Risk Factors for Dementia Development, Frailty, and Mortality in Older Adults with Epilepsy –
A Population-Based Analysis

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Abbreviations: ASM: Antiseizure medication; BMI: Body mass index; CCI: Charlson
Comorbidity Index; CHREB: Conjoint Health Research Ethics Board; CHUM: Centre
Hospitalier de l'Université de Montreal; CI: Confidence interval; CIHR: Canadian Institutes of
Health Research; CPRD: Clinical Practice Research Datalink; eFI: e-Frailty Index; EMR:
Electronic medical record; GP: General practitioner; HR: Hazard ratio; MHRA: Medicines and
Healthcare products Regulatory Agency; NHS: National Health Service; OR: Odds ratio; SAIL:
Secure Anonymized Information Linkage; THIN: Health Improvement Network; UCL:
University College London; UK: United Kingdom; WHO: World Health Organization

ABSTRACT

Objective: Although the prevalence of comorbid epilepsy and dementia is expected to increase, the impact is not well understood. Our objectives were to examine risk factors associated with incident dementia and the impact of frailty and dementia on mortality in older adults with epilepsy.

Methods: The CALIBER scientific platform was used. People with incident epilepsy at or after age 65 were identified using Read codes and matched by age, sex, and general practitioner to a cohort without epilepsy (10:1). Baseline cohort characteristics were compared using conditional logistic regression models. Multivariate Cox proportional hazard regression models were used to examine the impact of frailty and dementia on mortality, and to assess risk factors for dementia development.

Results: 1048 older adults with incident epilepsy were identified. The odds of having dementia at baseline were 7.39 [95% CI 5.21-10.50] times higher in older adults with epilepsy (n = 62, 5.92%) compared to older adults without epilepsy (n = 88, 0.86%). In the final multivariate Cox model (n = 326), age [HR: 1.20, 95% CI 1.09-1.32], Charlson comorbidity index score [HR: 1.26, 95% CI 1.10-1.44], and sleep disturbances [HR: 2.41, 95% CI 1.07-5.43] at baseline epilepsy diagnosis were significantly associated with an increased hazard of dementia development over the follow-up period. In a multivariate Cox model (n=1047), age [HR: 1.07, 95% CI 1.03-1.11], baseline dementia [HR: 2.66, 95% CI 1.65-4.27] and baseline e-frailty index score [HR: 11.55, 95% CI 2.09-63.84] were significantly associated with a higher hazard of death among those with epilepsy. Female sex [HR: 0.77, 95% CI 0.59-0.99] was associated with a lower hazard of death.

Significance: The odds of having dementia were higher in older adults with incident epilepsy. A higher comorbidity burden acts as a risk factor for dementia, while prevalent dementia and increasing frailty were associated with mortality.

Keywords: Epilepsy, dementia, frailty, mortality, elderly

1. INTRODUCTION

The annual cumulative incidence of epilepsy is 67.77 per 100,000 persons [95% Confidence Interval, CI 56.69–81.03] [1]. However, the annual incidence of epilepsy in older adults (typically those aged 65 or older) is higher, at 90 to 150 per 100,000 individuals [2]. The prevalence and incidence of epilepsy in older adults is increasing for many reasons. For example, the global population is aging and individuals who developed epilepsy at a young age are living longer [3], and individuals with strokes and dementia are now living long enough to develop epilepsy. Thus, special attention needs to be paid to epilepsy in older adults.

Individuals with epilepsy are more likely to develop dementia, and vice versa [4, 5]. This association is thought to be multifactorial. In those with temporal lobe epilepsy, it is hypothesized that the ongoing presence of seizures damage the hippocampus over time, which causes progressive memory loss leading to dementia [6]. Epilepsy could be triggering a neurodegenerative process similar to stroke, which leads to dementia. Additionally, there appears to be a relationship between vascular dementia and epilepsy [7]. Stroke can act as a nidus for seizures, and vascular risk factors like diabetes and hypertension may also be contributing factors for dementia development [8]. Recent literature shows individuals with adult onset epilepsy are at increased risk of developing incident dementia [9, 10]. In a recent systematic review [4], the period prevalence of dementia in epilepsy primarily in older adults ranged from 8.1 (in individuals aged 66 years or older) to 17.5 (in individuals aged 17 years or older, with over 50% of the cohort aged 60 and above) per 100 persons. Conversely, the pooled period prevalence of epilepsy in dementia (again primarily in older adults) was 5 per 100 persons [4].

With the aging population, the impact of frailty on those with epilepsy and dementia also needs to be explored. Frailty is a health state whereby individuals' overall well-being and ability to function independently is reduced, increasing the likelihood of health deterioration [11].

Frailty is associated with a higher risk of developing non-Alzheimer's dementias [12], and frail adults are eight times more likely to have some form of dementia [13]. Although the relationship between dementia and frailty is clear, there is limited knowledge regarding frailty in older adults with epilepsy. A study which assessed the prevalence of frailty in adults 60 years or older found that frailty was higher in older adults with epilepsy [14]. There are no studies to our knowledge examining the role that frailty plays in comorbid epilepsy and dementia.

