Title: Independent associations of incident epilepsy, enzyme-inducing, and non-enzyme-inducing antiseizure medications with the development of osteoporosis: a population-based analysis

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Authors:

Colin B Josephson MD, MSc[1,2,3,4,5]; Arturo Gonzalez-Izquierdo PhD[6,7]; Spiros Denaxas PhD[6,7,8]; Tolulope T. Sajobi PhD[1,2,3,4]; Karl Martin Klein MD PhD[1,2,3,9,10]; Samuel Wiebe MD, MSc[1,2,3,4,11]

Affiliations

1. Department of Clinical Neurosciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada
2. Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, AB
3. Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada
4. O'Brien Institute for Public Health, University of Calgary, Calgary, AB, Canada
5. Centre for Health Informatics, University of Calgary, Calgary, AB, Canada
6. UCL Institute of Health Informatics, London, UK
7. Health Data Research (HDR) UK
8. Alan Turing Institute, London, UK
9. Department of Medical Genetics, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
10. Alberta Children's Hospital Research Institute, University of Calgary, Calgary, Alberta, Canadalberta
11. Clinical Research Unit, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

Author for correspondence: Colin Josephson MD, MSc, FRCPC, Associate Professor of Neurology, Cumming School of Medicine, University of Calgary, Foothills Medical Centre, 1403 – 29 St NW, Calgary, Alberta, CANADA T2N 2T9, Ph: (403) 283 2270, Fax: (403) 283-2270

Key points

Question: What is the risk of incident osteoporosis following incident adult-onset epilepsy and antiseizure medication (ASM) use?

Findings: Time to incident osteoporosis is 41% faster following incident adult-onset epilepsy (time ratio [TR] 0.59; 95% confidence interval [95%CI] 0.52-0.67), independent of ASM use. The time is 23% faster (TR 0.77; 95%CI 0.76-0.78) when exposed to non-enzyme inducing ASMs and 9% faster (TR 0.91; 95%CI 0.87-0.95) for enzyme inducing ASMs, independent of epilepsy.

Meaning: Both the development of epilepsy and use of ASMs, irrespective of enzyme-inducing capacity, was associated with increased hazards for osteoporosis.

ABSTRACT

Importance: Both epilepsy and enzyme-inducing antiseizure medications (eiASM) having varying reports of association with increased risks for osteoporosis.

Objective: To quantify and model the independent hazards for osteoporosis.

Design: Observational open cohort study covering years 1998-2019 with a median follow-up of 5 years (interquartile range [IQR] 1.7-11.1).

Setting: Population-based linked primary care and hospital electronic health records.

Participants: All patients enrolled in Clinical Practice Research Datalink (CPRD). Patients were required to have CPRD-Acceptable data, be ≥18 years old, have follow-up after the HES patient care linkage date of 1998, and be free of osteoporosis at baseline.

Exposure: Incident adult-onset epilepsy using a 5-year washout and receipt of four consecutive antiseizure medications (ASMs).

Main outcomes and measures: The outcome was incident osteoporosis as determined through Cox proportional hazards or accelerated time failure models where appropriate. Incident epilepsy was treated as a time-varying covariate. Analyses controlled for age, sex, socioeconomic status, cancer, 1+ years of corticosteroid use, BMI, bariatric surgery, eating disorders, hyperthyroidism, inflammatory bowel disease, rheumatoid arthritis, smoking status, falls, fragility fractures, and osteoporosis screening tests. Subsequent analyses (i) excluded BMI, which was missing in 30% of patients, (ii) applied propensity matching for receipt of an eiASM, (iii) restricted analyses to only those with incident onset epilepsy, and (iv) restricted analyses to the cohort of people that developed epilepsy at age ≥65.

Results: Of 8,095,441 adults, we identified 6,275 people with incident adult-onset epilepsy (incidence rate 62 per 100,000 person-years) with a median age of 56 (IQR 38-73) and 3,220 (51%) were female. When controlling for osteoporosis risk factors, incident epilepsy was independently associated with an increased risk for osteoporosis (time ratio [TR] 0.59, 95% 0.52-0.67; p<0.001) as were eiASMs (TR 0.91, 95%CI 0.87-0.95; p<0.001) and non-eiASMs (TR 0.77, 95%CI 0.76-0.78; p<0.001). The independent associations between epilepsy, eiASMs, and non-eiASMs remained consistent in propensity matched analyses, cohorts restricted to adult-onset epilepsy, and cohorts restricted to late-onset epilepsy.

