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], Sohei Yoshimura MD, PhD[d], Kaarin J Anstey PhD[a,b], Craig S Anderson MD, PhD[b,e,f,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.]Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, 6-1 Kishibe-shimmachi, Suita, Osaka 564-8565, Japan
[e.]The George Institute for Global Health, Faculty of Medicine, University of New South Wales, 83-117 Missenden Road, Camperdown NSW 2050, Australia
[f.]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
[g.]Neurology Department, Sydney Local Area Health District, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia
[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

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Key Points

1. We confirm bidirectional relationships between seizures and AD.
2. Evidence gaps exist for AD in adults with child onset seizure.
3. Risk of seizure is greater in young onset AD.

Why Does this Paper Matter?

Understanding these relationships will promote referral, early seizure identification and intervention, and may delay AD.

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),

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

Prevalence of Seizures among People with AD

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

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

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

Six studies reported whether seizures were recurrent, where there were 74 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

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

Limitations

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

Finally, there may be under- or over-estimation. In our review, 61% of the seizures that occurred in people with AD were generalized onset seizures, whereas in the seizure population this number was 42%. The over representation of generalized seizures in those AD-oriented studies may be due to the lack of awareness and pre-specified questionnaires to record focal seizure, leading to underestimation. In the 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.

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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.

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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.

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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.

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50. Foster E, Malpas CB, Ye K, et al. Antiepileptic drugs are not independently associated with cognitive dysfunction. Neurology 2020;94(10):e1051-e1061.