The World Health Organization (WHO) has recognized both epilepsy and dementia as public health priorities [15, 16]. Further investigation is warranted given the incidence epilepsy and dementia, along with associated frailty, will continue to rise as the population ages, placing a significant burden on both individuals and healthcare systems [17, 18]. Our objectives were to examine risk factors for dementia development in older adults with epilepsy, and to examine the role that dementia and frailty play on mortality in older adults with epilepsy.

2. METHODS

2.1 Study Design and Data Sources

A secondary retrospective data analysis of the Clinical Practice Research Datalink (CPRD) primary care database from the United Kingdom (UK) was employed. This study was carried out as part of the CALIBER © programme (https://www.ucl.ac.uk/health-informatics/caliber). CALIBER, led from the University College London (UCL) Institute of Health Informatics, is a research resource providing validated electronic health record phenotyping algorithms and tools for national structured data sources [19, 20]. The CPRD utilizes the Read coding system for medical events [21]. At the time of this study, the CPRD

contained over 18 million individuals and their reliable primary care data on symptoms, diagnoses, and treatment that is broadly representative of the UK population [22]. The CPRD provides the means to investigate health outcomes in individuals with less common medical conditions, such as comorbid epilepsy and dementia. Therefore, CPRD was an ideal large, valid, and reliable database to address our objectives.

2.2 Population

Our population of interest was older adults who were living with epilepsy. A reliable electronic medical record (EMR) database phenotype has already been developed for adults with epilepsy in Secure Anonymized Information Linkage (SAIL), a similarly designed Welsh EMR database, with a reported sensitivity, specificity, positive predictive value, and Youden's Index of 87%, 98%, 98%, and 0.85 respectively [23]. Epilepsy was defined as at least one Read code for epilepsy and two prescriptions for the same antiseizure medication (ASM) within six months [23]. Given that both SAIL and CALIBER utilize the same Read coding system and that the above epilepsy definition has been used in CALIBER before [24], this epilepsy case definition was used in our study.

A validated dementia case definition developed for the Read coding system is contained within the online CALIBER research portal (https://www.caliberresearch.org/portal) [25]. To maintain inclusivity, our dementia definition was all-cause dementia, and we did not divide dementia into different subtypes. Temporality of the epilepsy and dementia diagnoses was determined by examining visit dates associated with diagnosis in the EMRs. Both validated epilepsy and dementia case definitions that were used were based on Read codes entered by general practitioners. However, the majority of individuals with dementia EMR Read codes have additional data which supports a likely dementia diagnosis (ex. record of dementia in multiple

data sources, multiple records of dementia in the same data source on different dates, multiple prescriptions of medications typically used to treat certain forms of dementia). Additionally, Read codes used as part of the utilized epilepsy case definition have been validated and compared to a gold standard (diagnosis based on case records assessed by epileptologist's blinded to the patients administrative codes) [26].

The literature suggests new onset epilepsy in older adults is clinically different to epilepsy that develops in younger individuals [2]. Recent studies suggest this clinically distinct form of epilepsy in older adults tends to occur in individuals between 65 and 75 years of age [27]. Therefore, we decided it would not be appropriate to combine individuals who developed epilepsy when they were younger with older adults who had recently developed epilepsy. As such, we used a cohort of older adults who developed incident epilepsy at 65 years of age or older. A five-year washout period for epilepsy Read codes before the epilepsy diagnosis date was applied to increase the chances of capturing an incident epilepsy cohort [28]. This means that individuals who had epilepsy codes in the five years preceding the index date for the first diagnosis of incident epilepsy were excluded as these were not "true" incident epilepsy cases. This has been shown to be an acceptable washout period [28]. No other exclusion criteria were applied, and duplicate data were removed.

2.3 Indices (comorbidity and frailty)

Two instruments were applied to our dataset: an e-frailty index (eFI) [29] and the Charlson comorbidity index (CCI) [30]. This eFI was designed and validated in the Health Improvement Network (THIN) [29], another United Kingdom EMR database that utilizes primary care EMR and Read codes. The eFI contains 36 health deficits (Appendix A) [29]. Each deficit is given an equal weight, with 0 being the lack of a deficit and 1 being the presence of a

deficit. The eFI is calculated as deficits present, divided by the 36 health deficits considered for each individual, resulting in a value between 0 and 1 and a higher index denotes a greater degree of frailty. The validated eFI we used proposed cut-offs for frailty categories. Individuals with scores between 0-0.12 are considered fit, scores between 0.12 to 0.24 indicate mild frailty, scores between 0.24 to 0.36 reflect moderate frailty, and a score great than 0.36 suggests severe frailty [29].

The Charlson Comorbidity Index (CCI) [30] is a validated tool used to predict mortality by weighting comorbidities [31]. The updated CCI contains information on 12 comorbidities and weights them according to disease severity, with a maximum possible score of 24 (Appendix A) [31]. A higher score on the CCI corresponds to a higher risk of death within one year. We used a version of the CCI developed in THIN [32].