Conclusions and relevance: Epilepsy is independently associated with a clinically meaningful increase in the risk for osteoporosis, as are both eiASMs and non-eiASMs. Routine screening and prophylaxis should be considered in all people with epilepsy.

Key Words: epilepsy, cohort study, osteoporosis, enzyme-inducing antiseizure medications, electronic heath records

INTRODUCTION

Active epilepsy affects almost 50 million people worldwide with age-standardised disability adjusted life-years of 182.6 per 100 000 population[1]. Although seizures account for a substantial proportion of this burden, epilepsy-associated comorbidities also exert significant influence. Osteoporosis is of particular interest given its association with high rates of fractures, morbidity, and mortality[2].

The mechanisms behind the association between epilepsy and osteoporosis remain opaque. Considerable focus has centred on the putative role of antiseizure medications (ASMs). Both enzyme-inducing (eiASMs) and non-enzyme-inducing ASMs (non-eiASMs) have been associated with increased risks of fractures in a meta-analysis of case-control and cohort studies[3]. Certain ASMs, especially carbamazepine, are associated with enhanced vitamin D metabolism and accelerated bone turnover[4]. Despite this, studies have often yielded conflicting results regarding the effects of ASMs, even for eiASMs such as carbamazepine, on bone density[4]. Importantly, no studies performed to date have examined these associations at a population level with specific focus on a clinical diagnosis of osteoporosis.

Our objectives were to quantify the hazard of osteoporosis following incident epilepsy and ASM exposure in the general population. We also sought to determine if the hazard related to eiASMs is elevated compared to non-eiASMs in people with incident adult-onset epilepsy and late-onset epilepsy.

METHODS

Database

This study was carried out as part of the CALIBER © resource (https://www.ucl.ac.uk/health-informatics/caliber and https://www.caliberresearch.org/). CALIBER, led from the UCL Institute of Health Informatics, is a research resource providing validated electronic health record phenotyping algorithms and tools for national structured data sources[5,6]. The CALIBER resource (https://www.ucl.ac.uk/health-informatics/caliber)[11] contains UK nationally linked structured electronic health records (EHR) data from primary care, hospital care, and a cause-specific mortality registry up to March 31, 2019.

Study design

This was a retrospective open cohort study of patients aged >18 years. Primary care records are obtained from Clinical Practice Research Datalink (CPRD) which uses Read codes[7] version 2 for medical events and the British National Formulary to document prescriptions[8,9]. These data are linked to the Hospital Episode Statistics (HES) database, which contains secondary care and administrative data. Coding in HES uses the International Classification of Diseases (ICD-10) and the Office of Population Censuses and Surveys Classification of Interventions and Procedures terminology (OPCS-4). We followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for this study.

Case ascertainment and study population

We used the Secure Anonymised Information Linkage (SAIL) databank (Wales, UK) 'Epilepsy Only' case definition for epilepsy[10]. This definition has a sensitivity of 88% and specificity of 98% for identifying people with epilepsy in the SAIL dataset. The SAIL dataset is of a comparable data source to CPRD[10,11] (Appendix 1). We extracted an incident cohort of patients using a five-year washout from the CPRD-Acceptable Data Quality Date[11]. This comprises an epoch over which a patient cannot have received any codes for seizures or epilepsy, thus maximising chances of incident diagnoses. Because the risks of osteoporosis are particularly elevated in older adults, we also extracted a cohort of incident late-onset epilepsy, which was restricted to those diagnosed at age ≥65[12].

Exposure and outcome definitions

Incident epilepsy was the primary exposure. Medication exposure was defined by receiving four consecutive prescriptions for an ASM. Furthermore, we defined exposure to eiASM as all four prescriptions being for an eiASM (median time between first and fourth prescriptions was 4 months; interquartile range, 'IQR' = 3-7 months). We defined exposure to non-eiASM as at least the 4th prescription being for a non-eiASM. We chose four consecutive prescriptions given the assumption that the patient must be tolerating the medication with enough efficacy to merit continued use over multiple visits. We considered carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, rufinamide, and topiramate to be eiASMs[13]. In a sensitivity analysis, we categorized ASMs as strong inducers (carbamazepine, phenobarbital, phenytoin, and primidone)[14], weak inducers (including topiramate and oxcarbazepine)[14], and non-eiASMs. The outcome (endpoint of the analysis) was incident

