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The mortality burden attributable to non-trauma fracture for privately insured adults with epilepsy

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Summary

Objective: Individuals with epilepsy have poor bone development and preservation throughout the lifespan, and are vulnerable to non-trauma fracture (NTFx) and post-NTFx complications. However, no studies have examined the contribution of NTFx to mortality among adults with epilepsy. The objective was to determine if NTFx is a risk factor for mortality among adults with epilepsy.

Methods: Data from 2011-2016 were obtained from Optum Clinformatics® Data Mart; a nationwide claims database from a single private payer in the United States. Diagnosis codes were used to identify adults (≥18 years) with epilepsy, NTFx, and covariates (demographics and pre-NTFx cardiovascular disease, respiratory disease, diabetes, chronic kidney disease, cancer). Crude mortality rate per 100 person years was estimated. Cox regression estimated hazard ratios (HR and 95% confidence interval [CI]) for mortality, comparing epilepsy and NTFx (EP+NTFx; n=11,471), epilepsy without NTFx (EP without NTFx; n=50,384), without epilepsy and with NTFx (without EP+NTFx; n=423,041), and without epilepsy and without NTFx (without EP without NTFx; n=6.8M) after adjusting for covariates.

Results: The 3-, 6-, and 12-month crude mortality rates were highest among EP+NTFx (12-month mortality rate=8.79), followed by without EP+NTFx (12-month mortality rate=4.80), EP without NTFx (12-month mortality rate=3.06), and without EP without NTFx (12-month mortality rate=0.47). After adjustments, the mortality rate was elevated for EP+NTFx for all time points compared to EP without NTFx (e.g., 12-month HR=1.70; 95%CI=1.58-1.85), without EP+NTFx (e.g., 12-month HR=1.41; 95%CI=1.32-1.51), and without EP without NTFx (e.g., 12-month HR=5.23; 95%CI=4.88-5.60). Stratified analyses showed higher adjusted HRs of 12-month mortality for EP+NTFx for all NTFx sites (i.e., vertebral column, hip, extremities), all age categories (young, middle-aged, older), and for women and men.

Significance: Among adults with epilepsy and compared to adults without epilepsy, NTFx is associated with a higher 12-month mortality rate. Findings suggest that NTFx may be a robust risk factor for mortality among adults with epilepsy.

Keywords: epilepsy; mortality; non-trauma fracture

Introduction

Individuals with epilepsy typically require long-term treatment with antiseizure medications to prevent seizures. Seizures and antiseizure medications are well established factors for inadequate skeletal development in children,[1] leading to low bone mineral density and elevated fracture rate among children with epilepsy, in comparison to children without epilepsy.[2, 3] Three to four out of five adults with epilepsy have skeletal fragility (e.g., low bone mineral density),[4, 5] and fracture risk is considerably elevated among adults with epilepsy compared to the general population (relative risk, 1.7 to 6.2).[6]

Among the elderly general population, skeletal fragility- especially non-trauma fracture (NTFx)- is a primary contributor to loss of function,[7] chronic disease development,[8] poor quality of life,[9] and premature mortality.[7, 10, 11] Moreover, health status prior to sustaining a fracture is a strong predictor of post-fracture health, function, and survival outcomes.[7] Therefore, adults with epilepsy may have greater risk of post-NTFx mortality because of their poor skeletal development and preservation throughout the lifespan and other unhealthful aging processes. Specifically, individuals with epilepsy have greater risk of chronic diseases across biological systems, including cardiometabolic, respiratory, gastrointestinal, liver, and other neurological diseases, as well as a variety of mental health disorders.[12-14] Further, there is strong evidence to suggest that individuals with epilepsy have greater risk of premature mortality compared to individuals without epilepsy.[15] However, the contribution of skeletal fragility to health and survival outcomes for adults with epilepsy has not been investigated.

A better understanding of the link between skeletal fragility and mortality risk is needed for this vulnerable population. If skeletal fragility does increase risk for mortality, clinicians caring for patients with epilepsy should be aware of the need for strategies to prevent skeletal fragility and intensively manage NTFx and its related sequela, with the ultimate goal of maximizing healthful aging throughout the lifespan. Accordingly, the objective of this study was to determine if NTFx among adults with epilepsy is associated with greater 12-month mortality rate compared to adults with epilepsy that do not sustain an NTFx and compared to adults without epilepsy that sustain an NTFx. We hypothesized that adults with epilepsy that sustain an NTFx would have greater post-NTFx 12-month mortality rate compared to both groups, suggesting that: (1) NTFx is a risk factor for 12-month mortality among adults with epilepsy; and (2) the NTFx associated 12-month mortality rate is exacerbated for adults with versus without epilepsy.