2.4 Variables and Data Analysis

Older adults who developed incident epilepsy at 65 years of age or older were matched by age, sex, and general practitioner (GP) to a cohort of older adults without epilepsy, at a ratio of 1:10. For these cohorts, the following comorbidities and demographic information were captured: sex, ethnicity, alcohol usage, smoking status, body mass index (BMI), prescription of enzyme inducing antiseizure medications (ASMs), frailty, dementia, cirrhosis, chronic kidney disease, osteoporosis, osteoarthritis, Parkinson's disease, diabetes, dyslipidemia, hypertension, intracranial haemorrhage, ischaemic stroke, haemorrhagic stroke, heart failure, transient ischaemic attack, myocardial infarction, stable angina, unstable angina, mood disorders (i.e. anxiety, depression, eating disorders, psychosis/mania), and all the components captured by the eFI (Appendix A). Odds ratios and p-values were calculated using a conditional logistic

regression and extended McNemar's test to multiple controls per case to compare baseline

characteristics between individuals with incident epilepsy and individuals without epilepsy.

To examine risk factors for the development of dementia in individuals with epilepsy,

univariate and multivariate Cox regression models were used due to unequal follow-up times

from the exposures to the outcome (dementia development). We examined incident dementia

that developed after incident epilepsy diagnosis. Thus, the outcome was the presence of all-cause

dementia, which developed after the baseline epilepsy diagnosis. Based on the literature and the

available variables within the CALIBER scientific platform, the following risk factors were

examined: hazardous alcohol usage (defined as excess or binge drinking status), current smoker,

body mass index (BMI), depression, hearing loss, non-specific sleep disturbances, hypertension,

diabetes, falls, social vulnerability, parkinsonism and tremor. We further adjusted for age at

baseline epilepsy diagnosis, sex, and CCI score. While the CCI has dementia as one of its

variables, none of the individuals included in this analysis had dementia at baseline. All variables

included in the models were captured at baseline epilepsy diagnosis.

To assess the impact of dementia and frailty on mortality in older adults with epilepsy,

Cox proportional hazard regression models were generated. Univariate models for the following

variables at baseline epilepsy diagnosis were generated: age, sex, presence of dementia at

incident epilepsy diagnosis, eFI score (continuous), presence of frailty (not frail: score of 0-0.12,

frail: score > 0.12 as per established cut-offs) [29], CCI score, anxiety, and depression. In the

final model, the CCI score was not included as there is significant overlap in the comorbidities

contained in the CCI and the eFI. Furthermore, while we included the presence of frailty (i.e. a

dichotomous categorical variable based on eFI score) to compare with a continuous eFI score

variable in the univariate Cox modeling, we employed the eFI scale in a continuous fashion in

the multivariate Cox model because continuous eFIs better predict mortality compared to categorical cut-offs [33]. To ensure the assumption of proportionality was met, the Grambsch-Therneau test was used [34]. Demographic characteristics were compared between individuals who survived and individuals who died during the follow-up period. The date of the beginning of the follow up period was the date of the incident epilepsy diagnosis, and the date of death goes through certification and iterative quality control checks by the UK Office of National Statistics before these data are allowed to be used for research purposes [35].

As this was a secondary retrospective analysis of primary care EMR data, specific granular data surrounding the epilepsy and dementia diagnoses (seizure type, seizure severity, seizure frequency, type of dementia, etc.) were not present. Factors that may be associated with decreased dementia development (i.e. formal education, physical activity, and social engagement) were also not captured. Additionally, certain risk factors for dementia and epilepsy development (most notably traumatic brain injury) could not be incorporated as there is currently no validated case definitions in CALIBER.

Falls often result in traumatic brain injury (TBI) [36], and there is strong evidence in support of TBI as a risk factor for dementia development [37, 38]. Falls are common in persons with dementia, and they are also common in persons with epilepsy [39], especially in individuals who experience tonic-clonic seizures [40]. Because falls are associated with epilepsy (e.g. falling due to a seizure) and dementia (e.g. a fall leads to TBI which can cause dementia), falls could be a confounding variable. Conversely, falls could exist on the causal pathway between epilepsy, TBI, and dementia (for example, seizures → falls → TBI → dementia), although proving this would be difficult due to the complex relationship between all of these factors. Lastly, falls could

also be a surrogate for a common ancestor between epilepsy and dementia (e.g. stroke or neurodegenerative disease which cause falls, epilepsy, and dementia).

Statistical significance for all tests was set at a p-value of less than 0.05. All analyses were conducted using STATA, version 16. All variable definitions used were obtained from either the CALIBER portal [19], the eFI [29], or the CCI developed in THIN [32]. A data dictionary containing our full list of study variables and the associated Read codes was developed. Methodological flow charts describing details of the various analyses can be found in Appendix B.

2.5. Ethical Considerations

Ethics approval was obtained through both the University of Calgary Conjoint Health Research Ethics Board (CHREB) and the Medicines and Healthcare products Regulatory Agency (MHRA) Independent Scientific Advisory Committee for the Clinical Practice Research Datalink (CPRD). This project is operated within the UK and Canadian patient confidentiality laws, and all data were pseudonymized. All patients in the primary care networks in the UK have completed consent forms and can have their data excluded for research purposes at their request at any time. The study was approved by the MHRA (UK) Independent Scientific Advisory Committee (17_064RA) under Section 251 (NHS Social Care Act 2006). This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone.