osteoporosis as defined and validated in the CALIBER data resource[15]. This definition comprises diagnostic and investigational Read, Med, and ICD-10 codes (https://portal.caliberresearch.org/phenotypes/kuan-osteoporosis-wp8ckuqqpyvjznrhp27hgg). To identify the independent associations, age, sex, socioeconomic status (defined using the Index of Multiple Deprivation 2015 [IMD] which is divided into deciles; 1 being the lowest socioeconomic status and 10 being the highest[16]), cancer, 1+ years of corticosteroid use, body mass index (BMI), bariatric surgery, eating disorders, hyperthyroidism, inflammatory bowel disease, rheumatoid arthritis, and smoking history[17,18] were included as covariates in regression models. We also adjusted for falls and fragility fractures with the rationale that people with epilepsy may be more prone to both due to seizures, thus prompting investigations that could reveal previously undiagnosed osteoporosis. Likewise, we also controlled for osteoporosis screening (dual energy X-ray absorptiometry [DEXA], quantitative computed tomography, or serum bone turnover markers performed at any point in those without osteoporosis or prior to the diagnosis of osteoporosis in those who developed incident disease). Failure to include fragility fractures, falls, and osteoporosis screening could lead to inflated estimates of association due to ascertainment bias if not accounted for in the analyses. All covariates were defined using the Health Data Research UK's CALIBER Phenotype Library portal phenotypes (https://portal.caliberresearch.org/)[5,15,19].

Statistical Analyses

We used chi-squared (categorical) and Kruskal-Wallis (continuous) tests to compare demographic and clinical characteristics between those with and without incident epilepsy. In

the primary analysis we determined the hazard of incident osteoporosis using Cox proportional hazards models only after testing proportional hazards assumptions with the scaled Schoenfeld residuals[20]. If the model failed the proportional hazards assumption, we used an accelerated failure time model, reporting a time ratio (TR). The TR is the ratio of the time it takes for the exposed to develop the condition of interest compared to the unexposed. Thus, a TR of <1.0 means the exposed develops the condition quicker. For these analyses, the index date was the CPRD-Acceptable Data Quality Date. All people were followed until incident osteoporosis or last follow-up. Incident epilepsy was treated as a time-varying covariate, whereby all people start as unexposed. The person then moves from the unexposed to exposed group on the date that they develop epilepsy, thus mitigating risk of immortal time bias[21].

In an *a priori* sensitivity analysis, we repeated the primary analysis but omitted BMI, since it was missing in 2,417,807 (30%) of people. We then repeated the primary analysis using a propensity matched model. Propensity scores for eiASMs exposure were developed using the Matchit package in R[22]. For the propensity score, we considered the following as factors that could influence eiASM prescription: age at diagnosis, sex, an age by sex interaction term (to account for young females of child-bearing age), hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation, cirrhosis, chronic kidney disease, cancer, steroid use, depression, anxiety, psychosis, suicidal ideation, obesity (BMI >29.9), socioeconomic status[23]. We evaluated matching performance using mean standard error and graphical distributions of propensity scores. We used k-nearest neighbours to match the exposed and unexposed based on individual-level propensity scores. To directly compare the hazard of eiASMs to non-eiASMs, we then repeated

the primary analysis but isolated the population to only those 6,275 people with incident adult-onset epilepsy, using a dichotomous ASM variable (0=non-eiASM, 1=eiASM) in regression models. Finally, we repeated these steps on a pre-existing cohort where all 1,048 incident late-onset epilepsy patients in the database were matched 1:10 to controls based on age, sex, and GP-practice and the same methodology was applied as per the primary analysis. For this model, the index date was that on which the person turned 65.

All statistical analyses were performed using Stata version 16.1 (StataCorp LP)[24] and R version 3.6.2[25]. We considered p-values of <0.05 to be significant.

