman-Markovic B, Kosicek M, Planjar-Prvan M, Vuksic L, et al. Prevalence of epilepsy in Croatia: a population-based survey. Acta Neurol Scand 2007;116(6):361–7. https://doi.org/10.1111/j.1600-0404.2007.00881.x.
[15] Babunovska M, Boskovski B, Kuzmanovski I, Isjanovska R, Kiteva Trencevska G, Cvetkovska E. Incidence and prevalence of epilepsy in the republic of north macedonia: data from nationwide integrated health care platform. Seizure 2021; 87:56–60. https://doi.org/10.1016/j.seizure.2021.03.003.
[16] Josipovic-Jelic Z, Sonicki Z, Soljan I, Demarin V. Collaborative group for study of epilepsy epidemiology in sibenik-knin county, croatia. prevalence and socioeconomic aspects of epilepsy in the croatian county of sibenik-knin: community-based survey. Epilepsy Behav 2011;20(4):686–90. https://doi.org/10.1016/j.yebeh.2011.02.008.
[17] Pezelj N, Titlić M, Lusić I. Epilepsija u Splitsko-dalmatinskoj regiji - prevalencija i terapijski pristupi [Epilepsy in the Split-Dalmatia county - prevalence and therapeutic approaches]. Acta Med Croat 2009;63(2):153–7.
[18] MONSTAT. https://www.monstat.org ⟩ file ⟩ saopstenje; [accessed 14th February 2023].
[19] Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia 2017;58(4):531–42. https://doi.org/10.1111/epi.13671.
[20] Lilienfeld D. Stolley. foundations of epidemiology. New York: Oxford University Press; 1994.
[21] Ahmad OB, Boschi-Pinto C, Lopez AD. Age Standardization of Rates: A New WHO Standard. GPE Discussion Paper Series: No 31. World Health Organization, Geneva, 2001.
[22] Forsgren L, Beghi E, Oun A, Sillanpää M. The epidemiology of epilepsy in Europe – a systematic review. Eur J Neurol 2005;12:245–53. https://doi.org/10.1111/j.1468-1331.2004.00992.x.
[23] Annegers JF, Dubinsky S, Coan SP, Newmark ME, Roht L. The incidence of epilepsy and unprovoked seizures in multiethnic, urban health maintenance organizations. Epilepsia 1999;40:502–6. https://doi.org/10.1111/j.1528-1157.1999.tb00748.x.
[24] Sanders J, Shorvon SD. The epilepsies. In: Martyn C, Hughes R, editors. Epidemiology of Neurological Diorders. BMJ books; 1998. p. 138–67.
[25] Stephen LJ, Brodie MJ. Epilepsy in elderly people. Lancet 2000;355:1441–6. https://doi.org/10.1136/bmj.331.7528.1317.
[26] Rao DP, McFaull S, Thompson W, Jayaraman GC. Trends in self-reported traumatic brain injury among Canadians, 2005–2014: a repeated cross-sectional analysis. C Open 2017;5:e301–7. https://doi.org/10.9778/cmajo.20160115.
[27] Nguyen R, Fiest KM, McChesney J, Kwon CS, Jette N, Frolkis AD, et al. The international incidence of traumatic brain injury: a systematic review and meta-analysis. Can J Neurol Sci 2016;43(6):774–85. https://doi.org/10.1017/cjn.2016.290.
[28] Boyle CA, Boulet S, Schieve LA, Cohen RA, Blumberg SJ, Yeargin-Allsopp M, et al. Trends in the prevalence of developmental disabilities in US children, 1997–2008. Pediatrics 2011;127:1034–42. https://doi.org/10.1542/peds.2010-2989.
[29] Giussani G, Cricelli C, Mazzoleni F, Cricelli I, Pasqua A, Pecchioli S, et al. Prevalence and incidence of epilepsy in Italy based on a nationwide database. Neuroepidemiology 2014;43(3–4):228–32. https://doi.org/10.1159/000368801.