Methods

Data source

Data from 2011 to 2016 were extracted from Optum Clinformatics® Data Mart Database (OptumInsight™, Eden Prairie, MN, USA), which is an administrative claims database providing information from privately insured beneficiaries that had commercial or Medicare Advantage plans in the U.S.[16] This claims-based data include all health service utilization (e.g., inpatient, emergency department) for each individual throughout enrollment. To maintain patient confidentiality, researchers leveraging the Optum database are allowed either the Date of Death or Socioeconomic Status table. This study used the Date of Death table and some information regarding socioeconomic status (i.e., income, education) was not available. Data was de-identified and the University Institutional Review Board approved this study as non-regulated.

Sample selection

All medical conditions (e.g., epilepsy, fracture, comorbidities) were identified using the International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10), Clinical Modification codes to account for the shift in reporting codes on October 1, 2015, as previously described.[17] Information regarding how diagnoses were made or by whom (e.g., primary care physician) was not available in administrative claims data.

Adults ≥18 years of age with epilepsy were identified by at least one inpatient, outpatient, or emergency department claim for "epilepsy and recurrent seizures" (ICD-9, 345 family; ICD-10, G40 family) on at least two different days within 365 days of one another. Information regarding epilepsy etiology, type, or duration of diagnosis were either not available in claims data or not reliably coded (e.g., 46% had "unspecified" epilepsy), thus not allowing for stratification or statistical adjustment for the clinical subtypes of epilepsy. The group of adults without epilepsy included individuals with no claims for "epilepsy and recurrent seizures." Using claims to identify epilepsy has high sensitivity and specificity for clinical populations,[18] and the 2+ claim algorithm improves accuracy of identifying "non-event" medical conditions over a single claim (e.g., fracture is an "event").[19] For epilepsy, the 2+ algorithm has a positive predictive value of ~70%.[20]

We defined NTFx as a fracture without trauma codes (e.g., motor vehicle accident) 7 days before to 7 days after the index fracture date, as guided by previous studies.[17, 21, 22] Fractures of the vertebral column, hip (including proximal femur), non-proximal femur, tibia/fibula, humerus, ulna/radius, or unspecified location (ICD-9, 733.1 family, 805-813 families, 818-823 families, and 827-829 families; ICD-10, "initial encounter" codes from S12, S22, S32, S42, S52, S72, S82, and M80 families, M84.4, M84.6, and M84.7) were identified by at least one inpatient, outpatient, or emergency department claim between 2012 to 2015. This time frame was selected to allow for at least one full year of a "look back" period for those that fractured in 2012 to ascertain baseline comorbidity data and at least one full year of follow up for those that fractured in 2015 for the outcome. Using a single claim to capture fracture has excellent accuracy with up to 98% positive predictive value, which is similar or better than other algorithms (e.g., 2+ claims).[23]

The sample was then categorized based on epilepsy and NTFx status: (1) with epilepsy and NTFx (EP+NTFx); with epilepsy and without NTFx (EP without NTFx); without epilepsy and with NTFx (without EP+NTFx); and without epilepsy and without NTFx (without EP without NTFx). The start date of the follow up was the index date of NTFx or a randomly assigned date for those that did not sustain an NTFx. For the latter, we used a uniform distribution (visually inspected by author SB) to randomly assign a date during the individual's enrollment period between January 1, 2012 to December 31, 2015.

We included individuals that had at least 12 full months of continuous enrollment in a health plan prior to their start date of follow up to sequester baseline comorbidity data, as previously described.[19]

Outcome measure

All-cause mortality from 2012 to 2016 was determined as the number of days from the start date of follow up to date of death, and separated as 3-, 6-, and 12-month time points (6 and 12 months were cumulative).

Covariates

Covariates were selected based on their relevance to adults with epilepsy, NTFx, and mortality, as well as availability in the administrative claims databases. Sociodemographic

variables included age, sex, race, and US region of residence (West, Midwest, South, and Northeast). Baseline comorbidities were identified from 2011 to 2015 by at least: (1) one inpatient claim within the 12-months prior to the start date of follow up; or (2) two outpatient claims on different claim days within 365 days of one another, with the first outpatient claim occurring within the 12-months prior to the start date of follow up.[19] Comorbidities included cardiovascular disease (i.e., ischemic heart disease, heart failure, cerebrovascular disease), hypertension, diabetes (i.e., type 1, type 2), respiratory disease (i.e., acute respiratory infection, pneumonia, chronic obstructive pulmonary disease, interstitial/pleura disease, other respiratory disease), chronic kidney disease (stages I-V), or cancer anywhere in the body, as previously described.[17, 24]

Statistical analysis

Descriptive characteristics at baseline were summarized for each group. Mortality rates (MR) were estimated as the number of deaths divided by the amount of person-years, and expressed per 100 person years for each group. Mortality rate ratios (MRR) and 95% confidence intervals (CI) were estimated comparing each group to one another.

