Received: 30 September 2024 | Revised: 29 October 2024 | Accepted: 31 October 2024

DOI: 10.1002/epi4.13098

Epilepsia Open® Open Access

CRITICAL REVIEW

Mortality in older adults with epilepsy: An understudied entity

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Funding information
BAND foundation; American Epilepsy Society, Grant/Award Number: 1067206

Abstract

Despite the recognition of Sudden Unexpected Death in Epilepsy (SUDEP) and other risks of premature mortality in people with epilepsy (PWE), mortality in older PWE remains an understudied entity. This review provides a comprehensive overview of the multifaceted causes of premature mortality in older adults with epilepsy and emphasizes the need for targeted interventions to reduce mortality and enhance the quality of life in this vulnerable population. It underscores the heightened prevalence of epilepsy among older adults and the interplay of intrinsic and extrinsic factors contributing to their mortality. Further, this paper delves into the nuances of diagnosing SUDEP in older adults and the underestimation of its incidence due to misclassification and lack of standardized protocols. Factors such as frailty, comorbidities, and the bidirectional relationship between epilepsy and conditions such as dementia and stroke further compound the mortality risks. Key factors, including status epilepticus, comorbid conditions (such as cardiovascular diseases, cerebrovascular events, and neurodegenerative disorders), and external causes like accidents, falls, and suicide, are discussed. It also examines the implications of anti-seizure medications, particularly polypharmacy, and their adverse effects on this population. Future directions include implementing enhanced diagnostic protocols, developing treatment plans, and integrating real-time monitoring technologies to reduce the risk of sudden death and multifaceted premature mortality in this patient population. Increasing awareness among healthcare providers and families about the risks and management of epilepsy in older adults, along with fostering collaborative research efforts, is essential to improve mortality outcomes.

Plain Language Summary: There is a heightened risk of mortality in older people with epilepsy due to many causes unique to their population. Despite the risk, Sudden Unexpected Death in Epilepsy and early mortality in older adults with epilepsy are underestimated. Unique contributing factors include comorbid conditions like dementia, stroke, and frailty, adverse effects from polypharmacy, and increased risks of cardiovascular complications and external injuries such as

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falls and suicide. A careful consideration of all these factors can help mitigate the mortality in older adults with epilepsy.

KEYWORDS

epilepsy, mortality, older adults, seizure

1 | INTRODUCTION

The concept of premature mortality in people with epilepsy (PWE) is a long-studied phenomenon. Initially elucidated in the 19th century, this phenomenon has since garnered considerable attention.[1] The concept of Sudden Unexpected Death in Epilepsy (SUDEP) emerged distinctly in the 1900s, marking a pivotal moment in the understanding of mortality in PWE. In general, PWE are at an increased risk for mortality, with the all-cause mortality in epilepsy estimated to be 2-3X higher than the general population.[2] The causes of early mortality in PWE are complex and involve factors both intrinsic to epilepsy and external influences (Figure 1).[3]

Globally, individuals >65 represent the fastest-growing age group, estimated to rise to 1.2 billion in 2025.[4] This population is also most vulnerable to factors that predispose them to greater mortality risk. Approximately 2.8 million deaths were reported in the US in a survey by the CDC in 2019. The majority (74%) of these were among adults ≥65.

Epilepsy is particularly prevalent among older adults, more so than in any other age group, with the highest incidence above 65. The incidence rate of epilepsy for persons older than 65 is ~100/100000, which is double that among younger adults.[5] This is attributable to factors such as declining neuronal function with age, the onset of pathologies such as stroke, dementia, and malignancy, which may precipitate seizures, and the initiation of medications that may increase seizure susceptibility, among other causes.[6]

Older PWE have an elevated mortality risk due to both their age and disease pathology. However, premature mortality in older PWE remains understudied. SUDEP and epilepsy as causes of death are often underestimated in this demographic because death is frequently attributed to other causes.[7,8] While we think that it is under recognized, due to the intrinsic difficulties of diagnosing it in older PWE, its exact incidence in this population remains unknown.

This review explores the many unique aspects of premature mortality, including SUDEP and other important factors that can concurrently impact mortality in older PWE. We highlight the emerging evidence on the effects of antiseizure medication (ASM) usage, the presence of comorbidities, cardiac complications, external causes, and frailty on mortality in older PWE. Understanding these multifaceted causes is essential for developing targeted interventions to reduce premature mortality in this vulnerable population.

Key points

- Older people with epilepsy are at an increased risk for premature mortality due to factors unique to this population.
- SUDEP remains an underdiagnosed and understudied entity, particularly in older people with epilepsy.
- The mortality outcomes in older people with epilepsy are not only attributed to epilepsy and status epilepticus but also significantly influenced by the presence of comorbidities such as neurodegenerative disease, stroke, and frailty.
- Specific cardiovascular risk factors, polypharmacy, antiseizure medication usage, and external factors such as falls and suicide further compound the risk of premature mortality in older people with epilepsy.
- Assessment of premature mortality risk factors and SUDEP, along with its implications, can improve the management and mortality outcomes of older PWE.

2 | EXCESS MORTALITY IN OLDER PWE

Around 180 000 annual deaths are caused by epilepsy worldwide.[9] Epilepsy, Status epilepticus (SE), and SUDEP all contribute to premature mortality in PWE.[10] External causes of death like drowning, accidents, burns, substance abuse, and suicide are also more common in PWE.[9] These external injuries, accidents and falls also contribute to greater frailty, leading to an accumulation of deficits and worsened health outcomes, increasing mortality in this demographic.[11] Uncontrolled seizures may potentiate

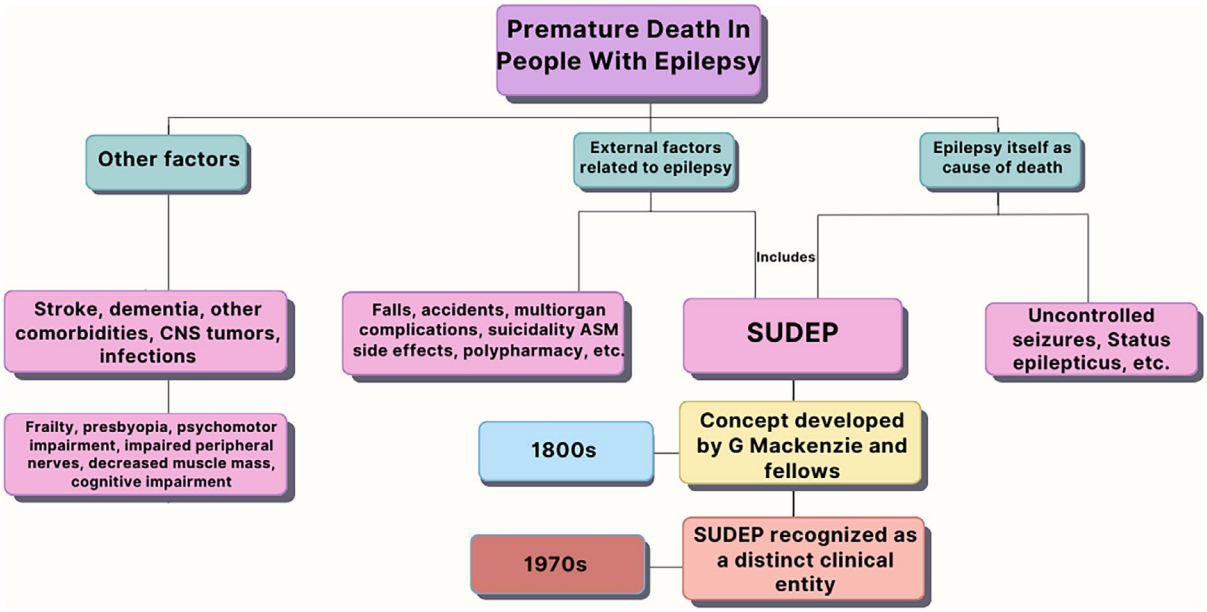

FIGURE 1 The evolving concept of premature mortality in older adults with epilepsy. ASM, Antiseizure Medication; CNS, Central Nervous System; SUDEP, Sudden Unexpected Death in Epilepsy.