[30] Christensen J, Vestergaard M, Pedersen MG, Pedersen CB, Olsen J, Sidenius P. Incidence and prevalence of epilepsy in Denmark. Epilepsy Res 2007;76:60–5. https://doi.org/10.1016/j.eplepsyres.2007.06.012.
[31] Syvertsen M, Nakken KO, Edland A, Hansen G, Hellum MK, Koht J. Prevalence and etiology of epilepsy in a Norwegian county - a population based study. Epilepsia 2015;56:699–706. https://doi.org/10.1111/epi.12972.
[32] Bell GS, Neligan A, Sander JW. An unknown quantity- the worldwide prevalence of epilepsy. Epilepsia 2014;55(7):958–62. https://doi.org/10.1111/epi.12605.
[33] Deuschl G, Beghi E, Fazekas F, Varga T, Christoforidi KA, Sipido E, et al. The burden of neuro- logical diseases in Europe: an analysis for the global burden of disease study 2017. Lancet Public Health 2020;5(10):e551–67. https://doi.org/10.1016/S2468-2667(20)30190-0.
[34] Lee SY, Chung SE, Kim DW, Eun SH, Kang HC, Cho YW. Committee on epidemiology of korean epilepsy society estimating the prevalence of treated epilepsy using administrative health data and its validity: ESSENCE Study. J Clin Neurol. 2016;12:434–40. https://doi.org/10.3988/jcn.2016.12.4.434.
[35] Kurisu A, Sugiyama A, Akita T, Takumi I, Yamamoto H, Iida K, et al. Incidence and prevalence of epilepsy in Japan: a retrospective analysis of insurance claims data of 9,864,278 insured persons. J Epidemiol 2024;34(2):70–5. https://doi.org/10.2188/jea.JE20220316.
[36] Mac TL, Tran DS, Quet F, Odermatt P, Preux PM, Tan CT. Epidemiology, aetiology, and clinical management of epilepsy in Asia: a systematic review. Lancet Neurol 2007;6:533–43. https://doi.org/10.1016/S1474-4422(07)70127-8.
[37] Helmers SL, Thurman DJ, Durgin TL, Pai AK, Faught E. Descriptive epidemiology of epilepsy in the U.S. population: a different approach. Epilepsia 2015;56:942–8. https://doi.org/10.1111/epi.13001.
[38] Kim H, Thurman DJ, Durgin T, Faught E, Helmers S. Estimating epilepsy incidence and prevalence in the US pediatric population using nationwide health insurance claims data. J Child Neurol 2016;31:743–9. https://doi.org/10.1177/0883073815620676.
[39] GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:459-480. doi: 10.1016/S1474-4422(18)30499-X.
[40] Ip Q, Malone DC, Chong J, Harris RB, Labiner DM. An update on the prevalence and incidence of epilepsy among older adults. Epilepsy Res 2018;139:107–12.
[41] Beghi E, Giussani G. Aging and the epidemiology of epilepsy. Neuroepidemiology 2018;51(3–4):216–23. https://doi.org/10.1159/000493484.
[42] GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol 2021;20:795-820. doi: 10.1016/S1474-4422(21)00252-0.
[43] Béjot Y. Forty years of descriptive epidemiology of stroke. Neuroepidemiology 2022;56:157–62. https://doi.org/10.1159/000525220.
[44] Thurman DJ, Beghi E, Begley CE, Berg AT, Buchhalter JR, Ding D, Hesdorffer DC, Hauser WA, Kazis L, Kobau R, Kroner B, Labiner D, Liow K, Logroscino G, Medina MT, Newton CR, Parko K, Paschal A, Preux PM, Sander JW, Selassie A, Theodore W, Tomson T, Wiebe S. ILAE commission on epidemiology. standards for epidemiologic studies and surveillance of epilepsy. Epilepsia 2011;52(Suppl 7): 2–26. https://doi.org/10.1111/j.1528-1167.2011.03121.x.