# Osteoporosis: The Brittle Reality of an Epilepsy Diagnosis

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**Independent Associations of Incident Epilepsy and Enzyme-Inducing and Non-Enzyme-Inducing Antiseizure Medications With the Development of Osteoporosis**

Josephson CB, Gonzalez-Izquierdo A, Denaxas S, Sajobi TT, Klein KM, Wiebe S. *JAMA Neurol*. 2023;80(8):843-850. doi:10.1001/jamaneurol.2023.1580

Importance: Both epilepsy and enzyme-inducing antiseizure medications (eiASMs) having varying reports of an association with increased risks for osteoporosis. Objective: To quantify and model the independent hazards for osteoporosis associated with incident epilepsy and eiASMS and non-eiASMs. Design, Setting, and Participants: This open cohort study covered the years 1998 to 2019, with a median (IQR) follow-up of 5 (1.7-11.1) years. Data were collected for 6275 patients enrolled in the Clinical Practice Research Datalink and from hospital electronic health records. No patients who met inclusion criteria (Clinical Practice Research Datalink-acceptable data, aged 18 years or older, follow-up after the Hospital Episode Statistics patient care linkage date of 1998, and free of osteoporosis at baseline) were excluded or declined. Exposure: Incident adult-onset epilepsy using a 5-year washout and receipt of 4 consecutive ASMs. Main Outcomes and Measures: The outcome was incident osteoporosis as determined through Cox proportional hazards or accelerated failure time models where appropriate. Incident epilepsy was treated as a time-varying covariate. Analyses controlled for age, sex, socioeconomic status, cancer, 1 or more years of corticosteroid use, body mass index, bariatric surgery, eating disorders, hyperthyroidism, inflammatory bowel disease, rheumatoid arthritis, smoking status, falls, fragility fractures, and osteoporosis screening tests. Subsequent analyses (1) excluded body mass index, which was missing in 30% of patients; (2) applied propensity score matching for receipt of an eiASM; (3) restricted analyses to only those with incident onset epilepsy; and (4) restricted analyses to patients who developed epilepsy at age 65 years or older. Analyses were performed between July 1 and October 31, 2022, and in February 2023 for revisions. Results: Of 80 95 441 adults identified, 6275 had incident adult-onset epilepsy (3220 female [51%] and 3055 male [49%]; incidence rate, 62 per 100 000 person-years) with a median (IQR) age of 56 (38-73) years. When controlling for osteoporosis risk factors, incident epilepsy was independently associated with a 41% faster time to incident osteoporosis (time ratio [TR], 0.59; 95% CI, 0.52-0.67; $P < .001$). Both eiASMs (TR, 0.91; 95% CI, 0.87-0.95; $P < .001$) and non-eiASMs (TR, 0.77; 95% CI, 0.76-0.78; $P < .001$) were also associated with significant increased risks independent of epilepsy, accounting for 9% and 23% faster times to development of osteoporosis, respectively. The independent associations among epilepsy, eiASMs, and non-eiASMs remained consistent in propensity score-matched analyses, cohorts restricted to adult-onset epilepsy, and cohorts restricted to late-onset epilepsy. Conclusions and Relevance: These findings suggest that 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.

## Commentary

The concept of a "brain-bone axis" gained traction in the 1900s.[1] Extensive research has explored the connection between epilepsy and endocrine function, particularly in the context of changes in the hypothalamic-pituitary axis. Beyond anticipated endocrine effects, there is a growing recognition of an abnormal environment in the central nervous system having additional impacts on bone health. This has sparked increased interest in understanding the bidirectional relationship between the brain and bone, considering factors like cytokine release, the blood–brain barrier, and the regulatory roles of these organs. One could then reasonably hypothesize that the diagnosis of a brain disorder, such as epilepsy, might influence bone health.

Osteoporosis progressively reduces bone density and bone microarchitecture elevating the risk of fractures over time. In 1994, the World Health Organization defined osteoporosis on a bone mineral density (BMD), using a T-Score 25% lower than

the average 30-year-old or $\leq -2.5$ standard deviations below the mean.[2] The International Osteoporosis Foundation provides staggering statistics, noting a global occurrence of an osteoporosis fracture every 3 seconds and pointing out that with a demographic shift toward older age groups, these numbers are rapidly increasing. The paper at hand by Josephson et al[3] highlights the incidence of osteoporosis in epilepsy, which can be equally or sometimes more detrimental to a patient's quality of life than seizures themselves. With this background, the authors discuss osteoporosis as a significant comorbid condition, not solely attributable to enzyme inducing anti-seizure medications (ASMs) as previously acknowledged but potentially associated independently with the diagnosis of epilepsy.