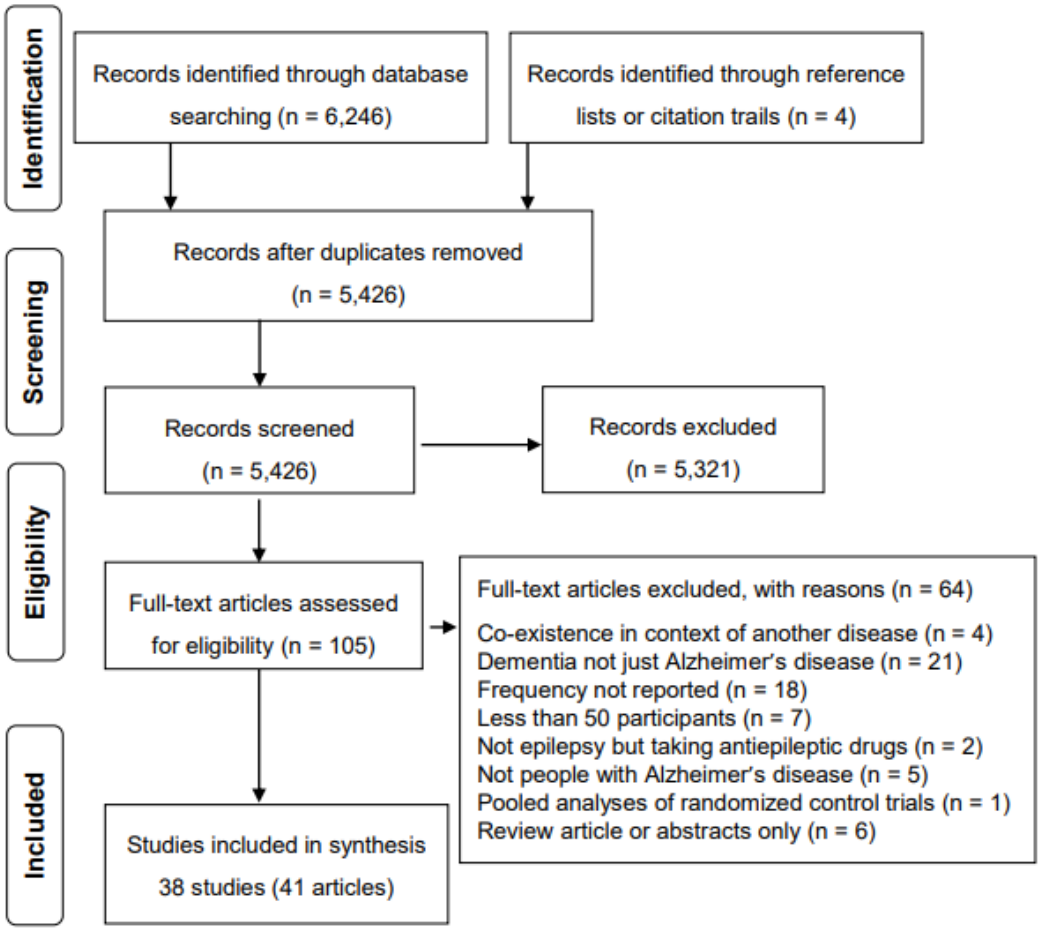

Figure 1 Flow diagram for systematic review

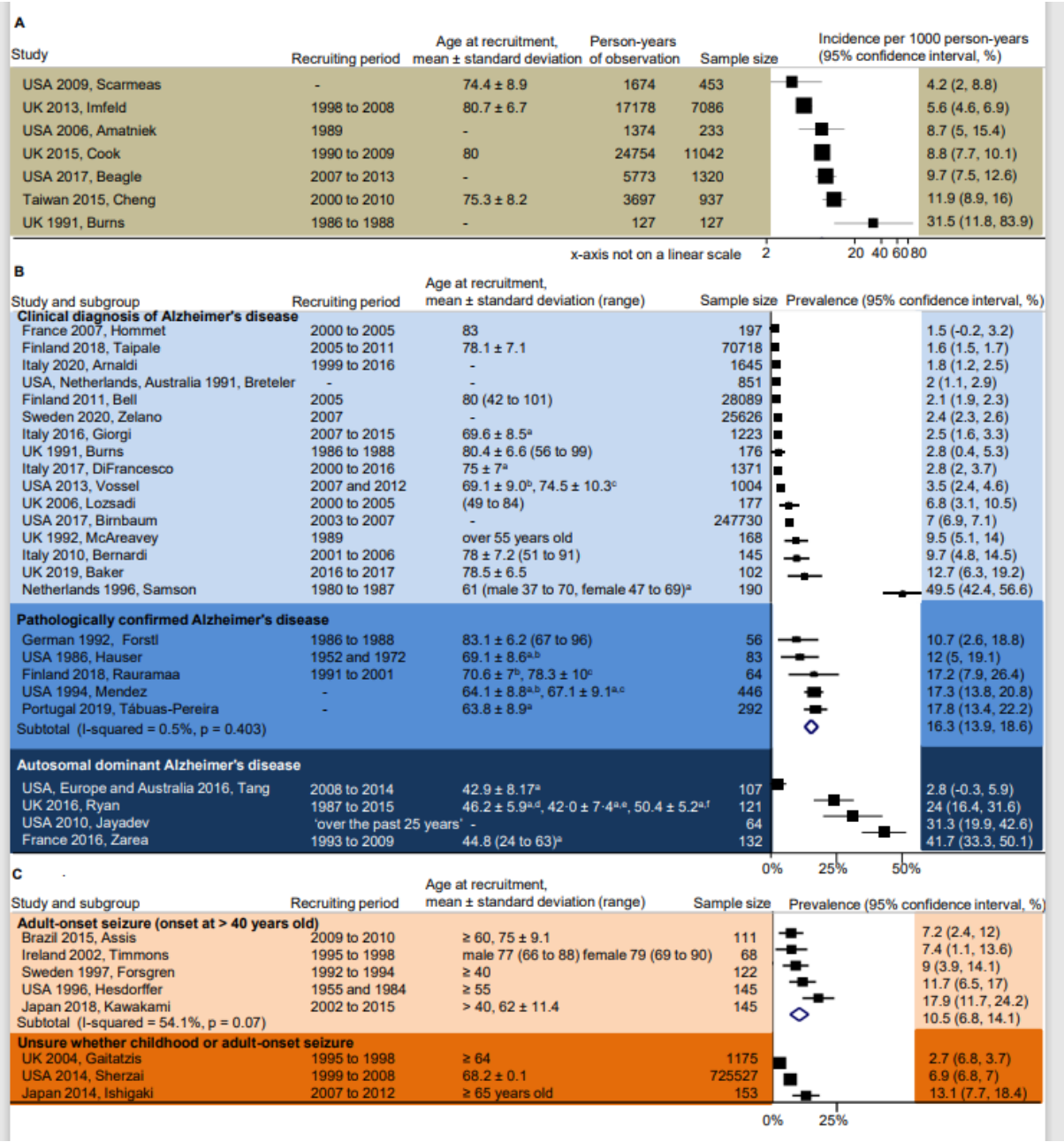

Figure 2 Incidence and prevalence reported in the included studies

A. Incidence of seizures among people with Alzheimer's Disease

The x-axis shows the number of incident seizures per 1,000 person-years. To allow the representation of the data, a non-linear scale has been used.

