---

**Article:**
Xu, Y., Lavrencic, L., Radford, K. et al. (5 more authors) (2021) Systematic review of coexistent epileptic seizures and Alzheimer's disease : incidence and prevalence. Journal of the American Geriatrics Society, 69 (7). pp. 2011-2020. ISSN 0002-8614

https://doi.org/10.1111/jgs.17101

---

# Systematic review of coexistent epileptic seizures and Alzheimer`s disease: incidence and prevalence

Ying Xu MD, PhD[a,b], Louise Lavrencic PhD[a,b], Kylie Radford PhD[a,b], Andrew Booth PhD[c], Kaarin J Anstey PhD[a,b], Craig S Anderson MD, PhD[b,d,e,f], Sohei Yoshimura MD, PhD[g], Ruth Peters PhD[a,b,h]

[a.]Neuroscience Research Australia (NeuRA), Margarete Ainsworth Building, Barker Street, Randwick, NSW 2031, Australia
[b.]University of New South Wales, Sydney, NSW 2052, Australia
[c.]School of Health and Related Research (ScHARR), University of Sheffield, Sheffield England S1 4DA, UK
[d.]The George Institute for Global Health, Faculty of Medicine, University of New South Wales, 83-117 Missenden Road, Camperdown NSW 2050, Australia
[e.]The George Institute for Global Health at Peking University Health Science Centre, Level 18, Tower B, Horizon Tower, No. 6 Zhichun Rd, Haidian District, Beijing, 100088, P.R. China
[f.]Neurology Department, Sydney Local Area Health District, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia
[g.]Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, 6-1 Kishibe-shimmachi, Suita, Osaka 564-8565, Japan
[h.]School of Public Health, Imperial College London, London W2 1PG, UK

**Correspondence author:** Ying Xu

Neuroscience Research Australia (NeuRA), Margarete Ainsworth Building, Barker Street, Randwick, NSW 2031, Australia
T +61 02 9399 1888, Email: y.xu@neura.edu.au, Twitter handle @DrYingXu

Running title: Coexistent seizures and Alzheimer`s disease

Words count for abstract 239, Word count for Main Text 3,482, Number of Tables 0, Number of Figures 2

This paper has been presented at the Alzheimer's Association International Conference (AAIC) Neuroscience Next as a poster, and the International Webinar run by Dementia Prevention the International Research Network on Dementia Prevention (IRNDP) as a pre-recorded presentation.

## Impact Statement

We certify that this work is a confirmatory of recent novel clinical research (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 06;58:962-972). This research specifically adds the following to the literature.

1. Incidence of epileptic seizures was up to over 3 per 100 person-years in people with Alzheimer's disease (AD).
2. Prevalence of seizures among people with AD showed variability, but consistent evidence was shown for people with pathologically verified AD.
3. Generalised seizures were over represented in people with AD.
4. Greater attention may be paid to the monitoring of seizures among people with autosomal dominant AD and younger AD patients.
5. Evidence gaps exist for the incidence of AD among people with seizures, and the rates of AD among adults with childhood onset seizures.

## Abstract

**Background/Objectives:** Co-existent seizures add complexity to the burden of Alzheimer's disease (AD). We aim to estimate the incidence and prevalence of co-existent seizures and AD, and summarize characteristics.

**Design:** A systematic review and meta-analysis (PROSPERO protocol registration CRD42020150479).

**Setting:** Population-, community-, hospital-, or nursing home-based.

**Participants and Measurements:** 39 studies reporting on seizure incidence and prevalence in 21,198 and 380,777 participants with AD, respectively, and AD prevalence in 727,446 participants with seizures. When statistical heterogeneity and inconsistency (assessed by Q statistic and $I^2$) were not shown, rates were synthesized using random effect.

**Results:** Studies were conducted in Australia, Brazil, Finland, France, Ireland, Italy, Japan, Netherlands, Portugal, Sweden, Taiwan, UK and USA. The incidence of seizures among people with clinically diagnosed AD ranged from 4.2 to 31.5 per 1,000 person-years. Prevalence of seizures among people with clinically diagnosed AD ranged from 1.5% to 12.7% generally, but it rose to the highest (49.5% of those with early-onset AD) in one study. Meta-analysis reported a combined seizure prevalence rate among people with pathologically verified AD at 16% (95% confidence interval (CI), 14% to 19%). Prevalence of seizure in autosomal dominant AD (ADAD) ranged from 2.8% to 41.7%. Being younger was associated with higher risk of seizure occurrence. Eleven percent of people with adult-onset seizures had AD (95%CI, 7% to 14%).

**Conclusion:** Seizures are common in those with AD, and seizure monitoring may be particularly important for younger adults and those with ADAD.