inflammation and oxidative stress, which can contribute to accelerated aging and premature death.[12]

Older adults are predisposed to excess mortality due to a multitude of reasons. Certain factors that increase mortality are also unique to older adults. The presence of comorbid conditions such as cerebrovascular, cardiovascular diseases (CVD), dementia, brain tumors, and psychiatric comorbidities significantly elevate the risk of premature mortality in older PWE.[10] A study indicated that PWE and psychiatric comorbidities have more than twice the incidence of SUDEP compared to those without psychiatric issues, with the risk ~5X higher among females.[13] Furthermore, common neurological disorders among older PWE, such as stroke, Alzheimer's (AD), and Parkinson's diseases (PD), not only lead to debilitation but also amplify the risk of early mortality.[14] The etiology of epilepsy can also disproportionately affect the rate of mortality in older PWE. When compared to idiopathic epilepsy, seizures resulting from remote symptomatic etiologies (such as brain tumors and neurodegenerative disorders) show higher mortality counts.[15] External factors such as injuries, ASM usage and polypharmacy further add to mortality risks, being not uncommon in older PWE.[9,16,17] (Figure 1).

3 | STATUS EPILEPTICUS AND MORTALITY IN OLDER PWE

SE, as defined by ILAE, is characterized by a single prolonged and self-sustaining seizure lasting 5 min, if convulsive, or 10 min, if focal or absence, or multiple intermittent seizures that occur frequently enough to prevent complete conscious recovery between seizures.[18] Considered the most extreme form of epilepsy, SE is one of the most common and devastating neurologic emergencies. In the United States, the incidence of SE is 18.3–41/100000 per year,[19] ~4X higher than in the 1970s, suggesting a high burden of illness in recent years. SE is associated with high mortality rates in PWE, particularly in acute symptomatic etiologies of SE, which account for 48%–63% of all SE cases.[18] SE distribution is bimodal with respect to age, showing the highest incidence among children <1 and adults >60.[20]

SE is particularly devastating in older adults and is a known culprit of excess mortality, with cerebrovascular events being the most common etiology, correlating with worse mortality.[21] SE has an annual incidence of 27.1/100000 in older adults, ~4-5X higher than younger adults.[22] The diagnosis and treatment of SE in older adults are challenging due to several factors. Older PWE tend to present more often with non-convulsive SE (NCSE),[20] as opposed to SE with motor symptoms that are observed in younger PWE.[23] This subtle presentation complicates diagnoses due to the complexity of many older peoples' comorbidities, declining cognitive functions, and polypharmacy.[20] Additionally, the diagnosis of NCSE requires an electroencephalogram (EEG)[18]; however, the time required to confirm NCSE on EEG delays treatment. Even once treatment is initiated, older PWE may be resistant to treatment due to the disease prognosis being dependent on the course of the

underlying etiology, such as stroke, metabolic or electrolyte disturbance, intoxication, sepsis, etc.[24] All of these factors may contribute to higher mortality rates in older PWE.

Refractory SE (RSE), which is resistant to standard therapy, also has a higher incidence in older PWE.[25] RSE is linked to increased mortality and overall poor functional long-term outcomes compared to treatable SE.[26] This further contributes to increased SE-related mortality among older PWE.

4 | CARDIAC MORTALITY IN SEIZURES AND STATUS EPILEPTICUS IN OLDER PWE

Epilepsy may be associated with cardiac complications, including a disturbed cardiac autonomic nervous system and acquired heart dysfunction, leading to an "epileptic heart" and an increased risk of sudden death.[27] Seizures affect the sympathetic and parasympathetic branches of the central autonomic nervous system, commonly involving the areas that control heart activity, including the insula, amygdala, and hypothalamus.[28,29] Sustained hypoxia during prolonged seizures can cause the release of inflammatory cytokines, adding to cardiac stress. This can lead to bradyarrhythmias, suppression of sinus node activity, and atrial fibrillation.[27,30] Cardiac microlesions, enhanced sympathetic tone, and altered expression of cardiac ion channels that occur in epilepsy may lead to altered cardiac repolarization, causing potentially fatal ventricular tachycardias.[27]

All of the aforementioned cardiac complications can have more dire consequences in older adults than younger ones, potentially leading to higher mortality. Older adults are already more prone to arrhythmias, autonomic nodal dysfunction, and sudden cardiac death than younger adults due to age-related degenerative changes in cardiac modeling.[31] Moreover, older PWE with DRE are at particularly higher risk of cardiac mortality due to interictal prolongation of QT intervals and seizure-related myocardial infarctions (MI).[27] Seizure-related MI is a serious complication observed in 6%–28% of PWE with GTCs, especially in those ≥70, with comorbid CVD risks or coronary artery disease.[32,33] They are attributed to the demand ischemia caused by the GTC and significantly increase the risk of mortality in older PWE.[33] Studies have found higher risks for MI, arrhythmia, and sudden death in PWE compared to non-epilepsy individuals[34] and a lesser likelihood of successful resuscitation after cardiac arrest in older PWE.[35]

ASMs can add to cardiac complications in older PWE. Some ASMs slow cardiac conduction, reduce heart rate variability, and rarely induce atrioventricular conduction block in older adults.[36] Drugs such as phenytoin, lacosamide, and carbamazepine have been associated with arrhythmias.[37,38] Around 13%–40% of ASM users experience hyperhomocysteinemia, a significant risk factor for CVD and thrombosis, with an increased mortality risk.[36]

5 | POLYPHARMACY IN OLDER PWE

Evidence suggests that polypharmacy may have an association with excess mortality.[16] Older adults on polypharmacy are more prone to drug–drug interactions and adverse reactions to the medications due to age-related physiological changes in the drug pharmacokinetics.[39] Medical errors in dosing, which are more likely when taking multiple medications, can have more significant implications for older PWE. Additionally, polypharmacy may contribute to poor adherence, which may have major clinical consequences such as an increase in hospitalization and falls with increased morbidity and possible mortality.[40] Therefore, polypharmacy particularly increases the risk of premature mortality in older PWE.