B. Prevalence of seizures among people with Alzheimer's Disease

The x-axis shows the prevalence of seizures among people with Alzheimer's Disease

The x-axis shows the prevalence of seizures among people with Alzheimer's Disease

[a] at AD symptom 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

The x-axis shows the prevalence of Alzheimer's Disease among people with seizures

The point estimates of incidence and prevalence reported in the constituent studies are presented using black squares. The area of each square is proportional to the study's weight within each panel (i.e. A, B and C). The weight of each study is calculated based on the inverse of within study variances (i.e. standard error). The incidence and prevalence values are sorted from lowest to highest, and the 95% confidence intervals are represented by horizontal lines for individual studies and by diamonds for the combined prevalence estimate.

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

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Xu Y, Lavrencic L, Radford K, et al. Systematic review of coexistent seizures and Alzheimer`s disease: incidence and prevalence.

Supplementary Text S1 Quality assessment tool

Quality assessment items	Risk of bias levels	Authors` comments
1. Was the study's target population a close representation of the national population with epileptic seizures or AD in relation to relevant variables, e.g. age, sex?	Yes (LOW RISK): The study's target population was a close representation of the national population. No (HIGH RISK): The study's target population was clearly NOT representative of the national population.	We judged this based on study design and on studies' "inclusion and exclusion criteria", to see whether there is anything making the target population unrepresentative of the national population with seizures or Alzheimer's Disease. For incidence or prevalence of seizures among people with Alzheimer's Disease, target population are people with Alzheimer's Disease, e.g. when they used restricted criteria on e.g. age, cognition (mini mental state examination 10 to 26 or clinical dementia rating scale 1 to 2), we would say "High Risk". For prevalence of Alzheimer's Disease among people with seizures, target population are people with seizures.
2. Was the sampling frame a true or close representation of the target population?	Yes (LOW RISK): The sampling frame was a true or close representation of the target population. No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population.	We mainly judge this based on how/where studies recruited the sample, or say the "recruiting sites", and consider "population-based" or "community-based" to be "Low Risk", and "hospital-based" to be "High Risk". If the targeted population were people with autosomal dominant Alzheimer`s disease, then "research center based" would be considered as "Low Risk".
3. Was some form of random selection used to select the sample, OR, was a census undertaken?	Yes (LOW RISK): A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).	This is about consecutive, random or convenience sampling. Studies with convenience sampling, e.g. "volunteer sample" or a sub sample from an existing study, were judged as "High Risk".

	No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	
4. Was the likelihood of non-response bias minimal?	Yes (LOW RISK): The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non-responders	Retrospective review of insurance, general practitioner registries and medical records can be done via data linkage without consent, and we would say “Low Risk”. Otherwise, when there is no report of responders vs non-responders, we would put “High Risk”.
	No (HIGH RISK): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders	
5. Were data collected directly from the subjects or their proxy?	Yes (LOW RISK): All data were collected directly from the subjects or their proxy.	We considered medical records to be collected from the subjects or their proxy.
	No (HIGH RISK): In some instances, data were collected from other investigations (e.g. magnetic resonance imaging, electroencephalography).	
6. Was an acceptable case definition used in the study?	Yes (LOW RISK): An acceptable case definition was used.	This is about the diagnostic criteria for seizures and/or Alzheimer's Disease. For example, for a study investigating prevalence of seizures among people with Alzheimer's Disease, we would check if the diagnostic criteria for seizures are acceptable.
	No (HIGH RISK): An acceptable case definition was NOT used.	

7. Was the study instrument that measured the parameter of interest (i.e. incidence and prevalence of epileptic seizures and AD) shown to have reliability and validity?	Yes (LOW RISK): The study instrument had been shown to have reliability and validity, e.g. centrally adjudicated.	We would say “Low Risk” only if the diagnosis of seizures (for studies on incidence or prevalence of seizures among people with Alzheimer's Disease) and the diagnosis of Alzheimer's Disease (for studies on prevalence of Alzheimer's Disease among people with seizures) were centrally adjudicated, or say reviewed again by the researchers, or positive predictive value etc have been reported.
	No (HIGH RISK): The study instrument had NOT been shown to have reliability and validity, e.g. centrally adjudicated.	
8. Was the same mode of data collection used for all subjects?	Yes (LOW RISK): The same mode of data collection was used for all subjects.	For example, for a study using both prospective and retrospective data collection, we would say “High Risk”.
	No (HIGH RISK): The same mode of data collection was NOT used for all subjects.	
9. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes (LOW RISK): The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of epileptic seizures or AD).	For prevalence studies, if all of 1) numerator 2) denominator and 3) prevalence rate were reported, we would say “Low Risk”. For incidence studies, if all of 1) number of incident cases 2) person-years of follow-up and 3) incidence rate were reported, we would say “Low Risk”. If we did any calculations to get the number, we would say “High Risk”.
	No (HIGH RISK): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	