**Keywords:** Epilepsy, epidemiology, dementia, ADAD

## Introduction

People with epilepsy (PWE) have 1.6 times higher hazard of incident Alzheimer's disease (AD) compared to those without epilepsy.[1] Conversely, a diagnosis of AD is associated with a six-fold increased risk of unprovoked seizures.[2] Apolipoprotein (*APOE) ε4* genotype and mutations in the amyloid β precursor protein gene (*APP*), presenilin-1 (*PSEN 1*) and presenilin-2 (*PSEN 2*) are associated with AD as well as epilepsy.[3,4] Amyloid β and tau-protein elicit epileptiform activity,[5] whereas cerebrospinal fluid (CSF) amyloid β and tau level elevate after seizures.[6,7] Overlapping regional pathology includes accrual of hippocampal damage over time (shown in experimental mice with temporal lobe epilepsy), which results in progressive memory loss.[8] Depending on differences in AD duration and severity of cognitive impairment among people with AD, the incidence and prevalence of seizures vary.[9-15] Conversely, the prevalence of AD among people with seizures also varies.[16,17] When two diseases co-exist, there are disagreements regarding whether focal[18] or generalized onset seizures[15] are more common, and whether seizures precede or follow AD.[2,13,19]

As there is no imminent restorative treatment for AD, whereas seizure control is possible through sleeping well, reducing stress, avoiding drugs and alcohol, and taking antiepileptic drugs (AEDs),[20] awareness of the co-existence may allow early seizure identification and intervention. To date, there is only one systematic review in this field, but it focuses on dementia rather than AD.[21] An up-to-date systematic review on the epidemiology and characteristics of comorbid seizure and AD would allow us to quantify the magnitude of this issue, so as to inform seizure and AD management guidelines.

## Methods

The protocol of this review was registered in PROSPERO [CRD42020150479]. The review is reported according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guideline and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

### Inclusion and exclusion criteria

This review was restricted to published observational studies reporting either or both 1) the incidence or prevalence of “a single epileptic seizure or epilepsy” (hereafter, called “seizures”) among people with AD, and 2) the incidence or prevalence of AD among people with seizures. All journal articles were considered without language limitations, but conference abstracts were excluded. All observational study designs were accepted with the exception of studies of fewer than 50 participants with AD or seizures, depending on the focus of the study, as there exists a high possibility of selection bias in small studies. Studies were excluded for any of the following: (1) selective sampling; (2) investigation of people with subclinical epileptiform activity, status epilepticus or taking AEDs (without reports on the diagnosis of seizures); (3) inclusion of people with dementia, but without further details on dementia types; and (4) comorbid seizures and AD in the context of other diseases (e.g. cortical dysplasia, Down's syndrome).

### Search strategy and screening

Four databases were searched: MEDLINE, EMBASE, PsycINFO and CINAHL (from inception to 5 September 2019, Table S1). The following search terms were used as free text or controlled vocabulary as appropriate: epilepsy, epileptic, seizure(s), convulsion(s) AND Alzheimer(s), dementia, cognitive dysfunction.

Titles and abstracts of all references were screened to identify those relevant to the review, including 20% screened independently by a second reviewer. Discrepancies were resolved through discussion. Full articles of relevant references were examined to determine whether they met the inclusion criteria. Lists of included and excluded studies in the full-text screening stage were checked independently by two reviewers. One reviewer sought further literature by examining the reference lists and citation trails of eligible studies.

**Data extraction and quality assessment**

Data extraction was completed by one reviewer, and all extractions were checked by a second reviewer, and included country, year of publication, author, recruiting sites and periods, case selection (e.g. population-, community-, hospital-, nursing home-based), study design (e.g. cohort with prospective or retrospective recruitment), sample size, diagnostic criteria for seizures and AD, number of males, age, incidence or prevalence rates. We judged articles to be from the same cohort if there was evidence of overlapping recruitment sites, study dates and similar participant characteristics. Incidence or prevalence rates in the reports with the most complete estimation for the same cohorts were extracted.

Quality assessment was conducted independently by two reviewers using a pre-existing quality assessment tool for prevalence studies (Text S1).[22] This tool considered the representativeness of the study sample, validity of diagnostic criteria for seizures and AD, and statistical methods. Discrepancies in the judgements were resolved through discussion and adjudication by a third reviewer.

## Statistical methodology

For incidence rates of seizures, the within study variances (i.e. standard error (SE)) were calculated as square root of the number of seizure cases, and the 95% confidence intervals (CIs) of incidence rates were calculated as $e^{Ln(incidence\ rate)\pm 1.96XSE}$. For prevalence rates, the within study variances were calculated as square root of $(p\times(1-p)/n)$, where p is the prevalence and n is the sample size. The incidence and prevalence rates were sorted from lowest to highest rates, and displayed in forest plots with CIs.