3. RESULTS

Of the total number of individuals registered in the CPRD from January 1998 up to January 2019 (n = 18,410,930), 11,307 individuals aged 18 years or older met the criteria for incident epilepsy (0.1%), including 1048 older adults who developed incident epilepsy at 65 years of age or older (Figure 1).

This cohort of older adults with epilepsy (n = 1048) was matched by age, sex, and GP to 10,259 older adults without epilepsy. The cohort of older adults with incident epilepsy had more comorbidities at baseline (Table 1). At baseline incident epilepsy diagnosis, 62 (5.92%) individuals had dementia. Comparatively, 88 (0.86%) of individuals without epilepsy had dementia at baseline. The odds of having dementia at baseline incident epilepsy diagnosis were 7.39 [95% CI 5.21-10.50] times higher in older adults with epilepsy. Older adults with epilepsy had lower odds of being fit (not frail) [OR: 0.32, 95% CI 0.28-0.37]. Conversely, older adults with epilepsy had higher odds of mild frailty [OR: 1.98, 95% CI 1.72-2.28], moderate frailty [OR: 2.75, 95% CI 2.23-3.40], and severe frailty [OR: 3.59, 95% CI 2.39-5.39].

3.1 Risk factor modeling for dementia development

After 62 individuals with dementia at baseline incident epilepsy diagnosis were removed, 985 individuals with incident epilepsy remained in the analyses. 77 individuals developed incident dementia. In the univariate models (Table 2), each one-point increment in the CCI score [HR: 1.35, 95% CI 1.23-1.49], age [HR: 1.27, 95% CI 1.19-1.36], hearing loss [HR: 2.13, 95% CI 1.24-3.66], sleep disturbances [HR: 3.12, 95% CI 1.79-5.43], hypertension [HR: 1.76, 95% CI 1.10-2.81], diabetes [HR: 2.13, 95% CI 1.16-3.90], falls [HR: 2.54, 95% CI 1.50-4.29], and Parkinsonism and tremors [HR: 3.65, 95% CI: 1.32-10.07] at baseline epilepsy diagnosis were

associated with a significant increase in the hazard of dementia development in older adults with epilepsy. Conversely, individuals who were currently drinking alcohol at baseline epilepsy diagnosis had a decreased hazard of dementia development [HR: 0.48, 95% CI 0.24-0.94].

In the final multivariate Cox model (n = 326) adjusted for age, sex, CCI score, alcohol usage, smoking status, depression, hearing loss, sleep disturbances and falls, only CCI score [HR: 1.26, 95% CI 1.10-1.44], age [HR: 1.20, 95% CI 1.09-1.32], and the presence of sleep disturbances [HR: 2.41, 95% CI 1.07-5.43] remained significantly associated with an increased hazard of dementia development.

3.2 Survival Analyses

1047 older adults with epilepsy were analyzed after one individual with no follow-up information was removed. Most demographic and comorbidity characteristics were similar between individuals who died versus individuals who survived (Appendix C). Significantly more individuals who died were housebound (37.55% vs 30.42%, p-value = 0.037) and experienced heart failure (12.65% vs 7.61%, p-value = 0.015) and stable angina (12.65% vs 8.23%, p-value = 0.038).

In the crude Cox modeling, age [HR: 1.06, 95% CI 1.02-1.09], presence of dementia [HR: 2.88, 95% CI 1.81-4.58], eFI score [HR: 6.26, 95% CI: 1.29-30.42], presence of frailty (not frail: eFI score of 0-0.12, frail: eFI score > 0.12) [HR: 1.46, 95% CI 1.13-1.89], and CCI score [HR: 1.20, 95% CI: 1.14-1.27] at baseline epilepsy diagnosis were significantly associated with an increased hazard of mortality (Table 3).

In the multivariate model, age [HR: 1.07, 95% CI 1.03-1.11], presence of dementia [HR: 2.66, 95% CI 1.65-4.27], and eFI score [HR: 11.55 for each 0.01 unit increase in eFI score, 95%

CI 2.09-63.84] were significantly associated with a higher hazard of death (Table 3).

Additionally, older females had a lower hazard of experiencing death [HR: 0.77, 95% CI 0.59-0.99] at any point during the follow up period (Table 3). The assumption of proportionality was not violated in the global adjusted model (Grambsch-Therneau test; χ^2, df 6 < 0.01, p-value = 0.9507), or on any of the sub-categories.

As demonstrated in a Kaplan-Meier curve (Figure 2), older adults with epilepsy and comorbid dementia at baseline epilepsy diagnosis had consistently lower cumulative survival across the entire follow up period. Based on the results of the Log-rank test, there is a statistically significant difference in survival between older adults with comorbid epilepsy and dementia and older adults with epilepsy and no dementia (χ^2, df 1 = 21.84, p-value < 0.0001). Based on the adjusted Cox regression model, older adults with comorbid dementia at baseline epilepsy diagnosis have a 2.66 [95% CI 1.65-4.27] times higher hazard of dying at any particular point during follow up period.

In a comparator multivariable model that adjusted for the same covariates but included CCI score instead of eFI score, similar results were seen with regards to the impact of age, sex, and presence of dementia (Table 4). For every one-unit increase in CCI score, the hazard of death increased by 1.18 [95% CI 1.12-1.25]. The assumption of proportionality was not violated in the global adjusted model (Grambsch-Therneau test; χ^2, df 6 < 0.01, p-value = 0.9731), or on any of the sub-categories.