Ethics

The study was approved by the MHRA (UK) Independent Scientific Advisory Committee [17_064RA3], under Section 251 (NHS Social Care Act 2006). Patient consent is waived due to the de-identified nature of the data

RESULTS

Patient population

We identified 18,410,930 patients of whom 16,071,111 (87%) had CPRD-Acceptable data. Of these, 10,916,166 were ≥18 years old and 8,267,161 had follow-up after the HES patient care linkage date of 1998. A total of 8,095,441 were free of osteoporosis prior to the CPRD-Acceptable Data Quality Date and incident epilepsy date. Of these people, 51,123 (0.6%) had prevalent epilepsy. Prevalent cases were removed leaving 6,275 with incident epilepsy

(incidence rate 62 per 100,000 person-years and incidence proportion 78 per 100,000). Compared to the 8,095,166 controls, the 6,275 people with incident epilepsy were older (median age 56, interquartile range, 'IQR', 38-73 *versus* median age 42, IQR 30-60) and were statistically more likely to be exposed to an ASM (100% *versus* 3%; p<0.001), to be on an eiASM (18% *versus* 0.5%; p<0.001), have a higher BMI (median 25.4, IQR 22.5-29 *versus* 24.7, IQR 22-28.1; p<0.001), have cancer (15% *versus* 6%; p<0.001), hyperthyroidism (2% *versus* 1%; p<0.001), or inflammatory bowel disease (2% *versus* 1%; p<0.001), have used steroids consecutively for at least 1-year (12% *versus* 3%; p<0.001), have vitamin D deficiency (2% *versus* 0.8%; p<0.001, lower serum calcium levels (2.28, IQR 2.21-2.36 mmol/L *versus* 2.31, IQR 2.24-2.38 mmol/L), and have had bariatric surgery (0.3% *versus* 0.1%; p<0.001; Table 1). Median duration of ASM exposure was 8.9 years (IQR 4.8-14.8 years).

Hazard of osteoporosis in the general population

Survival analysis using a Cox proportional hazards model treating incident epilepsy as a time-varying covariate failed the proportional hazards assumption (global p<0.001). In addition, an interaction between age and cancer was uncovered. The hazard of osteoporosis following cancer diagnosis was unexpectedly lower than those without cancer. However, this can be explained because the relative hazard in the old and young with cancer would be anticipated to be close to 1, whilst the relative hazard between the old and young without cancer is expected to be >1. Thus, the ratio of the hazard ratio (HR) of osteoporosis in the old *versus* young with cancer and the HR of the old *versus* young without cancer is expected to be below 1. This was confirmed by computing the HR associated with an age by cancer interaction term which is

significantly below 1 (HR 0.96; 95% confidence interval [95%CI] 0.96-0.97; p<0.001). When adjusting for the interaction term, cancer was significantly associated with incident osteoporosis.

We therefore used an adjusted accelerated failure time model with a Weibull distribution treating incident epilepsy as a time-varying covariate and incorporating an interaction term between age and cancer. Incident epilepsy was associated with a TR of 0.59 (95%CI 0.52-0.67; p<0.001) for incident osteoporosis (Tables 2 and 3; Figure 1). Median time from epilepsy diagnosis to incident osteoporosis was 2.5 years (IQR 1.0-5.0 years). Both eiASMs (TR 0.91; 95%CI 0.87-0.95; p<0.001) and non-eiASMs (TR 0.77; 95%CI 0.76-0.78; p<0.001) were also associated with statistically significant increased risks independent of epilepsy. The association between non-eiASM use and osteoporosis remained consistent when valproic acid was excluded from this group (TR 0.77; 95%CI 0.75-0.78; p<0.001). Median time from ASM exposure to incident osteoporosis was 4.1 years (IQR 1.5-8.7 years). These estimates remained consistent in a sensitivity analysis in which BMI was omitted due to 30% missing values ($TR_{epilepsy}$ = 0.54; 95%CI 0.48-0.62; p<0.001; TR_{eiASM} = 0.90; 95%CI 0.86-0.94; p<0.001; $TR_{non\text{-}eiASM}$ = 0.76; 95%CI 0.74-0.77; p<0.001). In a second sensitivity analysis, strong inducers and non-eiASMs were associated with accelerated times to osteoporosis ($TR_{strong\ inducer}$ = 0.91; 95%CI 0.87-0.95; p<0.001 and $TR_{non\text{-}eiASM}$ = 0.74; 95%CI 0.73-0.76; p<0.001) whilst there was a trend for weak inducers ($TR_{weak\ inducer}$ = 0.89; 95%CI 0.79-1.01; p=0.092). This likely relates to underpowering, since only 4% of ASM prescriptions were for weak inducers.