Statistical heterogeneity (i.e. variation in the incidence or prevalence rates between studies) and consistency were assessed using the standard Q statistic and $I^2$ (i.e. the percentage of total variation across studies that is due to heterogeneity rather than chance), with $P < 0.05$ indicating heterogeneity and $I^2 > 75\%$ indicating inconsistency. Rates were synthesized using a random effect inverse variance approach for weighting, when there was no heterogeneity or inconsistency. Subgroup analyses were conducted for the prevalence of seizures among people with AD, where studies were grouped based on the AD diagnosis (i.e. clinical, pathological or autosomal dominant (AD)AD). For the prevalence of AD among people with seizures, subgroup analyses were based on age of seizure onset (i.e. seizure onset at > 40 years versus age of seizure onset unknown). Publication bias was assessed by inspecting funnel plots. We also conducted Egger`s tests to assess funnel-plot asymmetry. All analyses were conducted using Stata 13.

## Results

The search results and selection process are summarised in a PRISMA flowchart (Figure 1). A total of 6,246 references were identified, of which 105 full text articles

were retrieved to assess for inclusion/exclusion. Sixty-three articles were excluded with reasons (Text S2) and a total of 39 studies (42 articles, Text S3) were considered eligible for inclusion, including one study reporting both incidence and prevalence of seizures among people with AD,[23] and one study published in Japanese. One study included records from a research center Brain Bank, where autopsies were requested by families for research participation and confirmation of the dementia diagnosis,[15] and thus could be considered a highly selective sample. We included this study for completeness, but also reported the combined prevalence after removing this study.

**Incidence of seizures among people with AD**

Seven studies (Table S2, Figure 2A) reported incidence of seizures among 21,198 people with clinically diagnosed AD, in whom 439 incident cases of seizures were reported. There was one population-based,[12] two community-based[10,24] and four hospital-based studies.[9,11,23,25] Incidence of seizures generally ranged from 4.2[9] to 11.9[12] per 1,000 person-years, with a higher rate of 31.5[23] per 1,000 person-years reported in the study with the shortest length of follow-up (1 year[23] versus 2.2[10] to 6 years[11] in the other studies). The highest reported incidence by age group was 42.6 per 1,000 person-years, in those aged 50 to 59 years old.[11] None of the studies reported etiology of seizures, but five studies partly excluded symptomatic seizures by excluding AD patients with a history of stroke or cortical lesions,[9,11,12,24,25] alcohol or drug abuse,[9,11] central nervous system infection,[11] or subdural hematomas,[25] and brain images were used in two studies to rule out structural causes of seizures.[11,12] Only one study reported on recurrence of seizures, where among seven participants with seizures, a single seizure occurred in four cases, and more than one seizure occurred in three cases.[9] Studies examined the associations between various factors and occurrence of seizures (e.g. sex, race, education, comorbidities, duration of AD),

192 with none of these except age (univariate analysis) reaching significance. Incidence
193 of seizure in AD patients decreased with older age in five studies.[9-11,24,25]

194 **Prevalence of seizures among people with AD**

195 Twenty-five studies (27 articles, Table S3a and S3b, Figure 2B) reported prevalence
196 of seizures among 380,777 people with AD, in whom 20,312 cases of seizures were
197 reported. For clinically diagnosed AD, the diagnoses were made mainly according to
198 the National Institute of Neurological and Communicative Disorders and Stroke and
199 the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).[26]
200 The lowest prevalence was 1.5% out of 197 hospitalized AD patients, where only
201 generalized onset or focal to bilateral tonic-clonic seizures were counted as
202 "seizures".[27] The highest prevalence was 49.5% of 190 patients who had initial AD
203 symptoms between 34 and 64 years old and had AD diagnosed before 70 years old.[28]

204 Prevalence estimates were statistically homogeneous ($P = 0.4$, $I^2 = 0.5\%$) among
205 people with autopsy[15,29-31] or CSF biomarker[32] verified AD, and the combined
206 prevalence of seizures was 16% (95%CI 14% to 19%), or 15% (95%CI 12% to 19%)
207 after excluding the mentioned study with highly selective sample ($P = 0.3$, $I^2 = 13\%$).[15]

208 The prevalence rates of seizures among people with ADAD were statistically
209 heterogeneous and inconsistent ($P < 0.0001$, $I^2 = 97\%$): 2.8% out of 107 ADAD
210 patients with *APP*, *PSEN 1* or *PSEN 2* mutations in the Dominantly Inherited Alzheimer
211 Network (DIAN) study,[33] 24% out of 121 ADAD patients with *APP* or *PSEN 1*
212 mutations,[34] 31.3% out of 64 ADAD patients with *PSEN 2* mutation,[3] and 41.7% out of
213 132 ADAD patients with *APP*, *PSEN 1* or *PSEN 2* mutations.[4]