4. DISCUSSION

This study employed a large EMR primary care database representative of the UK population to examine the association between dementia and frailty among older adults with epilepsy. Older adults with epilepsy were significantly more likely to have a wide array of comorbidities, including dementia, and experience some degree of frailty as compared to older adults without epilepsy. However, only CCI score, age and sleep disturbances were significantly associated with an increased risk of dementia development among older adults with incident epilepsy. Age, presence of dementia and eFI score at baseline epilepsy diagnosis all significantly increased the hazard of death in older adults with epilepsy. Given the nature of this secondary data analyses, certain relevant risk factors and etiologies for dementia and epilepsy could not be analyzed.

The prevalence of comorbid dementia at baseline incident epilepsy diagnosis was 5.92% (62/1048). This estimate is very close to the 5% pooled period prevalence of epilepsy in persons with dementia identified in our previous systematic review [4]. Furthermore, the odds of having dementia were 7.39 times higher among older adults developing incident epilepsy. This further consolidates the association between dementia and epilepsy. Additionally, older adults with epilepsy were more likely to experience some amount of frailty. This increased degree of frailty is likely related to the increased prevalence of various comorbidities in this population, including dementia.

4.1 Risk factors for dementia development in older adults with epilepsy

It was surprising that only CCI score, age, and sleep disturbances at baseline epilepsy diagnosis were significantly associated with an increased hazard of dementia development in older adults with incident epilepsy. The dementia *Lancet* commission, in their review of factors associated dementia, identified hazardous alcohol usage, current smoking, body mass index (BMI), depression, hearing loss, sleep disturbances, stroke, hypertension, diabetes, social vulnerability, parkinsonism and tremor as all impacting the risk for developing dementia [41]. Thus, we expected some of these factors to be significant in our models. Our findings highlight the challenges in determining the complex clinical relationship between epilepsy and other risk factors for dementia.

The lack of statistical significance could also have been due to imprecision in the hazard ratio estimates caused by the sample size, especially for variables where there were larger amounts of missing data like smoking status and alcohol usage. The prevalence of certain comorbidities within this primary care database may have also been underreported, because of the lack of incorporation of hospital admission diagnoses and the known issues with under-reporting of some conditions (e.g. depression) within EMR data. A recent systematic review detailing validated case definitions for depression in administrative data found that all of the identified ICD-10 and ICD-9 based case definitions for depression had low sensitivity (ranging from 28.9% to 35.6%) [42], though accuracy in EMRs may be higher, since they are recorded at point-of-care, a point that is corroborated by the fact our prevalence estimates closely resemble those reported in the literature (Table 1).

It was not surprising that CCI score was a significant predictor of developing dementia. The CCI contains many comorbidities known to be risk factors for dementia. Some of our 95% CI's were large, which may indicate that each of the dementia risk factors contribute a small amount,

but together have a major impact on dementia development. Incident epilepsy development in older adults is also a risk factor for dementia. A recent study found older adults with new onset epilepsy had a significantly higher hazard of dementia development compared to older adults without new onset epilepsy [HR: 3.05, 95% CI 2.65-3.51] [43]. The complex relationship between epilepsy, dementia, and various known risk factors for both diseases warrants further investigation.

The presence of sleep disturbances was also associated with an increased hazard of dementia development. The definition of sleep disturbance in the eFI included codes for insomnia, non-organic sleep disorders, disorders of the sleep-wake schedule, somnolence, and sleep disturbances. There are studies which report an association between sleep disturbances and cognitive decline [44-46]. Sleep disturbances could be a risk factor for dementia; alternatively, sleep disturbances could be a prodrome of dementia [47]. Therefore, the evidence about sleep disturbances as a risk factor for dementia development is unclear. Sleep disturbances are more common in persons with epilepsy because seizures can disrupt circadian rhythms [48], and certain antiseizure medications appear to also impact sleep patterns [49, 50]. One study found that individuals with parietal epilepsy experienced sleep disturbance twice as often (39%) compared to individuals without epilepsy (18%) in a 6-month period [51]. Given that persons with epilepsy often experience sleep disturbances, and sleep disturbances could be a risk factor for dementia, diagnosing and addressing sleep disturbances in older adults with epilepsy could reduce their risk of dementia development. Sleep disturbances in persons with epilepsy can also decrease quality of life, further supporting the need to address them [51].

Recent literature indicates there is a relationship between orexin and sleep disturbance in persons with moderate to severe AD [52]. Sleep disturbances may also be related to new onset

epilepsy in older adults, possibly in relation to dementia. Beta amyloid plaques are characteristic

pathologic findings in persons with AD. The accumulation of beta amyloid in the brain is also

associated with seizures, as well as sleep disturbances such as obstructive sleep apnea. This

suggests there may be a complex relationship between beta amyloid, sleep disturbances,

dementia and new onset epilepsy in older adults [53, 54].