Cox regression was used to adjust for all covariates when comparing MR, by estimating hazard ratios (HR and 95% CI) of mortality at all time points, comparing each group to one another. The primary group comparisons of interest were: (1) EP+NTFx versus EP without NTFx to determine if NTFx is a risk factor for mortality among adults with epilepsy; and (2) EP+NTFx versus without EP+NTFx to determine if NTFx exacerbates MR for adults with versus without epilepsy. Possible interactions between exposure status and age or sex were assessed by conducting separate analyses for age or sex strata (to estimate group effects) and by including product terms in the Cox models (to test for interactions). Individuals were right censored if they discontinued health plan enrollment or were alive at the end of the study period.

We then examined crude MR and MRR and adjusted HR of 12-month mortality by NTFx location to identify site-specific effects using the procedures described above.

Sensitivity analysis

Cox regression did not adjust for race to limit bias due to missing data (~14%). We therefore conducted two related sensitivity analyses to assess possible confounding and selection

bias. Sensitivity analysis #1 involved the restricted study population with complete data on race but not adjusting for race; sensitivity analysis #2 involved the same study population in #1 but adjusted for race. Results were compared from sensitivity analyses #1 and #2 to assess possible confounding by race. Results were also compared from sensitivity analysis #1 (restricted study population not adjusting for race) and the main analysis (full study population not adjusting for race) to assess possible selection bias from exclusion of adults without race data.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline descriptive characteristics of EP+NTFx (n=11,471), EP without NTFx (n=50,384), without EP+NTFx (n=423,041), and without EP without NTFx (n=6,787,743) is presented in **Table 1**. Notably, the two NTFx groups were older and had a higher proportion of women than the two non-NTFx groups.

Crude mortality rate

The crude MR and MRR is presented in **Table 2**. The crude MR for all time points were highest for EP+NTFx (e.g., 12-month MR=8.79 per 100 person years), followed by without EP+NTFx (e.g., 12-month MR=4.80), EP without NTFx (e.g., 12-month MR=3.06), and without EP without NTFx (e.g., 12-month MR=0.47). The MR remained relatively stable for the two non-NTFx groups from 3-months to 12-months, but declined in the two NTFx groups. The crude MRR was elevated for EP+NTFx compared to EP without NTFx and without EP+NTFx for all time points. When without EP without NTFx was the reference, the crude MRR was elevated for all groups for all time points, with a larger decline in MRR for the two NTFx groups compared to the EP without NTFx group.

Cox regression analysis of mortality

Adjusted mortality HRs are presented in **Table 3**. Compared to without EP without NTFx, the HR adjusting for all covariates was highest for EP+NTFx across all time points (e.g., 12-month HR=5.23; 95% CI=4.88-5.60), followed by without EP+NTFx (e.g., 12-month HR=3.71; 95% CI=3.64-3.78) and EP without NTFx (e.g., 12-month HR=3.08; 95% CI=2.92-3.25). The adjusted HR comparing EP+NTFx to EP without NTFx was elevated for all time

points with the group effect becoming smaller from 3-months (HR=2.87; 95% CI=2.47-3.33) to 12-months (HR=1.70; 95% CI=1.58-1.85). The adjusted HR comparing EP+NTFx to without EP+NTFx was elevated for all time points with the group effect becoming larger from 3 months (HR=1.11; 95% CI=1.00-1.23) to 12-months (HR=1.41; 95% CI=1.32-1.51).

Site-specific effect of NTFx on 12-month mortality rate

Table 4 shows the MR, MRR, and adjusted HR of 12-month mortality stratified by NTFx location. The site-specific patterns of MR were consistent for the two NTFx groups: hip had the highest MR, followed by vertebral column and extremities. The crude MR and MRR was elevated for adults with versus without epilepsy for all sites. After adjusting for all covariates, the HR for adults with versus without epilepsy was elevated for all sites, with the lower extremities (HR=1.92; 95% CI=1.61-2.30) and upper extremities (HR=1.79; 95% CI=1.51-2.12) having the highest HR.