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

Co-existence in context of another disease (n = 4)

1. Cooper S-A. High prevalence of dementia among people with learning disabilities not attributable to Down's syndrome. Psychol Med. 1997; 27 (3): 609-616.
2. Cordonnier C, Henon H, Derambure P, Pasquier F, Leys D. Early epileptic seizures after stroke are associated with increased risk of new-onset dementia. J Neurol Neurosurg Psychiatry. 2007; 78 (5): 514-516.
3. Cordonnier C, Henon H, Derambure P, Pasquier F, Leys D. Influence of pre-existing dementia on the risk of post-stroke epileptic seizures. J Neurol Neurosurg Psychiatry. 2005; 76 (12): 1649-1653.
4. Gholipour T, Mitchell S, Sarkis RA, Chemali Z. The clinical and neurobehavioral course of Down syndrome and dementia with or without new-onset epilepsy. Epilepsy Behav. 2017; 68: 11-16.

Dementia not just Alzheimer’s disease (n = 20)

1. Baran M, Stecker MM. Epilepsy in a rural elderly population. Epileptic Disord. 2007; 9 (3): 256-270.
2. Bloechliger M, Ruegg S, Jick SS, Meier CR, Bodmer M. Antipsychotic drug use and the risk of seizures: follow-up study with a nested case-control analysis. CNS Drugs. 2015; 29 (7): 591-603.
3. Breteler MMB, De Groot RRM, Van Romunde LKJ, Hofman A. Risk of dementia in patients with Parkinson's disease, epilepsy, and severe head trauma: a register-based follow-up study. Am J Epidemiol. 1995; 142 (12): 1300-1305.
4. Canoui-Poitrine F, Bastuji-Garin S, Alonso E, et al. Risk and prognostic factors of status epilepticus in the elderly: a case-control study. Epilepsia. 2011; 52 (10): 1849-1856.
5. Chandra V, Bharucha NE, Schoenberg BS. Conditions associated with Alzheimer's disease at death: case-control study. Neurology. 1986; 36 (2): 209-211.
6. Darcel G, Verstichel P, Herbaud S, Taillandier-Heriche E, Paillaud E. Status epilepticus in the elderly patients. A retrospective study of 63 in-patients [French]. Rev Neurol. 2008; 164 (11): 935-942.
7. Dogan EA, Genc E, Genc BO, Erdogan C. Efficacy, tolerability, and retention rates of zonisamide in older adult patients with focal-onset epilepsy: experiences from two tertiary epilepsy centers. Epilepsy Behav. 2017; 76: 19-23.
8. Jacob L, Hamer HM, Kostev K. Persistence with antiepileptic drugs in epilepsy patients treated in neurological practices in Germany. Epilepsy Behav. 2017; 73: 204-207.
9. Jadeja N, Zarnegar R, Legatt AD. Clinical outcomes in patients with generalized periodic discharges. Seizure. 2017; 45: 114-118.
10. Loiseau P, Loiseau J, Picot MC. One-year mortality in Bordeaux cohort: the value of syndrome classification. Epilepsia. 2005; 46 Suppl 11: 11-14.

11. 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.
12. Nuyen J, Schellevis FG, Satariano WA, et al. Comorbidity was associated with neurologic and psychiatric diseases: a general practice-based controlled study. J Clin Epidemiol. 2006; 59 (12): 1274-1284.
13. Pugh MJ, Knoefel JE, Mortensen EM, Amuan ME, Berlowitz DR, Van Cott AC. New-onset epilepsy risk factors in older veterans. J Am Geriatr Soc. 2009; 57 (2): 237-242.
14. Rao SC, Dove G, Cascino GD, Petersen RC. Recurrent seizures in patients with dementia: frequency, seizure types, and treatment outcome. Epilepsy Behav. 2009; 14 (1): 118-120.
15. Roberts MA, Caird FI. The contribution of computerized tomography to the differential diagnosis of confusion in elderly patients. Age Ageing. 1990; 19 (1): 50-56.
16. Saez ME, Gonzalez-Perez A, Gaist D, Johansson S, Nagy P, Garcia Rodriguez LA. Risk of seizure associated with use of acid-suppressive drugs: an observational cohort study. Epilepsy Behav. 2016; 62: 72-80.
17. Si Y, Xiao X, Sun H. Mortality-specific comorbidity among inpatients with epilepsy: a preliminary cross-sectional study in West China. Epilepsy Behav. 2018; 84: 70-73.
18. Tellez-Zenteno JF, Matijevic S, Wiebe S. Somatic comorbidity of epilepsy in the general population in Canada. Epilepsia. 2005; 46 (12): 1955-1962.
19. Verma A, Kumar A. Clinical and etiological profile of epilepsy in elderly: a hospital-based study from rural India. Acta Neurol Belg. 2017; 117 (1): 139-144.
20. Yoshimura H, Matsumoto R, Ueda H, et al. Status epilepticus in the elderly: prognostic implications of rhythmic and periodic patterns in electroencephalography and hyperintensities on diffusion-weighted imaging. J Neurol Sci. 2016; 370: 284-289.