Hazard of osteoporosis in an eiASM propensity matched cohort.

A 5:1 subcohort of controls to eiASM exposed cases was generated through propensity matching on measures that could predict prescription behaviour (n=193,225 controls and 38,645 exposed to four consecutive eiASMs). The mean standard difference between matched eiASM and non-eiASM groups was ≤0.01 for all variables apart from age, age by sex interaction, psychosis, and suicidal ideation l (e-Table 1), and propensity scores were evenly distributed between the matched eiASM and non-eiASM patients (e-Figures 1 and 2).

The model again failed the proportional hazards assumption (global test <0.001), so we proceeded with an accelerated failure time model using incident epilepsy as a time-varying covariate and incorporating an interaction term between age and cancer. In this propensity matched analysis, incident epilepsy was significantly associated with incident osteoporosis (TR 0.72; 95%CI 0.47-0.97; p=0.011; e-Table 2), as were non-eiASMs (TR 0.80; 95%CI 0.74-0.86; p<0.001) and eiASMs (TR 0.89; 95%CI 0.84-0.94; p<0.001).

Hazard of osteoporosis secondary to eiASMs versus non-eiASMs in incident epilepsy patients.

When restricting the cohort to the 6,275 patients with incident adult-onset epilepsy, we had to omit bariatric surgery due to the relative lack of cases. The survival model failed proportional hazards assumptions (global p-value =0.035). An accelerated failure time model incorporating an age by cancer interaction term revealed the risk of incident osteoporosis did not differ significantly between eiASMs and non-eiASMs (TR 1.01; 95%CI 0.86-1.18; p=0.87; Table 4). The

estimates did not change when BMI was omitted ($TR_{eiASEMs}$ *versus* $TR_{non\text{-}eiASMs}$ 1.01; 95%CI 0.87-1.18; p=0.84).

Hazard of osteoporosis in incident late-onset epilepsy.

This analysis involved 11,143 people (1,048 with late-onset epilepsy and 10,095 controls). The survival model for late-onset epilepsy failed proportional hazards assumptions (global p-value <0.001). Using an accelerated failure time model incorporating an age by cancer interaction term, late-onset epilepsy is associated with an elevated risk of incident osteoporosis (TR 0.81; 95%CI 0.72-0.90; p<0.001), as were non-eiASMs (TR 0.90; 95%CI 0.83-0.97; p=0.007). The association was not statistically significant for eiASMs (TR 0.95; 95%CI 0.81-1.11; p=0.56; e-Table 3). This may be due to underpowering since only 298 (3%) of the patients in this analysis were exposed to eiASMs, compared to 1696 (15%) who were exposed to non-eiASMs and 9,149 (82%) who lacked exposure to any ASMs.

DISCUSSION

This study demonstrates a clear and robust association between incident adult-onset epilepsy and incident osteoporosis, independent of medications, common risk factors, fragility fractures, and falls. There are also clear and independent associations between both eiASM and non-eiASM use and incident osteoporosis, independent of incident epilepsy. This risk continued to rise over 15 years following epilepsy diagnosis (Table 3; Figure 1). These associations remained consistent in propensity matched analyses, cohorts restricted to incident adult-onset epilepsy, and all cases of incident late-onset epilepsy. Finally, the hazard related to late-onset epilepsy

was comparable to that of adult-onset epilepsy, indicating the risk does not appear to be further elevated in an older population.

These findings corroborate and build upon prior studies. Few report the hazard related to epilepsy alone, especially at a population level, but focus instead on ASM use. The prevailing theory has been that eiASMs convey a higher risk than non-eiASMs due to interactions with the cytochrome P450 system. This could accelerate metabolism of vitamin D, leading to compensatory increases of parathyroid hormone. Parathyroid hormone releases active vitamin D metabolites in an attempt to replenish stores, but the undesirable consequence is increased bone turnover[4]. However, prior studies have reported conflicting results on the effects of ASMs. Some indicate that strong inducers, like carbamazepine, decrease bone density and bone turnover[26], whilst others have reported no association[27]. Consistent with our results, prior literature has highlighted that even non-eiASM use, such as valproate[28] and levetiracetam[29], is associated with low bone mass density, with effect sizes comparable to or even greater than eiASMs[30]. The risk attributable to eiASMs appears comparable to non-eiASMs in Alzheimer's disease (HR 1.10; 95%CI 0.77-1.57)[31], a finding consistent with our analyses in a general population with and without epilepsy.