6 | ANTI-SEIZURE MEDICATIONS AND MORTALITY IN OLDER PWE

Enzyme-inducing ASM (EIASM) is associated with a significant rise in low-density lipoprotein-C and non-high-density lipoprotein-C levels in people over 65. The resultant dyslipidemia can increase the risk of CVD[17] and death in older PWE. Statin therapy to counteract the rising lipid levels also increases musculoskeletal disorders and cognitive dysfunction, causing an increased likelihood of frailty and, subsequently, risk of mortality.[41] Carbamazepine use is associated with neuro- and cardiotoxicity,[42] which can lead to an increase in the risk of mortality in older PWE.

The use of multiple ASMs is associated with adverse effects, contributing to increased mortality in older PWE. PWE taking three ASMs have a higher risk of SUDEP than those on monotherapy, even after adjusting for seizure frequency.[43] Older adults often have multiple comorbidities and take various medications.[44] ASMs can interact with other medications, leading to serious side effects such as sedation, cognitive impairment, and ataxia, which increase the risk of falls and injuries, thereby worsening outcomes and increasing mortality risks.[45,46]

EIASM alters vitamin D metabolism, leading to osteoporosis and consequently increasing fracture risk. Osteoporotic fractures are associated with disability,

reduced quality of life and may increase mortality.[47] Since older PWE are already prone to fractures related to seizure-associated trauma, concurrent EIASM usage can increase fracture risk and worsen their outcomes and mortality rate.[48,49] Weight gain is a common side effect of ASMs, increasing the risk of metabolic disease, which can have dire consequences in older PWE.[50] ASMs like carbamazepine and oxcarbazepine can also cause hyponatremia. This risk of hyponatremia is higher in older PWE.[51] In turn, hyponatremia can cause confusion and headaches and worsen seizures.[52] Many ASMs can impair cognitive function. This is particularly detrimental in older adults who may already be experiencing age-related cognitive decline, compounded further by epilepsy.[53] Cognitive impairment can further affect the ability of older PWE to manage their daily activities, increasing the risk of accidents and poor health outcomes, including mortality.[54]

7 | EXTERNAL CAUSES OF MORTALITY IN OLDER PWE

External causes are another common cause of excess mortality in older PWE. Falls are particularly prevalent among this demographic, compounded by the increased likelihood of sustaining severe, life-threatening injuries during seizures.[55] Sustaining traumatic brain injury (TBI) has also been observed to decrease survival in PWE, especially if occurring within 6 months of the onset of epilepsy.[56] Additionally, accidents, burns, and drownings are common external causes of mortality in older PWE.[57] These incidents are exacerbated by age-related conditions such as frailty, presbyopia, impairment in psychomotor speed, impaired peripheral nerves, decreased muscle mass, and cognitive impairment.[14] Together, these factors significantly heighten the risk of accidents and injuries and subsequent mortality in older PWE.

8 | PSYCHIATRIC COMORBIDITIES AND MORTALITY IN OLDER PWE

Comorbid psychiatric illness is also frequent among older PWE and may influence mortality. Up to 30% of individuals with epilepsy experience depression.[58] A later age at onset of seizures has been associated with increased depression.[59] New-onset epilepsy has been correlated with a three-fold increased relative odds of psychiatric admission in older people.[60] Many ASMs carry the risk of increased psychiatric disturbances.[61] Since older patients are more sensitive to the side effects of ASMs,[62] this risk increases disproportionately in them. These factors combine to worsen health outcomes in older PWE, increasing their risk for mortality. Suicidality increases during the life course, with older people showing the highest suicide rate globally.[63] The risk is further increased in people with neurological conditions and stress,[63] particularly predisposing older PWE to increased suicidality. Implementing screenings for suicidal thoughts in PWE may help identify those who could benefit from specific behavioral and pharmacological treatments.[64]

9 | SOCIAL ASPECTS OF LIFESTYLE AND MORTALITY IN OLDER PWE

Older adults are more likely to experience isolation than the general population. Around 17% of older adults communicate with their relatives <once/week, and half of those >75 live alone[65] This issue becomes worse in older PWE due to the stigma associated with epilepsy; older people experience this stigma at a greater extent than younger adults. They also have an increased dependency with feelings of helplessness, fear of loss of control, and independence including transportation problems, all of which contribute to a reduction in the quality of life in older PWE, which can subsequently impact their care.[66] Older PWE had almost half the rate of employment than others, which also limits their financial independence,[66] and possibly also lead to delays in seeking care, worsening health outcomes.

10 | SUDDEN UNEXPECTED DEATH IN EPILEPSY (SUDEP)

The official definition of SUDEP initially proposed in the 1990s has since evolved, and in 2012, Nashef et al. proposed a unified definition of SUDEP. Definite SUDEP is defined as "*sudden, unexpected, witnessed or unwitnessed, nontraumatic, and non-drowning death in an individual with epilepsy with or without evidence of a terminal seizure and excluding documented status epilepticus (seizure duration ≥30 min or seizures without recovery in between), in which investigation and postmortem examination, including toxicology, do not reveal a cause of death other than epilepsy*".[67,68] Overall, SUDEP is a cause of death that occurs when there is no known structural cause of mortality in PWE. The mechanisms and conditions underlying SUDEP are diverse.[67] However, the application of SUDEP definitions in the clinical setting has shown ambiguity in its identification, particularly in those having comorbidities or near resuscitation. Therefore, greater standardization of criteria is needed.[68]

11 | SUDEP, AN UNDERESTIMATED ENTITY IN OLDER PWE

SUDEP constitutes the most important cause of death that is directly related to epilepsy in PWE. Its incidence in different groups varies. Being rare in new-onset epilepsy, the incidence increases in chronic epilepsy to 1–2/1000 person-years and is highest in drug-resistant epilepsy (DRE) (3–9/1000).[69] When comparing different populations, its incidence is lowest in population-based studies (0.35/100 person-years), higher in referral populations (0.8–5.9/100 person-years), and clinical trials of adjunct drugs for complex partial epilepsy (2.8–3.9/100 person-years), and highest in surgical series (9.3/100 person-years).[70]

But what about the incidence of SUDEP, specifically in older PWE? Historically, SUDEP incidence in older PWE has been reported to be significantly lower than in younger adults and children due to multiple reasons (Figure 2). While we do consider that SUDEP is underdiagnosed in older PWE, it must also be acknowledged that due to the intrinsic difficulty of diagnosing SUDEP, its exact incidence in this population is unknown. This consideration makes the underdiagnosis of SUDEP a possibility, rather than a definitive occurrence.