Interactions of group with age and sex

Table 5 (age) and **Table 6** (sex) shows the MR, MRR, and adjusted HR of mortality by age category (18-40, 41-64, and ≥65 years) and sex (both *P* for interaction <0.001). There were too few deaths in the EP without NTFx and EP+NTFx groups for 18-40 year age category for analyses (n≤40). EP+NTFx had an elevated MR, MRR, and adjusted HR compared to EP without NTFx and without EP+NTFx for the 41-64 year and ≥65 year age group and for both women and men. The ≥65 year age group for all groups by epilepsy and NTFx status had higher MR than the 18-40 and 41-64 year age groups. The absolute difference in MR for EP+NTFx versus EP without NTFx and without EP+NTFx was larger in the ≥65 year versus younger age groups, but the relative MRR was larger for EP+NTFx versus EP without NTFx and without EP+NTFx in the 41-64 year versus ≥65 year age group. Men had a higher MR for all groups compared to women. The absolute difference in MR was larger for men than women for EP+NTFx versus EP without NTFx and without EP+NTFx, and the relative MRR was larger for men than women for EP+NTFx versus EP without NTFx.

Sensitivity analysis

There were 6,257,223 individuals with complete data on race. The adjusted HR was higher for EP+NTFx versus EP without NTFx for 3 months (covariate adjusted and covariate+race HR rounded to the same values; both HR=2.98; 95% CI=2.54-3.50), 6 months (covariate adjusted HR=2.33; 95% CI=2.07-2.62: covariate+race HR=2.34; 95% CI=2.08-2.63), and 12 months (covariate adjusted HR=1.71; 95% CI=1.56-1.88: covariate+race HR=1.72; 95% CI=1.57-1.88). The adjusted HR was higher for EP+NTFx versus without EP+NTFx for 3 months (covariate adjusted HR=1.13; 95% CI=1.01-1.27: covariate+race HR=1.12; 95% CI=1.00-1.25), 6 months (covariate adjusted HR=1.31; 95% CI=1.20-1.43: covariate+race HR=1.29; 95% CI=1.18-1.41), and 12 months (covariate adjusted HR=1.43; 95% CI=1.33-1.54: covariate+race HR=1.41; 95% CI=1.31-1.52). A comparison of the HR estimates from sensitivity analysis #1 and #2 yielded similar results, suggesting that race is not a confounder in the main analysis. A comparison of HR estimates from sensitivity analysis #1 with results from the main analysis show similar results, suggesting no evidence of selection bias.

Discussion

Findings from this study suggest that the elevated mortality burden for adults with epilepsy[15] may be exacerbated by skeletal fragility. One main finding of this investigation is that NTFx was associated with mortality within 12 months among adults with epilepsy, suggesting that NTFx is a risk factor for mortality for this population. The other main finding of this investigation was that among those that sustained an NTFx, adults with epilepsy had higher rates of mortality within 12 months compared to adults without epilepsy, suggesting a greater NTFx-attributable mortality burden for adults with epilepsy. These findings were evident across NTFx sites and after accounting for covariates that are associated with premature mortality. Taken together, study findings suggest that NTFx, an indicator of skeletal fragility, may be implicated in the pathogenesis of unhealthful aging for adults with epilepsy.

A recent systematic review including 46 studies concluded that individuals with epilepsy are at risk for premature mortality.[15] While the burden of premature mortality varied among epilepsy-related factors (e.g., etiology), the standardized mortality ratios were still elevated for most studies regardless of age, sex, etiology, type, and time since diagnosis. In the elderly general population, fracture is associated with mortality[7, 10, 11] and chronic diseases,[8, 25] and post-fracture chronic disease development may be involved in the fracture-mortality association.[8, 25, 26]

The most common causes of death for individuals with epilepsy include chronic diseases (e.g., cardiovascular and respiratory disease), injuries (e.g., seizures, falls), and cancer.[15, 27-29] Therefore, the current study provides new potential insights into factors that may be involved directly with mortality or indirectly with mortality via early pathological processes for adults with epilepsy, as NTFx is an adverse outcome of injuries (e.g., seizures, falls) and increases risk of chronic diseases.