4.2 Dementia, Frailty, and Mortality

Our models suggest increased hazard of death related to age, presence of dementia, eFI

and CCI scores at baseline epilepsy diagnosis. However, the degree of frailty at baseline epilepsy

diagnosis was the variable most strongly associated with an increased hazard of death. For every

0.01 unit increase in eFI score at baseline epilepsy diagnosis, the hazard of death increased by

11.55. Frail older adults are more likely to fall, develop delirium, have medication errors,

experience adverse events, and have longer lengths of stay in hospitals [55]. Frailty is also

known to be associated with increased mortality [56]. There are no studies, to our knowledge,

that have examined the impact of frailty in older adults with incident epilepsy diagnosis.

It appears that it is an accumulation of deficits among older adults with epilepsy that leads to

an increased risk of mortality, rather that one specific individual factor. The eFI places an

emphasis on this phenomenon [57]. Thus, screening for frailty in older adults with epilepsy could

be beneficial. The eFI could be automatically calculated based on information present in an

EMR. Recently, a team in Scotland piloted use of the same eFI index used in our study across

nine GP practices, in order to identify frailty and implement interventions [58]. They were able

to use the eFI to identify individuals who could benefit from additional support and referred

these people to anticipatory care planning nurses. While this study is still underway, the research

team anticipates a reduction in hospital admissions and increased specialized care planning in

these populations. Based on the eFI score, we may be able to classify older adults with epilepsy into new, clinically meaningful risk categories. Certain interventions, such as muscle strengthening activities and protein supplementation [59], could improve functioning and decrease the degree of frailty experienced by older adults with epilepsy.

4.3 Limitations

Despite our utilization of a large primary care dataset to identify a sizable population and community-based cohort of older adults with new onset epilepsy after the age of 65, our study has some limitations. As this was a secondary analysis of primary care EMR data, we were limited to the disease case definitions available in CALIBER when selecting our variables of interest. As a result, we did not have access to a case definition of traumatic brain injury, which was unfortunate given it is a significant risk factor for both dementia and epilepsy [41, 60, 61]. We also did not have access to factors that may decrease dementia development, such as years of formal education, physical activity and social engagement [60]. Additionally, there was no information available regarding seizure type, severity, and frequency, factors which could play a role in dementia development and mortality among older adults with epilepsy. Validated case definitions for type of dementia were also not available.

While we wanted to control for ethnicity in our statistical models, we were unable to do so because of the large amount of missing data. The ethnicity of older adults with incident epilepsy was not statistically significantly different compared to older adults without epilepsy. In both groups, approximately 32% of individuals were white, 1% where non-white, and about 66% of individuals had non-specified or missing ethnicity data (Table 1). An article published in 2014, which examined the completeness and usability in UK primary care data, found that about 42% of individuals in the UK primary care dataset (CRPD) had an ethnicity reported at some

point in time as of March 27th, 2011 [62]. The distribution of ethnicity data in the most UK

census (2011) was as follows: white: 87.2%; non-white: 12.7% [63]. In 2011, the CPRD was

comparable to that of the UK wide census (white: 86.6%; non-white: 13.4%) [62].

Given there were no significant differences in the amount of missing ethnicity data

between older adults with incident epilepsy and older adults without epilepsy, data appears to be

missing at random. However, the main reason multiple imputation is not appropriate in this case

is because of the large amount of missing ethnicity data.

We sought to reduce the effects of potential confounders, such as age, sex, practice

parameters, and socioeconomic status through matching. However, matching based on GP

practice, and by extension possibly socioeconomic status, could introduce selection bias. This

occurs because matching preferentially to an individual in the same practice could result in

similar socioeconomic profile, assuming they live in closely approximated neighbourhoods. This

would result in conservative estimates of effect, given the two groups would be artificially

similar with respect to their comorbid burden.

5. CONCLUSION

Older adults with epilepsy were more likely to experience some degree of frailty, and to

have dementia compared to older adults without epilepsy. The risk factors for dementia

development in older adults with epilepsy remain unclear, but epilepsy itself may play a large

role. The presence of dementia and the degree of frailty experienced by older adults with

epilepsy both significantly increase the hazard of death.