214 Six studies reported whether seizures were recurrent, where there were 74
215 participants with a single seizure and 121 participants with two or more

seizures.[4,15,30,35-37] Two studies recorded 660 cases of International League against Epilepsy defined “epilepsy”.[18,38] The majority (144/240, 60%) of participants where seizure type was reported (in 13 studies) had generalized onset seizures, and another 26 cases (11%) had focal to bilateral tonic-clonic seizures.[13-15,18,23,27,29-31,35-37,39] EEG was performed in 182 AD patients with seizures, in eight studies, with 58 (32%) of them having normal EEG.[4,13,15,18,27,31,35,36] None of the studies reported etiology of seizures, but three studies partly excluded symptomatic seizures by excluding, e.g. AD patients with a history of stroke,[18,39,40] alcohol abuse,[18] traumatic brain injury,[40] suspected brain tumor[18] or tumor caused seizures.[40] Seizures preceded the onset of cognitive symptoms or a diagnosis of AD in a total of 40 participants in six studies,[13,14,18,30,37,39] by an average of 4.6 years (range 0.5 to 29) in one study[13] and over 10 years in another.[14] The time gaps were not reported in the remaining four studies.[18,30,37,39] Seizures followed the onset of cognitive symptoms or a diagnosis of AD in a total of 408 participants in 12 studies,[4,13,15,18,28,30,31,35-37,39,40] with reported average time gaps ranging from 2.5[31] to 6.8 years.[15] In 21 participants from three studies, seizures occurred concomitantly with onset of cognitive symptoms or a diagnosis of AD.[14,18,39] AEDs (e.g. phenytoin, carbamazepine, valproate acid, topiramate and phenobarbital) were reported to have been started in most AD patients with seizures in 11 studies.[4,13-15,18,27,31,35-37,39] Among the factors tested across a total of 10 studies, being younger,[15,31,40] male,[35] having a longer duration of AD,[31] more severe AD (lower Mini-Mental State Examination (MMSE) score and higher level of CSF tau),[40] presence of myoclonus[34] were associated with higher risk of seizures, whereas hypertension[40] and diabetes[35] were associated with lower risk of seizures among AD patients.

## Prevalence of AD among people with seizures

Eight studies (nine articles, Table S4, Figure 2C) reported prevalence of clinically diagnosed AD among 727,446 people with seizures, in whom 50,180 cases of AD were reported. For participants who had onset of seizures after 40 years old,[2,17,19,41,42] there were statistically homogeneous prevalence estimations (P = 0.07, $I^2$ = 54.1%), and the combined prevalence of AD was 11% (95% CI 7% to 14%). Among them, seizures were remote symptomatic, verified clinically, or by computed tomography (CT) or magnetic resonance imaging (MRI) in 38% (26/68)[41] and 70% (86/122)[19] of the participants in two studies, whereas seizures with structural and other known causes were excluded in two studies.[2,17]

Less than half, 177/421 (42%) of those participants whose seizure type was reported had generalized seizures.[2,19,41,42] It was reported that seizures preceded the onset of cognitive symptoms or a diagnosis of AD (time gaps unreported),[17,41] or followed the onset of cognitive symptoms or a diagnosis of AD by 0.4 to 12 years.[2,19] Among the tested factors, being older was the only factor associated with occurrence of AD among people with seizures.[17]

## Publication bias and small study effects

Funnel plots provided little evidence for publication bias (Figure S1). Egger's tests showed no evidence for asymmetry to suggest publication bias in studies examining incidence (P = 0.69) or prevalence of seizures (P = 0.65), or prevalence of AD (P = 0.98).

## Quality assessment

Overall, 20 studies were reported as being at low risk, 17 at medium and two at high risk of bias (Table S5). The main source of bias was representativeness of the study

population, with the study population included in the most of studies (31/39, 79%) being judged as unlikely to be a close representation of their respective national populations with seizures or AD. For example, one study only included those with mild or moderate AD who experienced decreased social capacity over a period of at least three months, which was not generalizable to the national population with AD.[43]

## Discussion

We summarized data from 39 studies reporting on seizure incidence and prevalence respectively in 21,198 and 380,777 participants with AD, and AD prevalence in 727,446 participants with seizures. We found seizure incidence rates up to 31.5 per 1000 person-years, but mostly in the range of 4.2 to 11.9, higher than the 2.4 per 1,000 person-years in older people generally.[44] In general, estimates suggest that 10% of people with clinically diagnosed AD were affected by seizures, with this rising to 16% among people with pathologically verified AD and between three to over 40 percent of people with ADAD had co-existent seizures. Eleven percent of people with adult-onset seizures had AD. Increasing awareness of this co-existence and its importance is indicated by the number of studies documented in this review, where 17 (44%) were published in or after 2015.