Incident adult-onset epilepsy, independent of ASM use, appears to accelerate time to osteoporosis by approximately 41% compared to the general population. The underlying mechanisms linking epilepsy and osteoporosis have been insufficiently studied compared to the role of ASMs. Population-based investigations indicate people with epilepsy are less likely to

participate in physical activity and have lower rates of fruit and vegetable consumption, which are known risk factors for osteoporosis[18,32,33]. More sedentary behaviours and remaining homebound may also lead to reduced sun exposure in people with epilepsy[34]. Accidents and falls are common in epilepsy[35], and could increase risk for subsequent osteoporosis[18].

This highlights the importance of risk mitigation in all people with epilepsy. However, a recent large randomized controlled trial revealed daily supplementation with 2000 IU of vitamin D did not reduce the risk of bone loss over two years or factures over five years when compared to placebo, even when calcium was concomitantly administered[36,37]. Thus, although, vitamin D deficiency and lower serum calcium was more common in people with epilepsy (Table 1), controlling for supplementation would likely have minimal effect on our conclusions. There may still be benefit in those with low baseline free 25-hydroxyvitamin D levels[37], meaning efforts to study routine supplementation in all people with epilepsy are paramount given their risks of deficiency. The effects of supplemental calcium on fracture risk has been varied, and caution should be exerted recommending daily doses of >1000-1500 mg[17]. Algorithms for routine screening through lab work and bone mass densitometry should be validated and deployed for all people with epilepsy, given early detection could improve outcomes[38].

Strengths of this study include its large population-based cohort that is representative of the general UK populace. The epilepsy clinical phenotype has a high sensitivity and specificity[10], whilst the outcome and covariate definitions have all been validated as part of the CALIBER programme[15]. We captured all event data at multiple levels of primary and hospital-care. The

effect size related to epilepsy, eiASMs, and non-eiASMs remained robust and consistent through multiple analyses including standard survival analyses using time-varying methodology, propensity-matched models, adjustment for co-variates, and within specific sub-populations.

There are limitations. The assumption was that people taking four consecutive ASMs remained on this class of medication. We cannot guarantee that all prescriptions were enduring, but previous analyses applying similar methodology have validated the assumption[23]. Additionally, median prescription duration (time from first to last documented prescription) was almost 9 years, suggesting adherence. Our analyses lack granular data on epilepsy type, seizure type, and seizure frequency. Using a population-based study, though, we captured the full spectrum of disease, and by adjusting for falls, fragility fractures, and enhanced screening we have accounted for the major features of epilepsy and seizures that can confer risk or increase detection of osteoporosis. Theoretically, this could have led to greater detection rates for osteopenia in people with epilepsy, leading to disproportionate use of prophylactic treatment compared to controls. However, in a general population of older women, median time for 10% of the those with mild and moderate osteopenia to transition to osteoporosis was 17.3 and 4.7 years respectively[39]. Hence, intervention would be unlikely to prevent osteoporosis at a rate to nullify results in our population and, in the unlikely case it did, would mean our results represent a conservative estimate of even higher effect sizes. However, this limitation is critical to note since, theoretically, the effect sizes for both epilepsy and eiASMs could be even higher than we report given both likely prompt intensive screening strategies in modern clinics.

Our study has demonstrated robust and clinically meaningful independent associations between incident epilepsy and both eiASM and non-eiASM use with incident osteoporosis. This further consolidates the need for enhanced vigilance and consideration of prophylaxis for all people with epilepsy. People with epilepsy are more likely to be deficient in vitamin D[40], and those who are deficient may still benefit from routine supplementation[37]. Randomized controlled trials studying this approach universally in epilepsy are expediently required, as are evidence-based algorithms for routine osteoporosis screening irrespective of ASM type.

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DECLARATIONS AND CONFLICTS OF INTEREST

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Declarations:

- CBJ has received unrestricted educational grants from UCB Pharma Inc. and Eisai Inc. for work unrelated to this project.
- AG-I has nothing to declare.
- SD has nothing to declare.
- TTS has nothing to declare.
- KMK reports personal fees from UCB Pharma, Novartis Pharma AG, Eisai, and GW Pharmaceuticals unrelated to this project, grants from the federal state Hessen, Germany, through the LOEWE program and from the Canadian Institutes of Health Research for work unrelated to this project.
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All authors (except if noted below) declare that they have no conflicts of interest.