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REFERENCES

[1]   Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon C-S, Dykeman J, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology. 2017;88(3):296-303.
[2]   Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. Epilepsia. 1993;34(3):453-8.
[3]   Newton CR, Garcia HH. Epilepsy in poor regions of the world. The Lancet. 2012;380(9848):1193-201.
[4]   Subota A, Pham T, Jette N, Sauro K, Lorenzetti D, Holroyd-Leduc J. The association between dementia and epilepsy: A systematic review and meta-analysis. Epilepsia. 2017;58(6):962-72.
[5]   Sarkis RA, Dickerson BC, Cole AJ, Chemali ZN. Clinical and neurophysiologic characteristics of unprovoked seizures in patients diagnosed with dementia. The Journal of neuropsychiatry and clinical neurosciences. 2016;28(1):56-61.
[6]   Noebels J. A perfect storm: converging paths of epilepsy and Alzheimer's dementia intersect in the hippocampal formation. Epilepsia. 2011;52:39-46.
[7]   Imfeld P, Bodmer M, Schuerch M, Jick SS, Meier CR. Seizures in patients with Alzheimer's disease or vascular dementia: A population-based nested case–control analysis. Epilepsia. 2013;54(4):700-7.
[8]   Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. JAMA neurology. 2017;74(10):1246-54.
[9]   Kawakami O, Koike Y, Ando T, Sugiura M, Kato H, Hiraga K, et al. Incidence of dementia in patients with adult-onset epilepsy of unknown causes. Journal of the neurological sciences. 2018;395:71-6.
[10]   Keret O, Hoang TD, Xia F, Rosen HJ, Yaffe K. Association of Late-Onset Unprovoked Seizures of Unknown Etiology With the Risk of Developing Dementia in Older Veterans. JAMA neurology. 2020;77(6):710-5.
[11]   Hogan DB. Models, definitions, and criteria for frailty. Conn's handbook of models for human aging: Elsevier; 2018. p. 35-44.
[12]   Gray SL, Anderson ML, Hubbard RA, LaCroix A, Crane PK, McCormick W, et al. Frailty and incident dementia. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences. 2013;68(9):1083-90.
[13]   Kulmala J, Nykänen I, Mänty M, Hartikainen S. Association between frailty and dementia: a population-based study. Gerontology. 2014;60(1):16-21.
[14]   Farías-Antúnez S, Fassa AG. Frailty prevalence and associated factors in the elderly in Southern Brazil, 2014. Epidemiologia e Serviços de Saúde. 2019;28:e2017405.
[15]   Wortmann M. Dementia: a global health priority-highlights from an ADI and World Health Organization report. Alzheimer's research & therapy. 2012;4(5):40.
[16]   Organization WH. Epilepsy: a public health imperative: summary. World Health Organization; 2019.
[17]   Ramsay RE, Rowan AJ, Pryor FM. Special considerations in treating the elderly patient with epilepsy. Neurology. 2004;62(5 suppl 2):S24-S9.
[18]   Prince MJ. World Alzheimer Report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends: Alzheimer's Disease International; 2015.

[19]   Denaxas SC, George J, Herrett E, Shah AD, Kalra D, Hingorani AD, et al. Data resource profile: cardiovascular disease research using linked bespoke studies and electronic health records (CALIBER). International journal of epidemiology. 2012;41(6):1625-38.

[20]   Denaxas S, Gonzalez-Izquierdo A, Direk K, Fitzpatrick NK, Fatemifar G, Banerjee A, et al. UK phenomics platform for developing and validating electronic health record phenotypes: CALIBER. Journal of the American Medical Informatics Association. 2019;26(12):1545-59.

[21]   Chisholm J. The Read clinical classification. BMJ: British Medical Journal. 1990;300(6732):1092.

[22]   Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, Van Staa T, et al. Data resource profile: clinical practice research datalink (CPRD). International journal of epidemiology. 2015;44(3):827-36.

[23]   Fonferko-Shadrach B, Lacey AS, White CP, Powell HR, Sawhney IM, Lyons RA, et al. Validating epilepsy diagnoses in routinely collected data. Seizure. 2017;52:195-8.

[24]   Josephson CB, Gonzalez-Izquierdo A, Denaxas S, Fitzpatrick NK, Sajobi TT, Engbers JD, et al. Serotonin reuptake inhibitors and mortality in epilepsy: A linked primary-care cohort study. Epilepsia. 2017;58(11):2002-9.

[25]   Pujades-Rodriguez M, Assi V, Gonzalez-Izquierdo A, Wilkinson T, Schnier C, Sudlow C, et al. The diagnosis, burden and prognosis of dementia: A record-linkage cohort study in England. PloS one. 2018;13(6):e0199026.

[26]   Mbizvo GK, Schnier C, Simpson CR, Duncan SE, Chin RF. Validating the accuracy of administrative healthcare data identifying epilepsy in deceased adults: A Scottish data linkage study. Epilepsy Research. 2020;167:106462.

[27]   Josephson CB, Engbers JD, Sajobi TT, Jette N, Agha-Khani Y, Federico P, et al. Towards a clinically informed, data-driven definition of elderly onset epilepsy. Epilepsia. 2016;57(2):298-305.

[28]   Tu K, Wang M, Jaakkimainen RL, Butt D, Ivers NM, Young J, et al. Assessing the validity of using administrative data to identify patients with epilepsy. Epilepsia. 2014;55(2):335-43.

[29]   Clegg A, Bates C, Young J, Ryan R, Nichols L, Ann Teale E, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age and ageing. 2016;45(3):353-60.

[30]   Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases. 1987;40(5):373-83.

[31]   Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. American journal of epidemiology. 2011;173(6):676-82.

[32]   Josephson CB, Lowerison M, Vallerand I, Sajobi TT, Patten S, Jette N, et al. Association of depression and treated depression with epilepsy and seizure outcomes: a multicohort analysis. JAMA neurology. 2017;74(5):533-9.

[33]   Chao Y-S, Wu H-C, Wu C-J, Chen W-C. Index or illusion: The case of frailty indices in the Health and Retirement Study. PloS one. 2018;13(7):e0197859.

[34]   Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81(3):515-26.

[35]   Statistics OfN. User guide to mortality statistics. In: Statistics OfN, editor. 2019.

[36]   Sarani B, Temple-Lykens B, Kim P, Sonnad S, Bergey M, Pascual JL, et al. Factors associated with mortality and brain injury after falls from the standing position. Journal of Trauma and Acute Care Surgery. 2009;67(5):954-8.