Frequency not reported (n = 18)

1. Amr M, Amin TT, Al-Saeed U. Comorbid physical and psychiatric disorders among elderly patients: a study at an outpatient clinic in Saudi Arabia. Arab Journal of Psychiatry. 2013; 24 (2): 133-141.
2. Avidan MS, Searleman AC, Storandt M, et al. Long-term cognitive decline in older subjects was not attributable to noncardiac surgery or major illness. Anesthesiology. 2009; 111 (5): 964-970.
3. Burkhardt M, Bacher M, Kornmeier R, Kurth C, Staack AM, Steinhoff BJ. The general and social health long-term outcome of adult epilepsy patients at the Kork Epilepsy Center. Neurology International Open. 2018; 2 (2): E131-E135.
4. Carter M, Weaver D, Joudrey H, Carter A, Rockwood K. Epilepsy and antiepileptic drug use in elderly people as risk factors for dementia. J Neurol Sci. 2007; 252 (2): 169-172.
5. César KG, Brucki SMD, Takada LT, et al. Prevalence of cognitive impairment without dementia and dementia in Tremembé, Brazil. Alzheimer Dis Assoc Disord. 2016; 30 (3): 264-271.

6. Das SK, Biswas A, Roy T, et al. A random sample survey for prevalence of major neurological disorders in Kolkata. Indian J Med Res. 2006; 124 (2): 163-172.
7. El Tallawy HN, Farghaly WM, Rageh TA, et al. Door-to-door survey of major neurological disorders (project) in Al Quseir City, Red Sea Governorate, Egypt. Neuropsychiatr Dis TreatVol 9 2013, ArtID 767 - 771. 2013; 9.
8. Falip-Centellas M, Rovira RM, Gratacos-Vinyola M, Lluis C, Perez-Perez S, Padro-Ubeda L. First tonic-clonic generalized seizure: recurrence, and prognosis factors [Spanish]. Revista de Neurologia. 2002; 34 (10): 924-928.
9. Helmstaedter C, Elger CE. The phantom of progressive dementia in epilepsy. Lancet. 1999; 354 (9196): 2133-2134.
10. Hussain SA, Haut SR, Lipton RB, Derby C, Markowitz SY, Shinnar S. Incidence of epilepsy in a racially diverse, community-dwelling, elderly cohort: results from the Einstein aging study. Epilepsy Res. 2006; 71 (2-3): 195-205.
11. Johnson EL, Krauss GL, Lee AK, et al. Association between midlife risk factors and late-onset epilepsy: results from the Atherosclerosis Risk in Communities Study. JAMA Neurol. 2018; 75 (11): 1375-1382.
12. Klein CJ, Bird T, Ertekin-Taner N, et al. DNMT1 mutation hot spot causes varied phenotypes of HSAN1 with dementia and hearing loss. Neurology. 2013; 80 (9): 824-828.
13. Koubeissi M. Seize the day for a day with no seizures: modifiable midlife risk factors identified. Epilepsy Curr. 2019; 19 (1): 27-28.
14. Mahler B, Torbjorn T, Carlsson S, Andersson T. Impact of comorbidities on risk for injuries and accidents in epilepsy: a prospective, population-based cohort study. Epilepsia. 2017; 58 (Supplement 5): S26-S27.
15. Rohde NN, Baca CB, Van Cott AC, Parko KL, Amuan ME, Pugh MJ. Antiepileptic drug prescribing patterns in Iraq and Afghanistan war veterans with epilepsy. Epilepsy Behav. 2015; 46: 133-139.
16. Sarkis RA, Dickerson BC, Cole AJ, Chemali ZN. Clinical and neurophysiologic characteristics of unprovoked seizures in patients diagnosed with dementia. J Neuropsychiatry Clin Neurosci. 2016; 28 (1): 56-61.
17. Sepulveda-Falla D, Glatzel M, Lopera F. Phenotypic profile of early-onset familial Alzheimer's disease caused by presenilin-1 E280A mutation. J Alzheimers Dis. 2012; 32 (1): 1-12.
18. Warren J, Schott J, Fox N, et al. Brain biopsy in dementia. Brain. 2005; 128 (9): 2016-2025.