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FIGURES

Figure 1. Nelson-Aalen cumulative hazard graph of the risk of incident osteoporosis following incident diagnosis of adult-onset epilepsy. An initial five-year washout was applied to maximise the chances that the epilepsy is incident. Incident diagnosis of epilepsy is treated as a time-varying covariate and therefore everyone is unexposed for the first five years of follow-up. Patients remain unexposed until they develop epilepsy, at which exact point they switch from the unexposed to the exposed curve. The number of people with incident epilepsy thus rises as more people develop the condition and then falls as people either develop osteoporosis or are censored at last follow-up. Analysis time is in days and cumulative hazard for incident osteoporosis defines the y-axis. The red line is epilepsy with surrounding 95% confidence intervals (lighter red) whilst the blue line is non-epilepsy controls with surrounding 95% confidence intervals (lighter blue).

TABLES

TABLE 1: Demographic and clinical characteristics of the general population and incident adult-onset epilepsy patients identified between 1998 and 2019.

	Full cohort	**No epilepsy**	**Incident epilepsy**	**p-value***
n	8,095,441	8,089,166	6275	-
Age (IQR)	42 (30-60)	42 (30-60)	56 (38-73)	<0.001
Female sex	4,198,306 (52%)	4,195,086 (52%)	3,220 (51%)	0.387
IMD (IQR)	5 (4-6)	5 (4-6)	5 (4-6)	0.419
Ex- or current smoker	2,904,250 (36%)	2,902,182 (36%)	2,068 (33%)	<0.001
ASMs	275,526 (3%)	269,251 (3%)	6,275 (100%)	<0.001
eiASM	37,543 (0.5%)	36,406 (0.5%)	1,137 (18%)	<0.001
BMI	24.7 (22-28.1)	24.7 (22-28.1)	25.4 (22.5-29)	<0.001
Eating disorder	53,666 (1%)	53,604 (1%)	62 (1%)	0.001
Cancer	495,207 (6%)	494,294 (6%)	913 (15%)	<0.001
Hyperthyroidism	74,528 (1%)	74,425 (1%)	103 (2%)	<0.001
Inflammatory bowel disease	60,763 (1%)	60,663 (1%)	100 (2%)	<0.001
Rheumatoid arthritis	55,052 (1%)	54,976 (1%)	76 (1%)	<0.001
1+ consecutive years of steroid use	221,613 (3%)	220,891 (3%)	722 (12%)	<0.001
Vitamin D deficiency	66,467 (0.8%)	66,334 (0.8%)	133 (2%)	<0.001
Serum Ca^{2+} mmol/L (IQR)	2.31 (2.24-2.38)	2.31 (2.24-2.38)	2.28 (2.21-2.36)	0.001
Bariatric surgery	7,235 (0.1%)	7,219 (0.1%)	16 (0.3%)	<0.001
Osteoporosis screen**	901,312 (11%)	899,301 (11%)	2,011 (32%)	<0.001
Imaging	145,968 (2%)	145,548 (2%)	420 (7%)	<0.001
Bone turnover markers	793,677 (28%)	791,950 (10%)	1,727 (28%)	<0.001

Fragility fracture	432,187 (5%)	431,460 (5%)	727 (12%)	<0.001
Incident osteoporosis	142,203 (2%)	141,715 (2%)	488 (8%)	<0.001

*p-value is comparison between incident adult-onset epilepsy and no epilepsy

** Osteoporosis screening constitutes imaging (dual energy X-ray absorptiometry [DEXA] and quantitative computed tomography) and serum bone turnover markers and fragility fractures (both which prompt further investigations) performed at any point in those without osteoporosis or prior to the diagnosis of osteoporosis in those who developed incident disease.

ASM = antiseizure medication; BMI = body mass index; eiASM = enzyme-inducing antiseizure medication; IMD = index of multiple deprivation; IQR = interquartile range

TABLE 2: Results of the accelerated time failure model for incident osteoporosis stratified by an incident diagnosis of epilepsy. The index date is that of the CPRD-Acceptable Data Quality Date. Incident epilepsy is treated as a time-varying covariate with a five-year washout from the CPRD-Acceptable Data Quality Date. Time ratios are reported which is the ratio of the time to incident osteoporosis in those exposed *versus* those unexposed for each variable. Time ratios for continuous variables relate to each 1-unit increment in specific measure.