In the current study, the crude analysis found that MR was highest among EP+NTFx, followed by without EP+NTFx, EP without NTFx, and without EP without NTFx. Interestingly, the non-NTFx groups had a relatively consistent MR across the 3-, 6-, and 12-month time points, whereas the two NTFx groups had the highest MR at 3-months and a gradual decline to 12-months. Even with this decline, the MR was higher for all time points compared to the non-NTFx groups. This finding is consistent with the conviction that there may be a unique set of factors associated with short- and long-term mortality post-NTFx.[30] However, the mechanisms explaining the NTFx-induced mortality have yet to be elucidated and may be further confounded by the medical complexities of epilepsy (e.g., antiseizure medications).

We used Cox regression to adjust for demographics and several chronic diseases that are associated with NTFx and mortality to better understand the link between epilepsy, NTFx, and mortality beyond these covariates. In our primary comparisons of interest, we found that the adjusted rate of 3-, 6-, and 12-month mortality was higher for EP+NTFx compared to EP without NTFx and without EP+NTFx. Specifically, EP+NTFx had a 2.9-fold higher rate of mortality in the 3 months following the NTFx event compared to EP without NTFx. The adjusted risk declined over the time points, but still remained elevated with a 70% higher adjusted rate of mortality at 12-months. The adjusted rate of mortality for EP+NTFx compared to without EP+NTFx increased over the time points, from 11% higher rate at 3-months to 41% higher rate at 12-months.

When we stratified NTFx by location, we found that all sites were associated with higher adjusted 12-month mortality rate among adults with versus without epilepsy. However, we found that NTFx of the lower and upper extremities were associated with higher relative mortality rates compared to the hip and vertebral column (92%, 79%, 15%, and 30%, respectively). Although, it is important to note that the absolute mortality rate was still much higher for NTFx of the hip and vertebral column than extremities for adults with and without epilepsy. Therefore, NTFx at all of

these sites should be treated with urgency (e.g., aggressive monitoring and treatment interventions) for adults with epilepsy, and especially if NTFx occurs in the lower or upper extremities.

Finally, we found that the excess mortality burden attributable to NTFx for adults with epilepsy from the whole sample was consistent across the age spectrum (i.e., young, middle-aged, and older) and for women and men. However, we found that the group effect estimate was larger for middle-age than older age for EP+NTFx versus EP without NTFx and without EP+NTFx, and for men than women for EP+NTFx versus EP without NTFx. Taken together, these findings suggest that the NTFx-attributable mortality burden is more problematic for individuals with versus without epilepsy across the adult lifespan and for women and men, but that younger ages and men with epilepsy may have a higher relative vulnerability to the NTFx-mortality burden.

Pre-fracture diseases,[31] functional capcity,[32] and physical ability (e.g., muscle strength)[33] are risk factors for post-fracture premature mortality, and a follow up fracture further exacerbates mortality risk.[33] The systemic stress induced by an NTFx may create an unfavorable physiological environment that exacerbates risk for post-NTFx complications and premature mortality, either through direct or indirect mechanisms.[30] Individuals with epilepsy are particularly susceptible for post-NTFx complications because of their greater lifetime burden of unhealthful aging, as evidenced by an elevated prevalence of chronic diseases in adulthood.[12-14] Therefore, adults with epilepsy may already have a compromised physiological environment and skeletal fragility (e.g., history of NTFx), and sustaining an NTFx may further exacerbate risk of post-NTFx complications and premature mortality. Future studies are needed to disentangle the complex factors involved in post-NTFx mortality unique to individuals with epilepsy, and to what extent the NTFx-mortality association is mediated by preventable (e.g., serious falls, post-op complications), modifiable (e.g., physical activity), or treatable (e.g., chronic disease) factors.

The limitations of this study must be discussed. First, there is risk of biasing effect estimates from unmeasured confounding due to the limited set of comorbidities, the observational design, and the lack of medication information, as we were not able to ascertain pharmacy claims. In light of these factors, we computed E-values[34, 35] to determine the extent of unmeasured confounding (minimum strength of association with the exposure and outcome) needed to fully explain away a specific exposure-outcome association, conditional on the set of