Less than 50 participants (n = 7)

1. Horvath A, Szcs A, Hidasi Z, Csukly G, Barcs G, Kamondi A. Prevalence, semiology, and risk factors of epilepsy in Alzheimer's disease: an ambulatory EEG study. J Alzheimers Dis. 2018; 63 (3): 1045-1054.
2. Radford K, Lavrencic LM, Delbaere K, et al. Factors associated with the high prevalence of dementia in older aboriginal Australians. J Alzheimers Dis. 2019; 70: S75-S85.
3. Risse SC, Lampe TH, Bird TD, et al. Myoclonus, seizures, and paratonia in Alzheimer disease. Alzheimer Dis Assoc Disord. 1990; 4 (4): 217-225.

4. Romanelli MF, Morris JC, Ashkin K, Coben LA. Advanced Alzheimer's disease is a risk factor for late-onset seizures. Arch Neurol. 1990; 47 (8): 847-850.
5. Ruggles KH, Haessly SM, Berg RL. Prospective study of seizures in the elderly in the Marshfield Epidemiologic Study Area (MESA). Epilepsia. 2001; 42 (12): 1594-1599.
6. Smith K, Flicker L, Dwyer A, et al. Factors associated with dementia in aboriginal Australians. Aust N Z J Psychiatry. 2010; 44 (10): 888-893.
7. Weiner MF, Hynan LS, Parikh B, et al. Can Alzheimer's disease and dementias with Lewy bodies be distinguished clinically? J Geriatr Psychiatry Neurol. 2003; 16 (4): 245-250.

Not epilepsy but taking antiepileptic drugs (n = 2)

1. Harms SL, Eberly LE, Garrard JM, Hardie NA, Bland PC, Leppik IE. Prevalence of appropriate and problematic antiepileptic combination therapy in older people in the nursing home. J Am Geriatr Soc. 2005; 53 (6): 1023-1028.
2. Sarycheva T, Lavikainen P, Taipale H, et al. Antiepileptic drug use and the risk of stroke among community-dwelling people with Alzheimer disease: a matched cohort study. J Am Heart Assoc. 2018; 7 (18) (no pagination) (e009742).

Not people with Alzheimer’s disease (n = 5)

1. Brown PD, Buckner JC, O'Fallon JR, et al. Effects of radiotherapy on cognitive function in patients with low-grade glioma measured by the folstein mini-mental state examination. J Clin Oncol. 2003; 21 (13): 2519-2524.
2. Chin A, O'Connell H, Kirby M, et al. Co-morbid and socio-demographic factors associated with cognitive performance in an elderly community dwelling Irish population. Int J Geriatr Psychiatry. 2006; 21 (12): 1150-1155.
3. Soares WB, Dos Santos EB, Bottino CMC, Elkis H. Psychotic symptoms in older people without dementia from a Brazilian community-based sample: a seven years' follow-up. PLoS One. 2017; 12 (6): e0178471.
4. Sulkava R. Alzheimer's disease and senile dementia of Alzheimer type: a comparative study. Acta Neurol Scand. 1982; 65 (6): 636-650.
5. Voglein J, Noachtar S, McDade E, et al. Seizures as an early symptom of autosomal dominant Alzheimer's disease. Neurobiol Aging. 2019; 76: 18-23.

Pooled analyses of randomised control trials (n = 1)

1. Irizarry MC, Jin S, He F, et al. Incidence of new-onset seizures in mild to moderate Alzheimer disease. Arch Neurol. 2012; 69 (3): 368-372.

Review article or abstracts only (n = 6)

1. Baker J. Epileptic seizures in Alzheimer's disease: the Preside Study. Alzheimers Dement. 2018; 14 (7 Supplement): P804.
2. Beagle A, Darwish S, Karageorgiou E, Vossel K. Seizures and myoclonus in the early stages of frontotemporal dementia. Neurology conference: 67th American Academy of Neurology Annual Meeting, AAN. 2015; 84 (SUPPL. 14).