### Bi-directionality

Seizures variously preceded or followed the onset of cognitive symptoms, confirming the bi-directionality of the relationship between seizures and AD. Seizures increase amyloid β deposition and neuronal excitability,[7] which could be a further predisposition to develop seizures.[5] We note that the occurrence of seizures was sometimes as short as 5 months following[2] or concurrent with onset of AD or a diagnosis of AD,[14,18,39]

and AD was the only possible explanation for the new-onset seizures;[14] although, the 1984 NINCDS-ADRDA criteria list seizures at the onset or very early stage of AD as a feature making the diagnosis of probable AD uncertain or unlikely,[26] and this remains the case in the 2011 modification.[45]

**Impact of age and other risk factors**

We found consistent evidence of an increased risk of seizures during the study follow-up associated with younger age of AD symptom onset or diagnosis,[9-11,15,24,25,31,40] with the highest prevalence of seizures at 49.5% among those with clinically diagnosed early-onset AD.[28] Risk of developing seizure was the highest when AD started between 30 and 49 years old.[25] Potential explanations could include a more rapid disease progression in younger people with AD,[11] or younger people with AD being more vulnerable to seizure manifestation or more likely to have seizures recognized.[9] Conversely, older age was associated with increased risk for AD among people with seizures.[17]

We note the evidence gap related to rates of AD among adults with childhood onset seizures, despite adults with childhood-onset epilepsy, particularly APOE ε4 carriers, showing more brain amyloid accumulation in their 50s compared to the controls without epilepsy, suggesting that individuals with the APOE ε4 allele and idiopathic epilepsy syndromes might be particularly vulnerable to the development of amyloid pathology.[46] More evidence is required to determine whether duration and severity of AD, or other risk factors are associated with seizure occurrence, and what the risk factors are for AD among people with seizures.

## ADAD and other dementia types

People with ADAD had more rapid cognitive and functional decline,[47] and may be more likely to have seizures due to autosomal dominant *APP*, *PSEN 1* or *PSEN* 2 mutations,[3,4,34] but prevalence rates were inconsistent. The lowest prevalence rate of seizures (2.8%) may be due to the fact that many participants were at early stages of the ADAD (very mild n = 68 and mild n = 18) in the DIAN study.[33] Notably, this article also reported on the published literature noting a combined prevalence rate of seizures at 20.3% (95%CI 17.4% to 23.2%) in 188 publications reporting on 1,228 ADAD patients, albeit the heterogeneity between studies was not reported for the pooled estimation. None of the 188 publications met our inclusion criteria individually with most being case series of a few participants.[33]

Seizures occur in both AD and non-AD dementia, and it is unclear whether AD is the pathology most strongly associated with seizures. Some studies reported that AD was up to five times more commonly associated with seizures than non-AD dementia.[2,24] The highest reported prevalence of seizures among people with all-cause dementia was 9.1%,[48] similar to our finding of up to 10% of people with clinically diagnosed AD (excluding the study with only early-onset AD[28]), but lower than the combined prevalence of 16% among people with autopsy or CSF biomarker verified AD. Contradictory evidence was that the incidence of seizures among people with clinically diagnosed vascular dementia (VD) was 7.5 per 1,000 person-years, higher than the 5.6 per 1,000 person-years among people with clinically diagnosed AD.[10] We note the possibility of mixed pathology, e.g. only 34 out of 64 participants with pathologically verified AD in one included study had pure AD pathology, while there were concurrent Lewy body dementia (LBD, n = 12), VD (n = 11) and LBD and VD (n = 7).[31] Up to

336 23.6%[49] of older people with seizures had dementia, similar to our findings showing
337 up to 24% of people with seizures had AD.

338

339 **Limitations**

340 The heterogeneities present in the evidence base meant that meta-analysis was not
341 considered feasible thus meaning that we were unable to produce an overall point
342 estimate. Nevertheless, we have represented the body of literature using forest plots
343 to fully display the breadth and variation in the evidence. Secondly, although it is
344 common practice to exclude studies with low numbers of participants, we acknowledge
345 that some of the evidence base may have been inadvertently excluded. Furthermore,
346 we note that tests for funnel plot asymmetry, Egger`s tests, are only recommended
347 when there are at least 10 studies included in the meta-analysis. Thirdly, the available
348 information is insufficient to differentiate data based on a single epileptic seizure and
349 epilepsy, albeit the limited evidence from six studies suggested that over half (62%) of
350 seizure cases among AD patients had recurrent seizures. Fourthly, seizure types
351 were mostly determined clinically without EEG evidence, the etiology of seizures was
352 unclear, and CT or MRI was not adopted to identify structural causes of seizures in
353 most of the studies.