covariates. We used the fully adjusted Cox regression model for each analysis. The e-value (lower 95% CI) needed to fully explain away the effect for EP+NTFx versus EP without NTFx was 5.19 (4.38) for 3-months, 4.11 (3.60) for 6-months, and 2.79 (2.54) for 12-months. The e-value (lower 95% CI) needed to fully explain away the effect for EP+NTFx versus without EP+NTFX was 1.46 (1.00) for 3-months, 1.90 (1.67) for 6-months, and 2.17 (1.97) for 12-months. Given the careful selection of covariates in the design of the Cox regression models as well as the large e-values, it appears unlikely that unmeasured confounding (e.g., lack of medication information) largely biased effect estimates for the exposure variables. Second, we were unable to account for the type, etiology, or time since diagnosis of epilepsy, which may have provided deeper insight into the NTFx-mortality burden. Third, it is not possible to reliably determine the cause of fracture using claims data. Approximately one-third of fractures can be attributable to seizures for adults with epilepsy.[36] Seizures by themselves may not be considered traumatic and would therefore not be given a trauma code in the claims database (e.g., not including seizures that lead to a motor vehicle accident). Not having a trauma code around the date of fracture would be considered an NTFx in the current study. Fourth, epilepsy was not determined using diagnosis codes for a single seizure (ICD-10, G41 family codes) or convulsions (ICD-9, 780.3x; ICD-10, R56.8), in part due to a potential for misclassification of epilepsy; although, misclassification for this reason would have a negligible impact on study findings given the large sample size.

In conclusion, study findings suggest that NTFx is a risk factor for mortality among adults with epilepsy, and compared to adults without epilepsy, NTFx elicits a higher mortality rate for up to 12 months for adults with epilepsy. Further, while NTFx across all sites is associated with an elevated 12-month mortality rate for adults with versus without epilepsy, there may be a stronger mortality association with NTFx of the lower and upper extremities. Future clinical research is needed to identify strategies to prevent and better manage skeletal fragility with the aim of reducing the burden of skeletal fragility and improving healthful aging for adults with epilepsy. Future basic and translational studies are needed that examine mechanisms linking skeletal fragility with mortality specific to the population of adults with epilepsy.

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Conflict of interest

None of the authors has any conflict of interest to disclose.

Key Points

- Adults with epilepsy have increased risk of non-trauma fracture (NTFx) and premature mortality; however, the link between the two are unknown
- This private claims-based study from 2011-2016 found that NTFx is a risk factor for mortality among adults with epilepsy
- Among adults with epilepsy, NTFx was associated with a 187%, 134%, and 70% higher adjusted rate of 3-, 6-, and 12-month mortality, respectively
- Among adults that sustained an NTFx, adults with vs. without epilepsy had an 11%, 29%, and 41% higher adjusted rate of 3-, 6-, and 12-month mortality, respectively
- NTFx across all sites, and especially lower and upper extremities, were associated with an elevated 12-month mortality rate for adults with vs. without epilepsy

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Table 1. Baseline descriptive characteristics by status of epilepsy (EP) and non-trauma fracture (NTFx).

	EP+NTFx (n=11,471)	EP without NTFx (n=50,384)	without EP+NTFx (n=423,041)	without EP without NTFx (n=6,787,743)
	%	%	%	%
Demographic characteristics				
Age, mean (SD)	67.1 (15.9)	57.6 (18.6)	65.0 (18.5)	51.7 (18.5)
18-40 years	7.1	20.3	12.7	30.5
41-64 years	31.1	38.9	28.4	41.1
≥65 years	61.8	40.8	58.9	28.5
Sex				
Women	62.4	53.4	66.2	51.4
Men	37.6	46.6	33.8	48.6
Race				
White	66.2	63.9	68.9	63.7
Black	9.4	11.1	6.5	8.4
Hispanic	7.3	8.6	7.9	9.7
Asian	1.7	2.2	2.5	4.2
Unknown/missing	15.4	14.2	14.2	14.0
US region				
West	26.1	23.2	28.2	24.1
Midwest	22.3	23.4	24.5	25.2
South	38.9	41.1	36.2	40.5
Northeast	12.7	12.3	11.2	10.3
Comorbidities				
Cardiovascular disease[a]	43.4	28.7	21.7	7.8
Hypertension	65.4	49.0	51.7	27.5
Diabetes	25.6	20.4	19.9	11.5
Respiratory disease[b]	41.9	30.3	27.4	14.8

Chronic kidney disease	15.0	9.4	10.5	3.5
Cancer	24.1	19.2	19.2	11.2
Fracture distribution[c]				
Unspecified location	2.1		4.5	
Vertebral column	30.1		25.4	
Hip	22.7		16.7	
Femur, non-proximal	3.6		3.1	
Tibia/fibula	18.0		22.9	
Humerus	12.5		9.8	
Ulna/radius	12.8		19.2	

[a]Ischemic heart disease, heart failure, and/or cerebrovascular disease. [b]Acute respiratory infection, pneumonia, chronic obstructive pulmonary disease, interstitial/pleura disease, and/or other respiratory disease (e.g., respiratory failure). [c]Some individuals had an NTFx across multiple sites.