3. Ben Djebara M, Sidhom Y, Abuhassen A, et al. Neuropsychological impairment in patients with idiopathic generalized epilepsy (IGE). J Neurol Sci. 2017; 381 (Supplement 1): 688.
4. Dhikav V, Anand K. Potential predictors of hippocampal atrophy in Alzheimer's disease. Drugs Aging. 2011; 28 (1): 1-11.
5. Pillai ALPC, Bakaki P, Koroukian S, Kaiboriboon K. Comorbidity burden among medicaid beneficiaries with epilepsy. Epilepsy Curr. 2014; 1): 199-200.
6. Smith M, Burns D, Robinson D. Geriatric seizures. J Am Geriatr Soc. 2002; 50 (5): 974-975.

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

1. Cheng CH, Liu CJ, Ou SM, Yeh CM, Chen TJ, Lin YY, et al. Incidence and risk of seizures in Alzheimer's disease: a nationwide population-based cohort study. *Epilepsy Res*. 2015;115:63-66
2. Burns A, Jacoby R, Levy R. Neurological signs in Alzheimer's disease. *Age Ageing*. 1991;20:45-51
3. 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;54:700-707
4. 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;44:695-699
5. Amatniek JC, Hauser WA, DelCastillo-Castaneda C, Jacobs DM, Marder K, Bell K, et al. Incidence and predictors of seizures in patients with Alzheimer's disease. *Epilepsia*. 2006;47:867-872
6. Scarmeas N, Honig LS, Choi H, Cantero J, Brandt J, Blacker D, et al. Seizures in Alzheimer disease: who, when, and how common? *Arch Neurol*. 2009;66:992-997
7. 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;60:211-223
8. Bell J, Lonnroos E, Koivisto AM, Lavikainen P, Laitinen M-L, Soininen H, et al. Use of antiepileptic drugs among community-dwelling persons with Alzheimer's disease in Finland. *J Alzheimers Dis*. 2011;26:231-237
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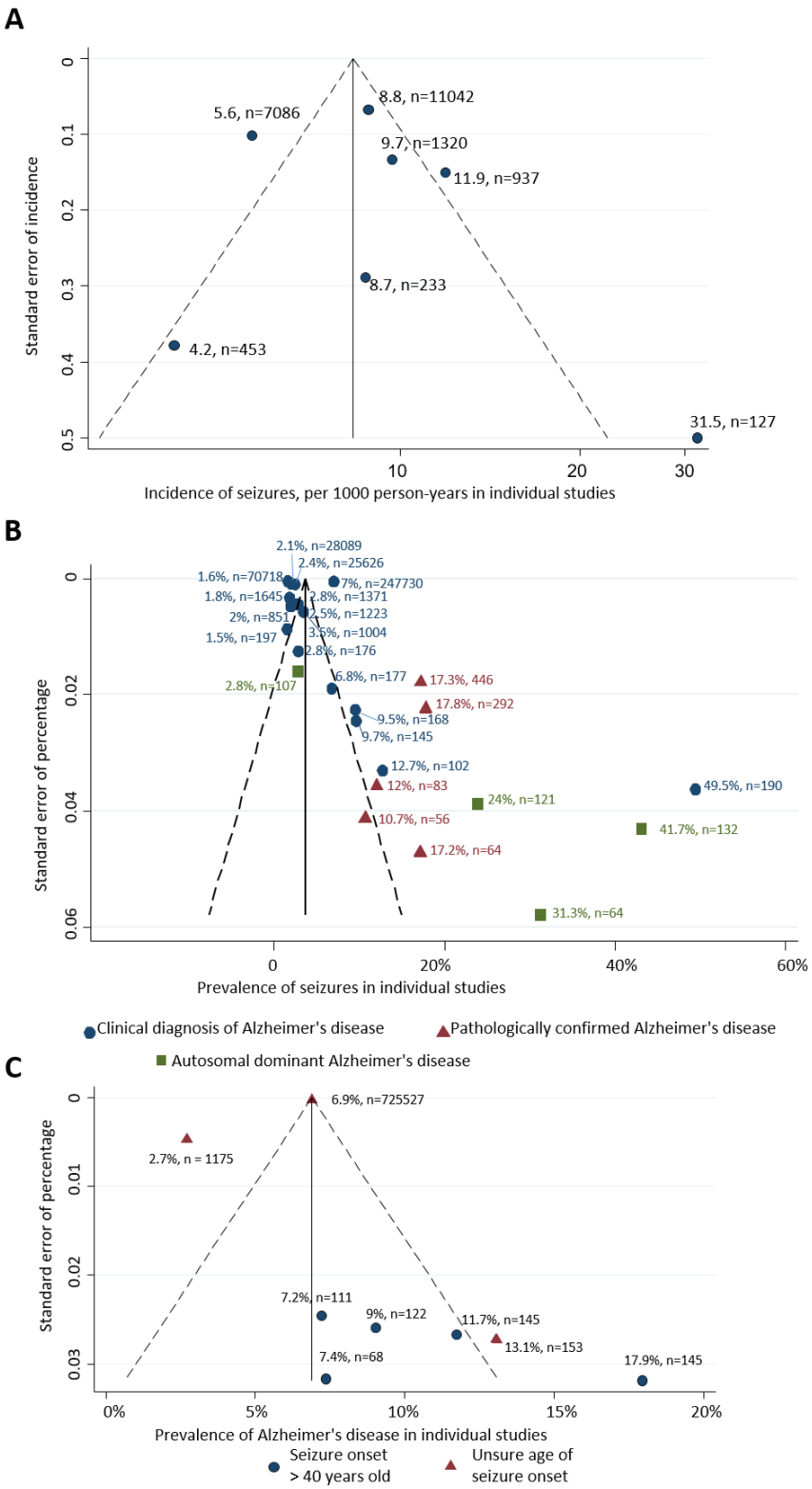
Supplementary Figure S1 Funnel plots with pseudo 95% confidence limits