354 Finally, there may be under- or over-estimation. In our review, 61% of the seizures
355 that occurred in people with AD were generalized onset seizures, whereas in the
356 seizure population this number was 42%. The over representation of generalized
357 seizures in those AD-oriented studies may be due to the lack of awareness and pre-
358 specified questionnaires to record focal seizure, leading to underestimation. In the
359 included studies, eight cases (2%) of acute symptomatic seizures[4,27] have been

reported among 329 AD patients. We note that alertness and attention alterations in AD, acute symptomatic seizures (especially for the older adults) and epilepsy mimics might have been counted as seizures in included studies, especially when the diagnosis of epilepsy was not centrally adjudicated by the researchers, leading to potential overestimation. In clinical practice, these need to be ruled out, before introducing AEDs, but there is no reason to postpone AEDs in confirmed cases, since AEDs have not been shown to be independently associated with cognitive dysfunction,[50] and good seizure control may have a potential for AD risk reduction. Presence of myoclonus increased the risk of developing seizures in one study,[34] however seizures and myoclonus did not co-exist in another study,[30] and 80 cases (18%) of myoclonus have been reported among 433 AD patients.[23,29,30,34] Myoclonus described as brief shock-like muscular contraction,[23] or due to neuronal loss in the aminergic brain-stem nuclei[29] may actually be unprovoked epileptic in nature leading to underestimation of seizure rates, whereas overestimation could have occurred if any seizures reported in studies are pure myoclonus.

The bi-directional relationship between seizures and AD was confirmed and there is increasing awareness of their co-existence. Further research on the risk factors for the co-existence and examination on whether early treatment of seizures might help delay or prevent clinical manifestation of AD could help advise ways to ease disease burden, and provide guidance on health services and care planning.

## Acknowledgements

### Conflict of Interest

K. J. Anstey has served as an Advisor for the StaySharp Platform which is supported by the American Association of Retired Persons. C. S. Anderson has received lecture fees and travel reimbursement from Takeda China. The remaining authors have no conflicts of interest.

### Author Contributions

Y Xu and R Peters contributed to the concept and rationale for the study. Y Xu built up the search strategy. Y Xu, L Lavrencic and K Radford screened titles and abstracts of identified records and full-texts of relevant studies. Y Xu screened the reference lists and citation trails of included studies, extracted data, and conducted quality assessment and statistical analyses. L Lavrencic and K Radford checked data extraction and conducted quality assessment. S Yoshimura conducted data extraction and quality assessment for the study published in Japanese. All authors interpreted data and revised the manuscript.

### Sponsor's Role

This study is supported by the National Health and Medical Research Council (NHMRC) project (APP1160373). We acknowledge Dr. Alejandra Malavera and Dr Yann Quide`s language assistance to exclude full-text articles in Spanish and France, and acknowledge Dr Takako Torii-Yoshimura`s assistance in the quality assessment for the included Japanese article. We acknowledge Dr. Tatyana Sarycheva and Professor Randall J Bateman providing additional data for their studies. Y. Xu acknowledges seed grant funding from the University of New South Wales Ageing Futures Institute. L. Lavrencic is funded by a Serpentine Foundation Fellowship. K.

405 Radford is funded by Australian National Health and Medical Research Council
406 (NHMRC) and Australian Research Council (ARC) Dementia Research Development
407 Fellowship (No. 1103312). K. J. Anstey is funded by the Australian NHMRC Research
408 Fellowship (No. 1002560) and acknowledges support from the NHMRC Centre of
409 Research Excellence in Cognitive Health (1100579). C. S. Anderson is funded by
410 Australian NHMRC Leadership grant (APP 1175861) and acknowledges grants from
411 the Australian NHMRC (APP1175861 and APP1149987), and grants for stroke
412 research (IISR-2017-101947 and IISR-2018-102649). R. Peters is funded by the
413 Australian NHMRC Dementia Centre for Research Collaboration.