Characteristic	Time ratio	95% confidence interval	p-value
Incident epilepsy	0.59	0.52-0.67	<0.001
eiASM*	0.91	0.87-0.95	<0.001
Non-eiASM*	0.77	0.76-0.78	<0.001
Age	0.95	0.95-0.96	<0.001
Female sex	0.29	0.29-0.30	<0.001
IMD	1.06	1.06-1.07	<0.001
Bariatric surgery	1.20	1.01-1.43	0.037
Cancer	0.11	0.10-0.12	<0.001
One-year corticosteroids	0.56	0.55-0.57	<0.001
Eating disorder	0.56	0.53-0.60	<0.001
BMI	1.03	1.02-1.03	<0.001
Hyperthyroidism	0.99	0.96-1.02	0.538
Inflammatory bowel disease	0.63	0.61-0.65	<0.001
Rheumatoid arthritis	0.61	0.60-0.63	<0.001
Ex- or current smoker	0.91	0.89-0.91	<0.001
Falls	0.86	0.85-0.87	<0.001
Fragility fracture	0.32	0.32-0.33	<0.001
Osteoporosis screen**	0.57	0.57-0.58	<0.001
Age x cancer interaction	1.02	1.02-1.03	<0.001

*compared to no ASM use

** Osteoporosis screening constitutive dual energy X-ray absorptiometry (DEXA), quantitative computed tomography, or serum bone turnover markers performed at any point in those without osteoporosis or prior to the diagnosis of osteoporosis in those who developed incident disease.

BMI = body mass index; eiASM = enzyme-inducing antiseizure medication; non-eiASM = non-enzyme-inducing antiseizure medication; IMD = Index of Multiple Deprivation (divided into deciles; the higher the number, the less socially deprived the area).

TABLE 3: Nelson-Aalen cumulative hazard for incident osteoporosis following a diagnosis of incident epilepsy controlling for ASM use and common osteoporosis risk factors. Incident epilepsy is treated as a time-varying covariate.

Time	No epilepsy	Incident epilepsy
0 years	0.00	0.00
5 years	0.02	0.03
7 years	0.03	0.05
10 years	0.04	0.07
15 years	0.06	0.13

TABLE 4: Results of the accelerated time failure model for incident osteoporosis in a cohort restricted to 6275 people with incident epilepsy. The index date is that of the CPRD-Acceptable Data Quality Date. Incident epilepsy is treated as a time-varying covariate with a five-year washout from the CPRD-Acceptable Data Quality Date. Time ratios are reported which is the ratio of the time to incident osteoporosis in those exposed *versus* those unexposed for each variable. Time ratios for continuous variables relate to each 1-unit increment in specific measure. Bariatric surgery was excluded due to no cases.

Characteristic	Time ratio	95% confidence interval	p-value
eiASM*	1.01	0.86-1.18	0.870
Age	0.98	0.97-0.98	<0.001
Female sex	0.59	0.51-0.67	<0.001
IMD	1.04	1.01-1.07	0.003
Cancer	0.35	0.18-0.68	0.002
One-year corticosteroids	0.67	0.58-0.77	<0.001
Eating disorder	0.89	0.49-1.61	0.710
BMI	1.02	1.01-1.03	<0.001
Hyperthyroidism	1.13	0.78-1.65	0.498
Inflammatory bowel disease	0.72	0.53-0.99	0.049
Rheumatoid arthritis	0.67	0.50-0.90	0.007
Ex- or current smoker	0.93	0.83-1.05	0.285
Falls	0.82	0.72-0.92	0.002
Fragility fracture	0.46	0.40-0.53	<0.001
Osteoporosis screen**	0.78	0.70-0.88	<0.001
Age x cancer interaction	1.01	1.01-1.02	0.001

*compared to non-eiASM use

** Osteoporosis screening constitutive dual energy X-ray absorptiometry (DEXA), quantitative computed tomography, or serum bone turnover markers performed at any point in those without osteoporosis or prior to the diagnosis of osteoporosis in those who developed incident disease.

BMI = body mass index; eiASM = enzyme-inducing antiseizure medication; non-eiASM = non-enzyme-inducing antiseizure medication; IMD = Index of Multiple Deprivation.