In 1999, Annegers et al. reported that the older people had a very small relative increase than the younger population in the reported incidence of SUDEP. While the incidence of sudden death in young adults with DRE was roughly 20 times higher than in the general population and well-controlled epilepsy, older PWE did not demonstrate similar trends. Instead, the incidence of sudden death among the general population, well-controlled epilepsy, and DRE were comparable among older PWE, at ~500/100000 person-years.[70] This apparent reduction in SUDEP risk with age has also been demonstrated in several earlier studies. In a 2012 study, among >12000 autopsy cases surveyed in Maryland, none of the cases were classified as SUDEP above the age of 63.[71] In 2014, a systematic review of epidemiologic studies of SUDEP found that SUDEP incidence declined markedly with age. It was 8% of all cases in 51–60-year-olds, 3% among 61–70-year-olds, and 1% in those above 70.[72]

Similarly, all-cause mortality rates in older PWE have been shown to be lower than in younger PWE. One study demonstrated that all-cause mortality in epilepsy was about 2–3 times higher than in the general population, but the ratio was significantly lower in older ages.[70]

However, given that the incidence and prevalence of epilepsy continue to rise after 65, this trend suggests that older adults may either have a natural resistance to SUDEP or that it is likely misidentified as the cause of death in this demographic.[71]

Recent studies suggest that a multitude of reasons may lead to misclassification of SUDEP as being the actual cause of death in older adults. Possible biases and failure to take relevant seizure history or recognition of seizure as the terminal cause of death cause an underestimation of SUDEP. Lack of identification of seizure-specific findings on autopsy (such as urinary incontinence and tongue biting) leading to other declarations as the cause of death has further hindered recognition of SUDEP in older adults.[7] Epilepsy itself is also frequently underdiagnosed in older adults, which may also lead to a failure to recognize its subsequent complications, such as SUDEP.[73]

The gold standard for diagnosing the cause of death is autopsy. However, it is often not performed commonly in older adults as a gesture of "kindness."[74] Families and clinicians may feel reluctant to inflict further "discomfort" upon the deceased.[74] The stigma and cost surrounding the process also cause families to decline autopsies for older adults.[74] In the cases where autopsies are eventually

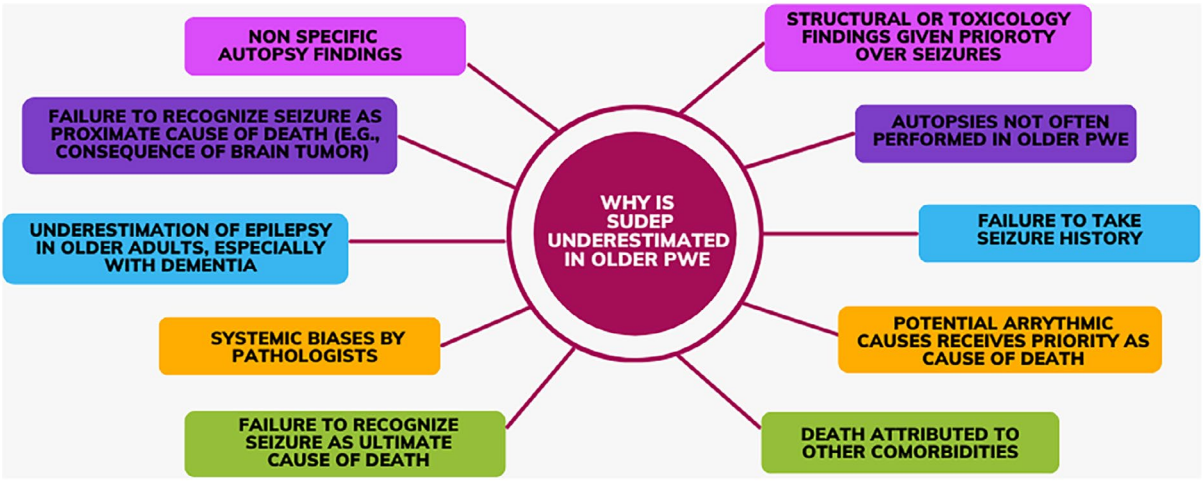

FIGURE 2 Reasons why sudden unexpected death in epilepsy (SUDEP) is underestimated in older people with epilepsy (PWE).

performed, the subjective decision of the coroner may also cause many SUDEP cases to go unrecognized.[75]

Common conditions such as heart disease, alcoholism, or metabolic disorders gain precedence as potential causes of death on autopsy.[76] Often, structural and toxicological findings (such as cardiomegaly and drug concentrations) are prioritized over seizures. Potential arrhythmic causes receive higher priority over SUDEP in sudden deaths with negative autopsy.[7] The lower relative contribution of SUDEP in older adults is often attributed to the increasing frequency of mortality from other causes with age.[13] While SUDEP recognition rates remain low among pathologists, they are even lower among non-pathology medical examiners or coroners with less training.[77] In a survey, 83.5% of pathologists acknowledged that SUDEP is a valid diagnosis if autopsy reveals no alternative cause of death in PWE. However, only 22.9% of these pathologists diagnosed SUDEP in the cases that met the criteria.[78] There is often a discordance in the classification of SUDEP among epileptologists and forensic investigators, as epileptologists are more likely to classify SUDEP as a cause of death. Therefore, it is crucial to establish standardization and improve coordination between epileptologists and forensic to enhance diagnostic accuracy.[77]

There is also a difficulty in differentiating between SUDEP and sudden cardiac death (SCD). A thorough history of the patient's medical comorbidities, terminal events before death, genetic evaluation and autopsy can help discern the two distinct entities.[79] However, the cardiopulmonary effects of seizures can lead to an overlap of symptoms and the existing literature on how to distinguish the two is lacking, which makes the distinction difficult.[79]

More recent rigorously conducted studies have challenged the notion of low SUDEP incidence in older adults and have suggested a high incidence of SUDEP in older PWE. A Swedish population-based cohort found that death certificates alone underestimated SUDEP. However, when the data from police reports and medical records were also considered, a higher rate of SUDEP was discovered with incidence of 1.29/1000 after 50.[13]

12 | RISK FACTORS FOR SUDEP

Evidence regarding risk factors for SUDEP has varied. Various studies have reported having generalized tonic–clonic seizures (GTCs), an increased frequency of GTCs, presence of nocturnal GTCs, use of polytherapy, duration of epilepsy >15 years, male gender, symptomatic etiology, lamotrigine therapy, alcohol dependence, and the combination of not sharing a bedroom as SUDEP risk factors.[80,81]

While previous studies have identified a younger age of onset as a potential risk factor,[80,81] recent data suggest otherwise. A recent robust American Academy of Neurology and American Epilepsy Society guideline summary, based on an extensive systematic review, found that younger age of epilepsy onset did not increase the risk for SUDEP, and the incidence was actually higher in adulthood compared to childhood. While affirming that the previously listed risk factors can impact the risk of SUDEP, the guideline identified that not being seizure-free for 1–5 years, having extratemporal epilepsy, not being treated with ASM, not adding an ASM in DRE, having intellectual disability and anxiolytic usage were factors that also confer a greater risk. Interestingly, along with nocturnal supervision, they found that the use of a nocturnal listening device, in particular, leads to a moderate SUDEP risk reduction.[82] Therefore, careful stratification of individual risk factors (Figure 3) should be done to assess the risk of mortality and SUDEP in older PWE.

13 | ADDITIONAL FACTORS ASSOCIATED WITH MORTALITY IN OLDER PWE

Various additional factors that are unique to this population influence mortality (Figure 4). Examining these factors is crucial to improving patient outcomes and tailoring treatment strategies for older PWE.