Table 2. Crude mortality rate and rate ratio (RR) by status of epilepsy (EP) and non-trauma fracture (NTFx).

	3-month mortality	6-month mortality	12-month mortality
Mortality cases	**N**	**N**	**N**
without EP without NTFx	7,150	14,297	28,505
without EP+NTFx	9,003	12,656	17,397
EP without NTFx	324	668	1,399
EP+NTFx	354	579	856
Crude mortality rate	**N per 100 person years**	**N per 100 person years**	**N per 100 person years**
without EP without NTFx	0.43	0.45	0.47
without EP+NTFx	8.90	6.51	4.80
EP without NTFx	2.63	2.77	3.06
EP+NTFx	12.89	11.01	8.79
Crude mortality RR	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
Reference: without EP without NTFx			
without EP+NTFx	20.54 (19.91, 21.19)	14.62 (14.27, 14.97)	10.23 (10.03, 10.41)
EP without NTFx	6.07 (5.43, 6.78)	6.22 (5.76, 6.73)	6.51 (6.17, 6.87)
EP+NTFx	29.75 (26.74, 33.10)	24.71 (22.74, 26.85)	18.72 (17.49, 20.03)

Reference: without EP+NTFx			
EP without NTFx	0.30 (0.26, 0.33)	0.43 (0.39, 0.46)	0.64 (0.60, 0.67)
EP+NTFx	1.45 (1.30, 1.61)	1.69 (1.56, 1.84)	1.83 (1.71, 1.96)
Reference: EP without NTFx			
EP+NTFx	4.91 (4.22, 5.70)	3.97 (3.55, 4.44)	2.88 (2.64, 3.13)

Table 3. Adjusted hazard ratio (HR) of mortality by status of epilepsy (EP) and non-trauma fracture (NTFx).

	3-month mortality	6-month mortality	12-month mortality

	HR (95% CI)	HR (95% CI)	HR (95% CI)
Reference: without EP without NTFx			
without EP+NTFx	7.19 (6.96, 7.43)	5.20 (5.07, 5.33)	3.71 (3.64, 3.78)
EP without NTFx	2.78 (2.48, 3.11)	2.88 (2.66, 3.11)	3.08 (2.92, 3.25)
EP+NTFx	7.96 (7.15, 8.87)	6.73 (6.19, 7.32)	5.23 (4.88, 5.60)
Reference: without EP+NTFx			
EP without NTFx	0.39 (0.35, 0.43)	0.55 (0.51, 0.60)	0.83 (0.79, 0.88)
EP+NTFx	1.11 (1.00, 1.23)	1.29 (1.19, 1.41)	1.41 (1.32, 1.51)
Reference: EP without NTFx			
EP+NTFx	2.87 (2.47, 3.33)	2.34 (2.09, 2.61)	1.70 (1.58, 1.85)

Adjusted for age, sex, US region, cardiovascular disease, respiratory disease, diabetes, chronic kidney disease, cancer, and hypertension.

Table 4. 12-month mortality rate, rate ratio (RR), and adjusted hazard ratio (HR) by status of epilepsy (EP) and NTFx location.

	Vertebral column	Hip	Lower extremities	Upper extremities
Mortality cases	**N**	**N**	**N**	**N**
without EP+NTFx	6,391	6,420	1,951	2,514
EP+NTFx	289	281	129	145
Crude mortality rate	**N per 100 person years**	**N per 100 person years**	**N per 100 person years**	**N per 100 person years**
without EP+NTFx	7.01	11.22	2.06	2.35
EP+NTFx	9.93	13.34	6.00	5.76
Crude mortality RR	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
Reference: without EP+NTFx				
EP+NTFx	1.42 (1.26, 1.59)	1.19 (1.06, 1.34)	2.92 (2.44, 3.49)	2.45 (2.07, 2.90)
Adjusted HR	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Reference: without EP+NTFx				
EP+NTFx	1.30 (1.16, 1.47)	1.15 (1.02, 1.30)	1.92 (1.61, 2.30)	1.79 (1.51, 2.12)

Adjusted for age, sex, US region, cardiovascular disease, respiratory disease, diabetes, chronic kidney disease, cancer, and hypertension.

Table 5. 12-month mortality rate, rate ratio (RR), and adjusted hazard ratio (HR) by status of epilepsy (EP) and non-trauma fracture (NTFx) by age categories.