414

## Reference


1. Schnier C, Duncan S, Wilkinson T, Mbizvo GK, Chin RFM. A nationwide, retrospective, data-linkage, cohort study of epilepsy and incident dementia. Neurology 2020;95(12):e1686-e1693.
2. Hesdorffer DC, Hauser WA, Annegers JF, Kokmen E, Rocca WA. Dementia and adult-onset unprovoked seizures. Neurology 1996;46(3):727-730.
3. Jayadev S, Leverenz JB, Steinbart E, et al. Alzheimer's disease phenotypes and genotypes associated with mutations in presenilin 2. Brain 2010;133(Pt 4):1143-1154.
4. Zarea A, Charbonnier C, Rovelet-Lecrux A, et al. Seizures in dominantly inherited Alzheimer disease. Neurology 2016;87(9):912-919.
5. Palop JJ, Mucke L. Epilepsy and cognitive impairments in Alzheimer disease. Arch Neurol 2009;66(4):435-440.
6. Matsui T, Maruyama M, Matsushita S, Arai H, Higuchi S, Maruyama K. A transient increase in cerebrospinal fluid tau level after epileptic seizure in an elderly patient. J Am Geriatr Soc 2007;55(12):2096-2097.
7. Shahim P, Rejdak R, Ksiazek P, et al. Cerebrospinal fluid biomarkers of beta-amyloid metabolism and neuronal damage in epileptic seizures. Eur J Neurol 2014;21(3):486-491.
8. Noebels J. A perfect storm: Converging paths of epilepsy and Alzheimer's dementia intersect in the hippocampal formation. Epilepsia 2011;52 Suppl 1:39-46.
9. Scarmeas N, Honig LS, Choi H, et al. Seizures in Alzheimer disease: who, when, and how common? Arch Neurol 2009;66(8):992-997.
10. 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):700-707.
11. Amatniek JC, Hauser WA, DelCastillo-Castaneda C, et al. Incidence and predictors of seizures in patients with Alzheimer's disease. Epilepsia 2006;47(5):867-872.
12. Cheng CH, Liu CJ, Ou SM, et al. Incidence and risk of seizures in Alzheimer's disease: a nationwide population-based cohort study. Epilepsy Res 2015;115:63-66.
13. DiFrancesco JC, Tremolizzo L, Polonia V, et al. Adult-onset epilepsy in presymptomatic Alzheimer's disease: a retrospective study. J Alzheimers Dis 2017;60(4):1267-1274.
14. Lozsadi DA, Larner AJ. Prevalence and causes of seizures at the time of diagnosis of probable Alzheimer's disease. Dement Geriatr Cogn Disord 2006;22(2):121-124.
15. Mendez MF, Catanzaro P, Doss RC, R AR, Frey WH, 2nd. Seizures in Alzheimer's disease: clinicopathologic study. J Geriatr Psychiatry Neurol 1994;7(4):230-233.
16. Gaitatzis A, Carroll K, Majeed A, Sander JW. The epidemiology of the comorbidity of epilepsy in the general population. Epilepsia 2004;45(12):1613-1622.
17. Kawakami O, Koike Y, Ando T, et al. Incidence of dementia in patients with adult-onset epilepsy of unknown causes. J Neurol Sci 2018;395:71-76.
18. Vossel KA, Beagle AJ, Rabinovici GD, et al. Seizures and epileptiform activity in the early stages of Alzheimer disease. JAMA Neurol 2013;70(9):1158-1166.
19. Forsgren L, Bucht G, Eriksson S, Bergmark L. Incidence and clinical characterization of unprovoked seizures in adults: a prospective population-based study. Epilepsia 1996;37(3):224-229.
20. Balamurugan E, Aggarwal M, Lamba A, Dang N, Tripathi M. Perceived trigger factors of seizures in persons with epilepsy. Seizure 2013;22(9):743-747.
21. 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):962-972.
22. Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol 2012;65(9):934-939.

23. Burns A, Jacoby R, Levy R. Neurological signs in Alzheimer's disease. Age Ageing 1991;20(1):45-51.
24. Cook M, Baker N, Lanes S, Bullock R, Wentworth C, Arrighi HM. Incidence of stroke and seizure in Alzheimer's disease dementia. Age Ageing 2015;44(4):695-699.
25. Beagle AJ, Darwish SM, Ranasinghe KG, La AL, Karageorgiou E, Vossel KA. Relative incidence of seizures and myoclonus in Alzheimer's disease, dementia with Lewy bodies, and frontotemporal dementia. J Alzheimers Dis 2017;60(1):211-223.
26. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34(7):939-944.
27. Hommet C, Hureaux R, Barre J, Constans T, Berrut G. Epileptic seizures in clinically diagnosed Alzheimer's disease: report from a geriatric medicine population. Aging Clin Exp Res 2007;19(5):430-431.
28. Samson WN, van Duijn CM, Hop WC, Hofman A. Clinical features and mortality in patients with early-onset Alzheimer's disease. Eur Neurol 1996;36(2):103-106.
29. Forstl H, Burns A, Levy R, Cairns N, Luthert P, Lantos P. Neurologic signs in Alzheimer's disease. Results of a prospective clinical and neuropathologic study. Arch Neurol 1992;49(10):1038-1042.
30. Hauser WA, Morris ML, Heston LL, Anderson VE. Seizures and myoclonus in patients with Alzheimer's disease. Neurology 1986;36(9):1226-1230.
31. Rauramaa T, Saxlin A, Lohvansuu K, Alafuzoff I, Pitkanen A, Soininen H. Epilepsy in neuropathologically verified Alzheimer's disease. Seizure 2018;58:9-12.
32. Tabuas-Pereira M, Duraes J, Lopes J, et al. Increased CSF tau is associated with a higher risk of seizures in patients with Alzheimer's disease. Epilepsy and Behavior 2019;Part A. 98:207-209.
33. Tang M, Ryman DC, McDade E, et al. Neurological manifestations of autosomal dominant familial Alzheimer's disease: a comparison of the published literature with the Dominantly Inherited Alzheimer Network observational study (DIAN-OBS). Lancet Neurol 2016;15(13):1317-1325.
34. Ryan NS, Nicholas JM, Weston PS, et al. Clinical phenotype and genetic associations in autosomal dominant familial Alzheimer's disease: a case series. Lancet Neurol 2016;15(13):1326-1335.
35. Bernardi S, Scaldaferri N, Vanacore N, et al. Seizures in Alzheimer's disease: a retrospective study of a cohort of outpatients. Epileptic Disord 2010;12(1):16-21.
36. Giorgi FS, Baldacci F, Dini E, Tognoni G, Bonuccelli U. Epilepsy occurrence in patients with Alzheimer's disease: clinical experience in a tertiary dementia center. Neurol Sci 2016;37(4):645-647.
37. Baker J, Libretto T, Henley W, Zeman A. The prevalence and clinical features of epileptic seizures in a memory clinic population. Seizure 2019;71:83-92.
38. Zelano J, Brigo F, Garcia-Patek S. Increased risk of epilepsy in patients registered in the Swedish Dementia Registry. Eur J Neurol 2020;27(1):129-135.
39. Arnaldi D, Donniaquio A, Mattioli P, et al. Epilepsy in neurodegenerative dementias: a clinical, epidemiological, and EEG study. J Alzheimers Dis 2020;74(3):865-874.
40. Tabuas-Pereira M, Duraes J, Lopes J, et al. Increased CSF tau is associated with a higher risk of seizures in patients with Alzheimer's disease. Epilepsy Behav 2019;98:207-209.
41. Timmons S, Sweeney B, Hyland M, O'Mahony D, Twomey C. New onset seizures in the elderly: aetiology and prognosis. Ir Med J 2002;95(2):47-49.
42. Assis TR, Bacellar A, Costa G, Nascimento OJ. Etiological prevalence of epilepsy and epileptic seizures in hospitalized elderly in a Brazilian tertiary center - Salvador - Brazil. Arq Neuropsiquiatr 2015;73(2):83-89.