Incident epilepsy in older adults is associated with higher 5 years mortality (62.8%), particularly when diagnosed after another neurological condition such as PD, traumatic brain injury (TBI), multiple sclerosis, and stroke.[83] Similarly, co-morbid disease burden, Medicaid co-insurance, age, baseline dementia, and frailty are also significantly associated with mortality in PWE.[83–85]

Late-onset epilepsy (LOE) in older adults is independently associated with premature mortality, with the majority (56%) of this excess mortality due to stroke and dementia, two common comorbidities in older PWE. Only 1.1% of deaths in LOE are related to epilepsy or SE, which may be indicative of the lower rate of GTCs and the relatively pharmaco-responsive nature of seizures in LOE.[86] Interestingly, female gender and certain races, such as Asian and Hispanic are associated with a lower risk of mortality.[83]

Stroke and dementia as mortality risks in older PWE are evident in other studies as well. In a single-center study in Israel, people with LOE of unknown etiology were followed for 10 years. The incidence of dementia was 22.2% and the mortality was higher in PWE with co-morbid dementia than PWE without dementia.[87] Among the co-morbidities present most frequently in PWE before death, a Lithuania nationwide study identified hypertension, cerebrovascular diseases, and congestive heart failure to

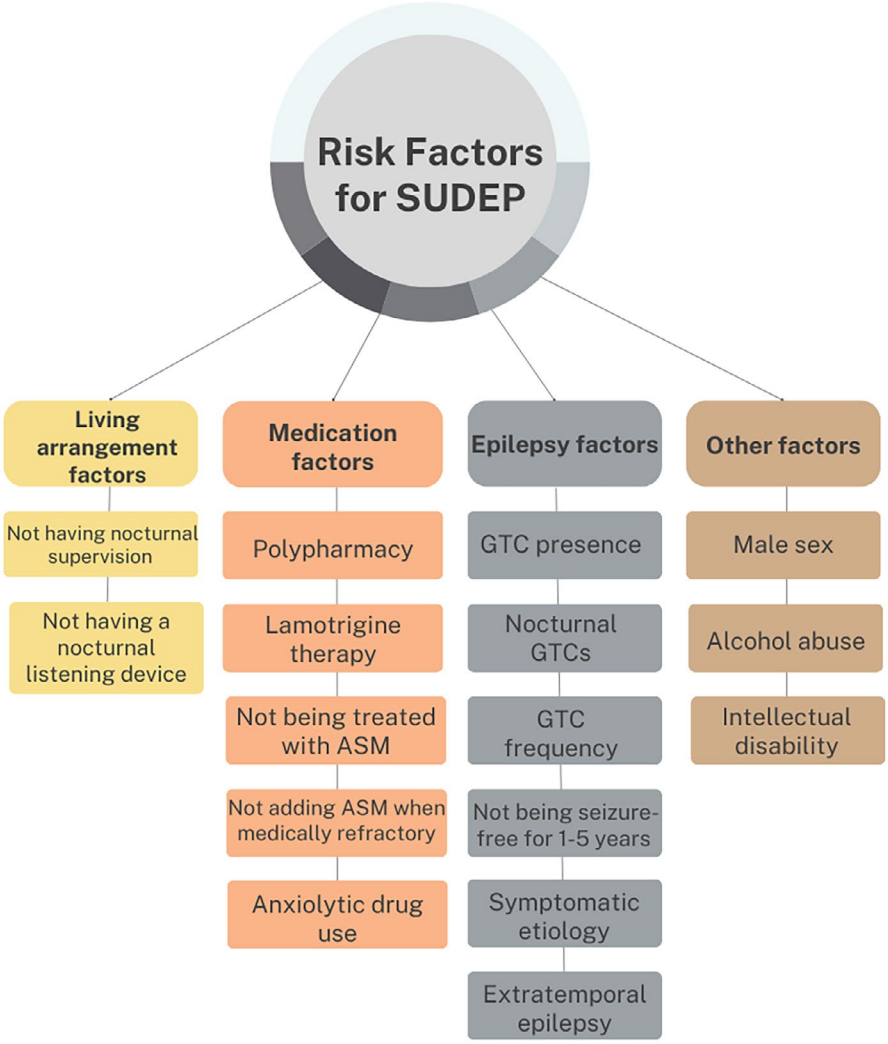

FIGURE 3 Risk factors for sudden unexpected death in epilepsy (SUDEP) in older people with epilepsy. ASM, Antiseizure Medication; GTC, Generalized Tonic–Clonic Seizures.

be the most common. The high prevalence of cerebrovascular conditions and dementia in this population suggests that the mortality associated with underlying causes of epilepsy or its comorbidities is becoming increasingly relevant in the aging population of PWE.[88]

14 | THE CHANGING TRENDS OF MORTALITY IN PWE OVERTIME

Between 1990 and 2015, there was a worldwide decrease in overall epilepsy death rates and disability-adjusted life-years (DALYs) due to epilepsy.[89] However, this worldwide incidence and mortality decrease is not demonstrated in older PWE.[90] There has been a five-fold increase in epilepsy incidence among individuals ≥65,[78,79] which is increasingly concerning.

There are several causes for this increase in mortality in older PWE. Epilepsy often exists with a host of comorbidities in older PWE. The most common comorbidities are neurological.[91] The rising population of older adults in the United States[92] results in a larger burden of disease in older PWE due to the additional burden of neurological disorders. This larger burden of neurological disorders may account for increased mortality. Additionally, there is evidence that comorbid CNS degenerative disorders, delirium, dementia, stroke, and malignancies have all increased significantly as etiological causes of death in epilepsy over the years.

More specifically, the proportion of mortality as a result of neoplasm, vascular dementia, and AD has increased (52.3%, 210.1%, 216.8%, respectively) between 1999 and 2017.[93] The annual age-adjusted mortality rates for AD and vascular dementia have increased by 2.06% and 4.90%, respectively, from 2007 to 2016.[94] This may account for the proportional increase in AD and vascular dementia-specific etiology increase in mortality in PWE.[94] In comparison, mortality with epilepsy-specific and CVD etiology has decreased (27.1%, 42.6%, respectively).[90] The drop in epilepsy-specific mortality aligns with worldwide decreases in epilepsy disease burden. CVD mortality rates have also been steadily decreasing since 2010,[95] with several potential mechanisms, but are consistent with the decrease in ischemic heart disease etiologies of