[37]   Plassman BL, Havlik R, Steffens D, Helms M, Newman T, Drosdick D, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology. 2000;55(8):1158-66.

[38]   Barnes DE, Kaup A, Kirby KA, Byers AL, Diaz-Arrastia R, Yaffe K. Traumatic brain injury and risk of dementia in older veterans. Neurology. 2014;83(4):312-9.

[39]   Wirrell EC. Epilepsy-related injuries. Epilepsia. 2006;47:79-86.

[40]   Devinsky O, Vezzani A, O'Brien TJ, Jette N, Scheffer IE, de Curtis M, et al. Epilepsy. Nature Reviews Disease Primers. 2018;4(1):18024.

[41]   Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. The Lancet. 2017;390(10113):2673-734.

[42]   Fiest KM, Jette N, Quan H, Germaine-Smith CS, Metcalfe A, Patten SB, et al. Systematic review and assessment of validated case definitions for depression in administrative data. BMC psychiatry. 2014;14(1):289.

[43]   Johnson EL, Krauss GL, Kucharska-Newton A, Albert MS, Brandt J, Walker KA, et al. Dementia in late-onset epilepsy: The atherosclerosis risk in communities study. Neurology. 2020.

[44]   Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. Jama. 2011;306(6):613-9.

[45]   Chang W-P, Liu M-E, Chang W-C, Yang AC, Ku Y-C, Pai J-T, et al. Sleep apnea and the risk of dementia: a population-based 5-year follow-up study in Taiwan. PloS one. 2013;8(10):e78655.

[46]   Sterniczuk R, Theou O, Rusak B, Rockwood K. Sleep disturbance is associated with incident dementia and mortality. Current Alzheimer research. 2013;10(7):767-75.

[47]   Ju Y-ES, Lucey BP, Holtzman DM. Sleep and Alzheimer disease pathology—a bidirectional relationship. Nature Reviews Neurology. 2014;10(2):115-9.

[48]   Bazil CW, Short D, Crispin D, Zheng W. Patients with intractable epilepsy have low melatonin, which increases following seizures. Neurology. 2000;55(11):1746-8.

[49]   Placidi F, Scalise A, Marciani MG, Romigi A, Diomedi M, Gigli GL. Effect of antiepileptic drugs on sleep. Clinical Neurophysiology. 2000;111:S115-S9.

[50]   Jain SV, Glauser TA. Effects of epilepsy treatments on sleep architecture and daytime sleepiness: an evidence-based review of objective sleep metrics. Epilepsia. 2014;55(1):26-37.

[51]   De Weerd A, De Haas S, Otte A, Trenité DKN, Van Erp G, Cohen A, et al. Subjective sleep disturbance in patients with partial epilepsy: a questionnaire-based study on prevalence and impact on quality of life. Epilepsia. 2004;45(11):1397-404.

[52]   Liguori C, Romigi A, Nuccetelli M, Zannino S, Sancesario G, Martorana A, et al. Orexinergic system dysregulation, sleep impairment, and cognitive decline in Alzheimer disease. JAMA neurology. 2014;71(12):1498-505.

[53]   Liguori C, Spanetta M, Romoli M, Placidi F, Cesarini EN, Mercuri NB, et al. Sleep disorders and late-onset epilepsy of unknown origin: Understanding new trajectories to brain amyloidopathy. Mechanisms of Ageing and Development. 2021:111434.

[54]	Polsek D, Gildeh N, Cash D, Winsky-Sommerer R, Williams S, Turkheimer F, et al. Obstructive sleep apnoea and Alzheimer's disease: in search of shared pathomechanisms. Neuroscience & Biobehavioral Reviews. 2018;86:142-9.

[55]	Lee L, Heckman G, Molnar FJ. Frailty: Identifying elderly patients at high risk of poor outcomes. Canadian family physician. 2015;61(3):227-31.

[56]	Romero-Ortuno R. The Frailty Instrument for primary care of the Survey of Health, Ageing and Retirement in Europe predicts mortality similarly to a frailty index based on comprehensive geriatric assessment. Geriatrics & gerontology international. 2013;13(2):497-504.

[57]	Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC geriatrics. 2008;8(1):24.

[58]	Devereux N, Ellis G, Dobie L, Baughan P, Monaghan T. Testing a proactive approach to frailty identification: the electronic frailty index. BMJ open quality. 2019;8(3):e000682.

[59]	Travers J, Romero-Ortuno R, Bailey J, Cooney M-T. Delaying and reversing frailty: a systematic review of primary care interventions. British Journal of General Practice. 2019;69(678):e61-e9.

[60]	Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. Alzheimer's & Dementia. 2015;11(6):718-26.

[61]	Annegers JF, Coan SP. The risks of epilepsy after traumatic brain injury. Seizure. 2000;9(7):453-7.

[62]	Mathur R, Bhaskaran K, Chaturvedi N, Leon DA, vanStaa T, Grundy E, et al. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. Journal of public health. 2014;36(4):684-92.

[63]	Office for National Statistics NRoS, Northern Ireland Statistics and Research Agency. 2011 Census aggregate data. In: Service UD, editor. 2011.