43. Bell J, Lonnroos E, Koivisto AM, et al. Use of antiepileptic drugs among community-dwelling persons with Alzheimer's disease in Finland. J Alzheimers Dis 2011;26(2):231-237.
44. Faught E, Richman J, Martin R, et al. Incidence and prevalence of epilepsy among older US Medicare beneficiaries. Neurology 2012;78(7):448-453.
45. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7(3):263-269.
46. Joutsa J, Rinne JO, Hermann B, et al. Association Between Childhood-Onset Epilepsy and Amyloid Burden 5 Decades Later. JAMA Neurol 2017;74(5):583.
47. Jacobs D, Sano M, Marder K, et al. Age at onset of Alzheimer's disease: relation to pattern of cognitive dysfunction and rate of decline. Neurology 1994;44(7):1215-1220.
48. McAreavey MJ, Ballinger BR, Fenton GW. Epileptic seizures in elderly patients with dementia. Epilepsia 1992;33(4):657-660.
49. Martin RC, Faught E, Richman J, et al. Psychiatric and neurologic risk factors for incident cases of new-onset epilepsy in older adults: data from U.S. Medicare beneficiaries. Epilepsia 2014;55(7):1120-1127.
50. Foster E, Malpas CB, Ye K, et al. Antiepileptic drugs are not independently associated with cognitive dysfunction. Neurology 2020;94(10):e1051-e1061.

## Legends

**Figure 1** Flow diagram for systematic review

**Figure 2** Incidence and prevalence reported in the included studies

A. Incidence of seizures among people with Alzheimer's Disease
B. Prevalence of seizures among people with Alzheimer's Disease
[a] at AD symptoms onset or diagnosis, [b] with seizures, [c] without seizures, [d] with presenilin-1 mutation, atypical cognitive presentations, [e] with presenilin-1 mutation, typical amnestic, [f] with amyloid β precursor protein gene mutation
C. Prevalence of Alzheimer's Disease among people with seizures

**Supplementary Text S1** Quality assessment tool

**Supplementary Text S2** List of excluded studies with reasons (n = 63)

**Supplementary Text S3** References of included articles (n = 42)

**Supplementary Figure S1** Funnel plots with pseudo 95% confidence limits

**Supplementary Table S1** Description of search strategy and results (5 September 2019)

**Supplementary Table S2** Characteristics of studies reporting incidence of seizures among people with Alzheimer's disease

**Supplementary Table S3a** Characteristics of studies reporting prevalence of seizures among people with Alzheimer's disease (Part I)

**Supplementary Table S3b** Characteristics of studies reporting prevalence of seizures among people with Alzheimer's disease (Part II)

**Supplementary Table S4** Characteristics of studies reporting prevalence of Alzheimer's disease among people with seizures

**Supplementary Table S5(a-i)** Quality assessment