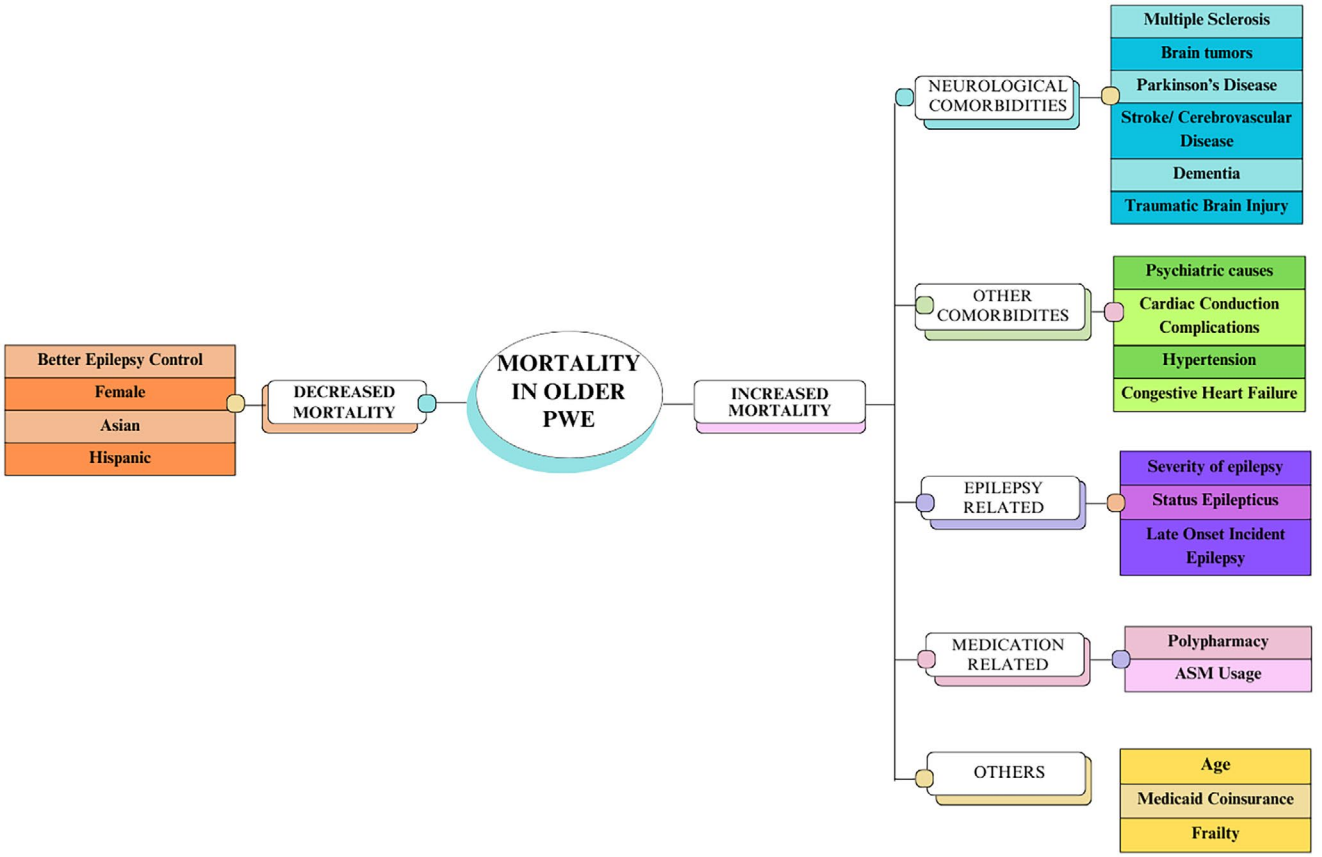

FIGURE 4 Factors associated with mortality in older people with epilepsy (PWE). ASM, Antiseizure Medication.

mortality in PWE. Finally, there have been declining rates of external causes of death in PWE, such as those due to accidents, falls, drowning, and burns.[90]

The increased mortality risk of the common comorbidities in older PWE plays an even larger role in the potential increase in overall mortality in older PWE and presents emerging challenges unique to this population. Unlike younger PWE, comorbidities associated with older PWE more significantly contribute to disproportionately higher rates of mortality, especially those associated with the central nervous system (i.e., neurodegeneration, dementia, cerebrovascular disease) and frailty, as noted in the above sections. Therefore, they deserve special attention. In the coming sections, these comorbidities will be further discussed in the context of their roles in mortality in older PWE.

15 | MORTALITY OUTCOMES IN OLDER PWE WITH DEMENTIA, AD AND OTHER NEURODEGENERATIVE DISORDERS

PWE have a higher risk of developing dementia, and dementia is associated with an increased risk of developing seizures.[96] AD and other dementias are associated with up to a 5–10-fold increase in epilepsy risk than the general population, with 10%–64% of patients with AD having at least one unprovoked seizure.[96,97] Dementia becomes a significant problem in older adults, being among the top three most common etiologies for epilepsy in older PWE.[96] PWE and co-morbid dementia exhibit a more aggressive disease course with a faster cognitive decline.[98] This can lead to worse morbidity and functional and cognitive outcomes in older PWE.[99]

Dementia is an uncontroversial risk factor for premature mortality in PWE. In a UK population-based study, dementia was among the three critical risk factors associated with mortality in older PWE.[84] In the United States, epilepsy mortality trends have shifted, with a 98.8% increase in age-adjusted mortality rates from 1999 to 2017 and a significant rise in deaths from vascular dementia by 210.1% and AD by 216.8%, as noted above.[93] Therefore, it is becoming evident that dementia is becoming an important contributor of mortality in PWE.

However, the contribution of epilepsy to subsequent mortality in people with dementia (PWD) is less well-established. In 1992, McAreavey et al. noted that although seizures were relatively common in hospitalized PWD, they rarely led to in-hospital mortality.[100] In 2015, in a

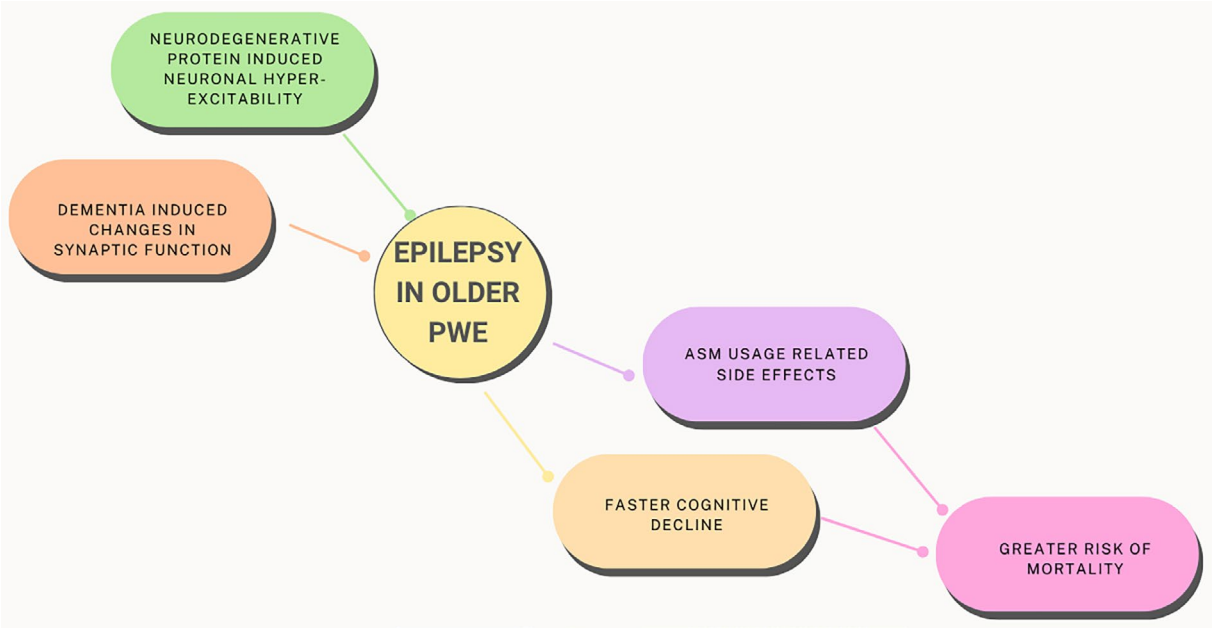

FIGURE 5 Neurodegeneration, older people with epilepsy (PWE), and Increased Mortality Risk. ASM, Antiseizure Medication.

single-center study of hospitalized older PWE, AD was identified as the third most common etiology of epilepsy but had no increased short-term hospital mortality.[101] In another study, the 2 years mortality rate was comparable between patients with Lewy Body Dementia with and without epilepsy.[102] However, most of these studies are either single-center or have small sample sizes.