The authors used a population level analysis to establish the risk of osteoporosis in incident epilepsy. The study revealed that an epilepsy diagnosis was linked to a 41% faster time to the onset of newly diagnosed osteoporosis. The Fracture Risk Assessment Tool (FRAX) considers various factors such as age, sex, BMI, history of fractures, smoking status, steroid use, rheumatoid arthritis, secondary osteoporosis, heavy alcohol use, and femoral neck BMD for 10-year fracture risk calculation.[4] Given the study's results, there may be a rationale to explore the inclusion of epilepsy as an additional risk factor if further studies support these findings.

Regarding ASMs use, the study found that enzyme inducing ASMs showed a 9% association but surprisingly, even non-enzyme inducing ASMs were associated with 23% faster time to osteoporosis. Traditionally, cytochrome p450 enzyme induction due to ASMs is linked to lower vitamin D levels, secondary hyperparathyroidism, and subsequently increasing bone catabolism.[5-7] A majority of prior literature on mechanisms and causality-based studies predict that this action plays an important role in the development of osteoporosis. The present study groups ASMs into strong, weak, and non-enzyme inducers however does not identify individual ASMs. If certain ASMs in the non-enzyme inducing group lead to a higher risk, potential shared mechanisms other than enzyme induction could be identified to explain the increased bone turnover. Although this retrospective population level study provides valuable insights, additional research is needed to fully elucidate the linkage between ASMs without enzyme induction and osteoporosis. Other questions that remain unanswered are whether the doses of ASMs have any significance. Furthermore, the data regarding effects on bone metabolism is limited for newer ASMs and will be important as they see growing utilization in clinical practice.

Another interesting aspect is that the incident epilepsy sample differed from the general population in several aspects such as older age group, presence of inflammatory bowel disease, use of steroids, higher BMI, low vitamin D, low calcium levels, and bariatric surgery. These notable differences in various risk factors suggest that patients with epilepsy might generally be more predisposed to osteoporosis and the risk may be multifactorial.

Despite the authors' attempts to adjust for multiple confounders, the study may not be able to capture all relevant risk factors comprehensively, for example heavy alcohol use or diagnosis of other inflammatory conditions. The authors did not account for the frequency of convulsive seizures and injuries except for falls or fractures which could potentially exert a deleterious effect on the brain-bone axis. Certain limitations exist in the sample and chosen subgroups for analysis. Postmenopausal women face a heightened risk of osteoporosis, fractures, and associated morbidity.[8] While the authors presented data for age >65, the risk for postmenopausal women was not specifically addressed. The data analysis lacks another significant classifier—race. There is evidence suggesting racial disparities exist in osteoporosis diagnosis.[9] Unfortunately, race and ethnicity information were only available for a minority in the dataset leading to exclusion for the analysis.

The study took measures to prevent over inflation of estimates by controlling for bone turnover testing, falls, and fractures. The statistical methods employed by the authors to provide accurate measures on a population level are commendable. The paper's strength lies in its focus on incident epilepsy, allowing the authors to establish a population-level connection between newly diagnosed epilepsy and osteoporosis by excluding the prevalence cohort. The duration median ASM exposure was 8.9 (4.8-14.8) years in the incident epilepsy population. Controlling for ASM use there was an accrued risk for osteoporosis over 15 years. However longer follow-ups would be necessary for a more robust understanding of the cumulative effects of long-term ASMs use in epilepsy and bone metabolism.

In the broader context, various neurological conditions like multiple sclerosis, Parkinson disease, acute stoke are associated with a change in the "brain-bone axis."[1] This poses the question of whether the risk of osteoporosis in epilepsy is different, elevated, or comparable to other neurological conditions. As acknowledged by the authors, factors such as sedentary lifestyle, poor diet, and lack of exercise could contribute to this accelerated rate of bone damage. However, whether these contribute significantly and specifically to osteoporosis associated with epilepsy requires additional research to provide more insight into this matter.

Indeed, in clinical practice, the epileptologist may be more vigilant about the risk of osteoporosis associated with enzyme inducing ASMs. This paper brings to our attention the necessity of maintaining alertness when providing a diagnosis of epilepsy regardless of ASM choices. The question at hand is the optimal timing for checking bone density scans and bone turnover markers and whether these should be recommended for every individual with epilepsy? If further studies show similar results, this could represent a paradigm shift in current clinical practice.

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## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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