	18-40 years	41-64 years	≥65 years
Mortality cases	**N**	**N**	**N**
without EP without NTFx	312	3,612	24,581
without EP+NTFx	64	1,325	16,008
EP without NTFx	40	292	1,067
EP+NTFx	≤10	149	699

Crude mortality rate	**N per 100 person years**	**N per 100 person years**	**N per 100 person years**
without EP without NTFx	0.02	0.15	1.38
without EP+NTFx	0.14	1.28	7.50
EP without NTFx	0.44	1.64	5.70
EP+NTFx	1.14	4.81	11.80
Crude mortality RR	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
Reference: without EP without NTFx			
without EP+NTFx	8.09 (6.18, 10.58)	8.81 (8.27, 9.38)	5.46 (5.35, 5.57)
EP without NTFx	[a]	11.24 (9.98, 12.66)	4.15 (3.90, 4.41)
EP+NTFx	[a]	33.04 (28.05, 38.92)	8.58 (7.96, 9.25)
Reference: without EP+NTFx			
EP without NTFx	[a]	1.28 (1.12, 1.45)	0.76 (0.72, 0.81)
EP+NTFx	[a]	3.75 (3.17, 4.45)	1.57 (1.46, 1.70)
Reference: EP without NTFx			
EP+NTFx	[a]	2.94 (2.41, 3.58)	2.07 (1.88, 2.28)
Adjusted HR	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Reference: without EP without NTFx			
without EP+NTFx	6.32 (4.81, 8.31)	5.21 (4.88, 5.57)	3.48 (3.41, 3.55)
EP without NTFx	[a]	4.43 (3.92, 5.01)	2.65 (2.49, 2.82)
EP+NTFx	[a]	8.78 (7.43, 10.38)	4.54 (4.21, 4.90)
Reference: without EP+NTFx			
EP without NTFx	[a]	0.85 (0.75, 0.97)	0.76 (0.72, 0.81)
EP+NTFx	[a]	1.68 (1.42, 2.00)	1.30 (1.21, 1.41)
Reference: EP without NTFx			
EP+NTFx	[a]	1.98 (1.63, 2.41)	1.71 (1.56, 1.88)

Adjusted for age, sex, US region, cardiovascular disease, respiratory disease, diabetes, chronic kidney disease, cancer, and hypertension. [a]Sample size insufficient for analysis.

Table 6. 12-month mortality rate, rate ratio (RR), and adjusted hazard ratio (HR) by status of epilepsy (EP) and non-trauma fracture (NTFx) by sex.

	Women	Men
Mortality cases	**N**	**N**
without EP without NTFx	13,773	14,732
without EP+NTFx	10,343	7,054
EP without NTFx	682	717
EP+NTFx	464	392
Crude mortality rate	**N per 100 person years**	**N per 100 person years**
without EP without NTFx	0.44	0.50
without EP+NTFx	4.27	5.87
EP without NTFx	2.80	3.36
EP+NTFx	7.52	10.99
Crude mortality RR	**RR (95% CI)**	**RR (95% CI)**
Reference: without EP without NTFx		
without EP+NTFx	9.66 (9.42, 9.91)	11.76 (11.43, 12.10)
EP without NTFx	6.33 (5.86, 6.84)	6.72 (6.23, 7.24)
EP+NTFx	17.03 (15.53, 18.68)	22.00 (19.90, 24.32)
Reference: without EP+NTFx		
EP without NTFx	0.66 (0.61, 0.71)	0.57 (0.53, 0.62)
EP+NTFx	1.76 (1.61, 1.94)	1.87 (1.69, 2.07)
Reference: EP without NTFx		
EP+NTFx	2.69 (2.39, 3.03)	3.28 (2.90, 3.70)
Adjusted HR	**HR (95% CI)**	**HR (95% CI)**
Reference: without EP without NTFx		

without EP+NTFx	3.20 (3.12, 3.29)	4.43 (4.30, 4.57)
EP without NTFx	3.05 (2.82, 3.29)	3.11 (2.88, 3.35)
EP+NTFx	4.35 (3.97, 4.78)	6.39 (5.78, 7.07)
Reference: without EP+NTFx		
EP without NTFx	0.95 (0.88, 1.03)	0.70 (0.65, 0.76)
EP+NTFx	1.36 (1.24, 1.49)	1.44 (1.30, 1.60)
Reference: EP without NTFx		
EP+NTFx	1.43 (1.27, 1.61)	2.06 (1.82, 2.33)

Adjusted for age, US region, cardiovascular disease, respiratory disease, diabetes, chronic kidney disease, cancer, and hypertension.