Recent evidence from a large prospective multicenter study suggests that even after adjusting for age, sex, race, ethnicity, hypertension, diabetes, hyperlipidemia, dementia severity, education, stroke, TBI, PD, alcohol abuse, depression, and dominant AD mutation, epilepsy control was associated with significantly higher mortality in PWD.

Similarly, another demographic that deserves special mention in the context of epilepsy-related mortality in PWD is the aging population of Down syndrome (DS). People with AD and DS are at a significantly increased risk of mortality if they develop seizures.[103] The risk of death in people with intellectual disability such as DS and epilepsy is 3–16 times higher than the general population.[104] Epilepsy in DS is as high as 46% in those >50, particularly in symptomatic AD. Over 50% of DS with co-morbid AD develop epilepsy, which is clinically characterized by generalized myoclonic seizures, named late onset myoclonic epilepsy (LOMEDS). LOMEDS worsens cognitive and functional outcomes in AD, and is an independent risk factor for mortality in DS.[105]

ASM use is also an independent risk factor for mortality in PWD. Finnish MEDALZ (Medication Use and AD) study demonstrated that the risk of death was higher among ASM users than nonusers. Mortality was highest among the first 90 days of ASM usage, and death rates were higher with older-generation ASMs than newer ones.[106] Since some ASMs, such as carbamazepine and valproic acid, may be used for behavioral and psychological symptoms of dementia, this population has high ASM usage, regardless of the presence of epilepsy.[106] These factors should be considered when managing such patients (Figure 5).

16 | MORTALITY OUTCOMES IN OLDER PWE WITH STROKE

Recent studies also suggest a bidirectional link between stroke and epilepsy.[86] Post-stroke epilepsy (PSE) accounts for ~30%–50% of newly diagnosed epilepsy cases in those ≥60.[107]

Multiple factors contribute to the increase in mortality in PSE **(**Figure 6**)**. In the Atherosclerosis Risk in Communities Study, mortality risk was significantly increased in LOE with prior stroke.[86] This excess mortality may result from the increase in seizures due to the lower seizure threshold that occurs because of stroke. ASMs may interact with secondary stroke prophylaxis and have a detrimental impact on lipid profiles, increasing the risk of subsequent strokes and, hence, mortality. Side effects of ASMs or seizure-related risks may also interfere with rehabilitation and post-stroke care, conferring a greater mortality risk.[108] In another study, older people with PSE had higher mortality than younger PWE due to CVD, signifying the importance of CVD treatment in high-risk populations for reduction in mortality.[109]

Multiple risk factors have been associated with PSE. Some of these including early seizures, stroke severity, cortical involvement, middle cerebral artery involvement,

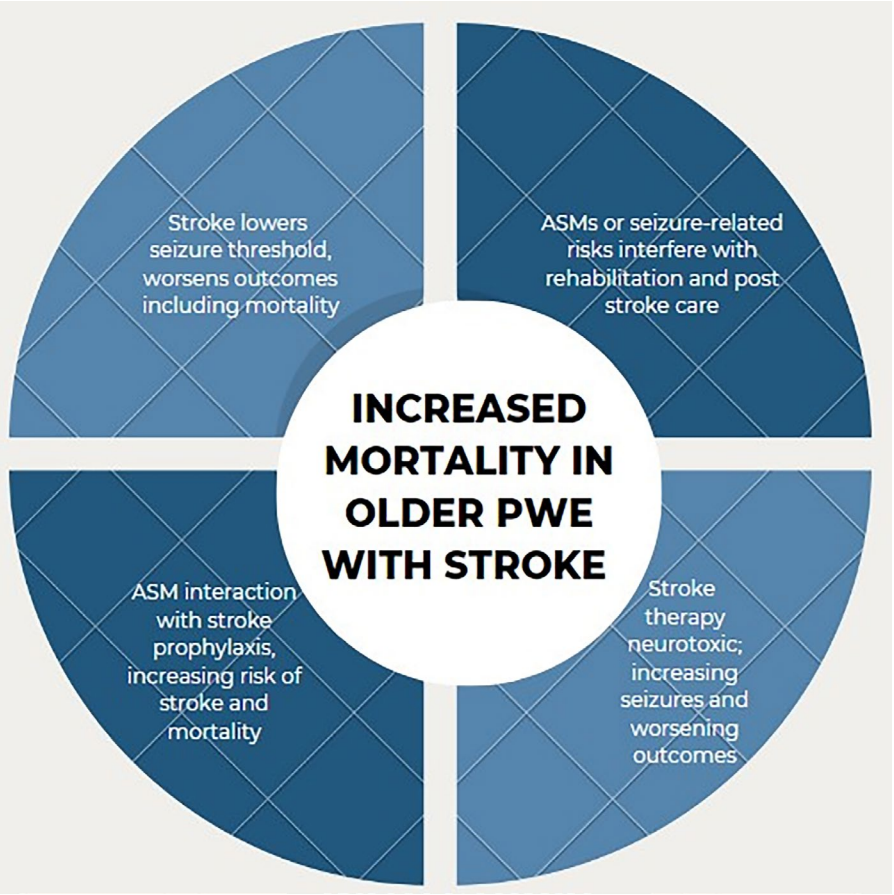

FIGURE 6 Increased mortality in PWE with Stroke. ASM, Antiseizure Medication.

and large-artery atherosclerotic etiology, have been combined to form the SeLECT score for the prediction of PSE development.[110] Additional risk factors may include young age, hyponatremia, and alcohol use.[111] Stroke therapy has a neurotoxic effect, which can predispose individuals to having an increased risk of seizures.[112] A study identified watershed stroke and lower Barthel index as possible predictors of PSE, with older age being significantly associated with a higher risk of in-hospital mortality in PSE.[107] These risk factors can be used to identify high-risk individuals who can be monitored closely for timely intervention for PSE, to prevent mortality. Early initiation of prophylactic ASM may also be considered in select cases.

17 | MORTALITY OUTCOMES IN OLDER PWE WITH FRAILTY

Frailty is a health state in which individuals' overall well-being and ability to function independently is reduced, increasing the likelihood of health deterioration.[113] In clinical practice, it is considered a complex age-related clinical condition characterized by a decline in physiological capacity across several organ systems, leading to an increased susceptibility to stressors.[11,114] It is a precursor for worse health outcomes and exposes older adults to increased risk of falls, injuries, disability, and morbidity, all of which contribute to an increase in mortality in older PWE.[114]

While frailty can occur at any age, it is more prevalent in PWE. In a population-based study, the prevalence of frailty was found to be increased in both older adults and PWE.[115] The increase in frailty is attributed to increased stress levels and reduced quality of life in epilepsy.[116] Seizure-related falls and injuries increase the burden of physical frailty, while social isolation and psychosocial comorbidity increase psychological frailty.[116,117] Additionally, patients using multiple ASMs have significantly higher frailty and are associated with detrimental effects on several health measures previously linked to frailty, including vitamin D levels and blood lipid control.[116] ASM-induced osteoporosis increases the risk of fractures, with subsequent immobility increasing the risk of frailty, morbidity, and mortality.[118,119]

The association between epilepsy, dementia, and frailty cannot be understated. Frailty may contribute towards cognitive decline in PWE, while the risk of epilepsy development can be up to 10-fold higher in PWD who are also more frail.[11] The cognitive burden of frailty, resulting from the deficit accumulation, may need better evaluation and

management, for improving health outcomes to prevent mortality in older PWE.

All these factors eventually contribute to worsened health outcomes and increased mortality in older PWE (Figure 7). Frailty has a significant correlation with length of hospital admission, discharge status, the outcomes of breakthrough seizure-related hospitalization, and mortality, all of which are likely worse in frail older PWE.[120] In a study, among 81 frail and 10 severely frail individuals, 38.3% and 50% were discharged to non-home locations such as nursing or rehabilitation facilities, including 6.2% and 20% of people who died, respectively.[121] Therefore, targeted interventions to reduce frailty in older PWE can contribute to decreasing mortality in this population.

18 | LIMITATIONS

Our review has several limitations. This review did not include studies indexed in databases other than Google Scholar, PubMed Web of Science, and Medline. The inclusion criteria for the review of selected studies relied on the writers' experience. There may be a limitation of generalizability of our review findings due to the differences in the study methodology, patient characteristics and sample size of the papers reviewed. Therefore, greater research is needed in prospective, larger sampled projects to expand upon our results.

19 | FUTURE DIRECTIONS AND CONCLUSION

Older PWE are prone to excess mortality due to a multitude of reasons, which are unique from the younger PWE. Despite an increased risk of SUDEP in older PWE, it remains a significantly under-estimated entity. SE and comorbidities of dementia, stroke, cardiovascular disease, frailty, polypharmacy, and their subsequent complications often predispose older PWE to early mortality. Therefore, carefully considering and promptly addressing these factors is imperative in preventing the rising mortality in this patient population.

Future research should focus on improving diagnostic accuracy for SUDEP in older adults through standardized

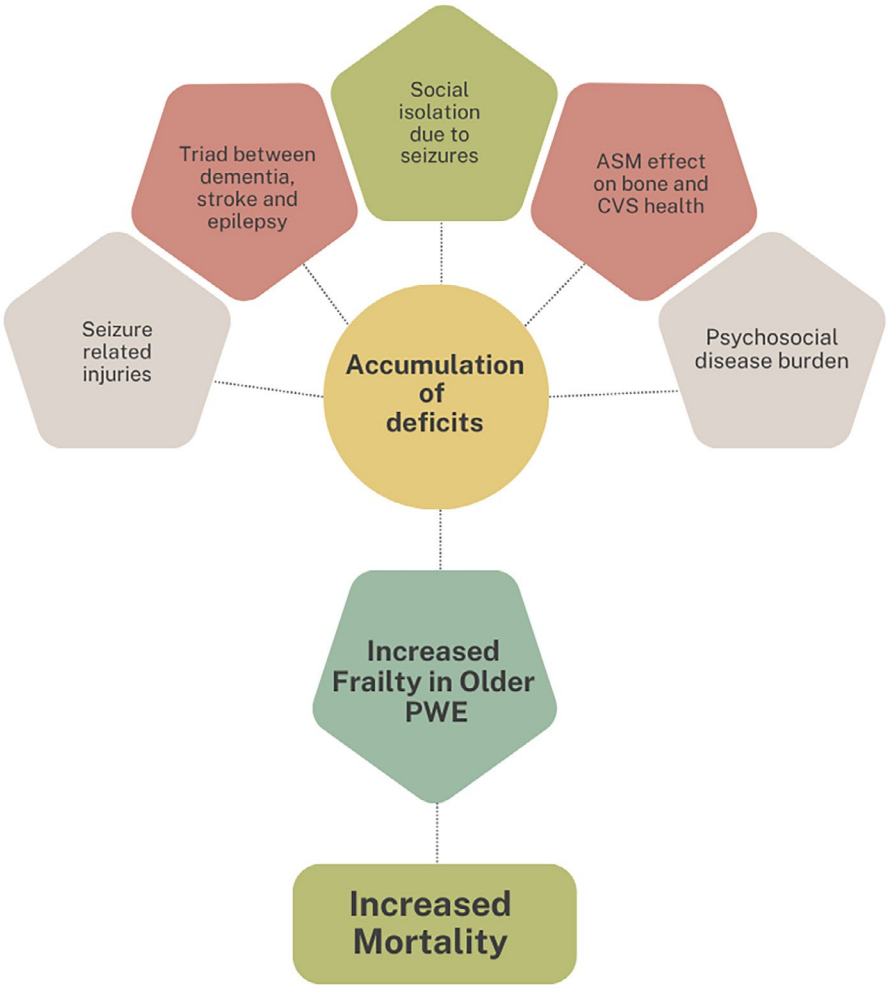

FIGURE 7 Increased frailty and mortality in older PWE. ASM, Antiseizure Medication; CVS, Cardiovascular system.

autopsy protocols and enhanced multidisciplinary collaboration. Interventions targeting comorbidities, especially dementia and cerebrovascular disease, and frailty could reduce premature mortality in older PWE.

Developing personalized treatment plans that consider the unique risks faced by older adults, such as cardiovascular issues and the impact of ASMs, is critical. Carefully selecting ASMs when treating older PWE could reduce mortality. Aggressively treating seizures, encouraging appropriate lifestyle modification, monitoring for triggers and counseling for social support may be beneficial.[64] Additionally, increasing awareness and education among healthcare providers and families about the risks and management of epilepsy in older adults can lead to better outcomes. Nocturnal supervision should be encouraged as it can reduce the risk of SUDEP with an OR up to 0.4.[122] Conducting longer EEG studies, including sleep can increase the yield of seizure detection as most epileptiform activity in older adults is detected during sleep.[123] Integrating technology, such as wearable devices for real-time monitoring, nocturnal listening monitors and subcutaneous EEG devices, along with early detection and management of seizures, may also play a significant role in reducing mortality in older PWE. Wearable seizure detection devices demonstrate a sensitivity of more than 90% in detecting seizures.[122] They are particularly useful in offering reliable nocturnal GTC detection as up to 55% of nocturnal GTCs are otherwise unreported.[124] These devices can be utilized to detect and treat seizures early to reduce SUDEP risks[124] Ultra-long subcutaneous EEG devices have also demonstrated efficacy in epilepsy early seizure detection and tailored ASM management.[125] This improved treatment response monitoring can help refine treatment strategies for likely preventing seizure complications including mortality.

AUTHOR CONTRIBUTIONS

All authors contributed to the design and drafting of the manuscript. All authors critically revised the manuscript and approved its submitted version.

ACKNOWLEDGMENTS

The authors have nothing to report.

FUNDING INFORMATION

This work is supported by the American Epilepsy Society (Award ID: 1067206) and the BAND foundation.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

All the data from this review are available online.

ETHICAL STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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How to cite this article: Hashmi SA, Gundlapalli R, Zawar I. Mortality in older adults with epilepsy: An understudied entity. Epilepsia Open. 2025;10:15–30. https://doi.org/10.1002/epi4.13098