A. Incidence of seizures among people with Alzheimer's Disease
B. Prevalence of seizures among people with Alzheimer's Disease
C. Prevalence of Alzheimer's Disease among people with seizures

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

Database	Search strategy	Number of articles
Medline	1. exp epilepsy/ (includes “seizures/”, “seizures” is used for “convulsions”)	107891
	2. (epilep* or seizure* or convulsi*).tw.	177814
	3. 1 or 2	196606
	4. exp dementia/ (includes “Alzheimer disease/”)	157113
	5. cognitive dysfunction/	13142
	6. (dementia* or Alzheimer*).tw.	171534
	7. 4 or 5 or 6	215992
	8. epidemiologic studies/	8064
	9. exp case control studies/	1015158
	10. exp cohort studies/	1892116
	11. case control.tw.	102951
	12. (cohort adj (study or studies)).tw.	150203
	13. cohort analy$.tw.	6033
	14. (follow up adj (study or studies)).tw.	43634
	15. (observational adj (study or studies)).tw.	77180
	16. longitudinal.tw.	189512
	17. retrospective.tw.	406655
	18. cross sectional.tw.	258674
	19. cross-sectional studies/	302176
	20. Or/8-19	2606958
	21. 3 and 7 and 20	**551**
EMBASE	1. exp “seizure, epilepsy and convulsion”/	387725
	2. (epilep* or seizure* or convulsi*).tw.	307706
	3. 1 or 2	431061
	4. exp cognitive defect/ (includes “dementia/” and “Alzheimer disease/”)	469650
	5. (dementia* or Alzheimer*).tw.	282753
	6. 4 or 5	509631
	7. clinical study/	169028
	8. case control study/	145496
	9. family study/	27199
	10. longitudinal study/	130790
	11. retrospective study/	825468
	12. prospective study/	550897
	13. randomized controlled trials/	167797
	14. 12 not 13	545205
	15. cohort analysis/	504279
	16. (Cohort adj (study or studies)).mp.	275074
	17. (Case control adj (study or studies)).tw.	126494
	18. (follow up adj (study or studies)).tw.	66295
	19. (observational adj (study or studies)).tw.	151249
	20. (epidemiologic$ adj (study or studies)).tw.	105956

	21 (cross sectional adj (study or studies)).tw.	196392
	22. Or/7-11,14-21	2504326
	23. 3 and 6 and 22	2971
	24. limit 23 to human	**2791**
PsycINFO	1. exp epilepsy/ or exp seizures/ (“seizures/” is also used for “convulsions”)	33921
	2. (epilep* or seizure* or convulsi*).tw.	54253
	3. 1 or 2	54627
	4. cognitive impairment/ or dementia/ or Alzheimer’s disease/	93442
	5. (dementia* or Alzheimer*).tw.	96786
	6. 4 or 5	118056
	7. 3 and 6	2866
	8. Limit 7 to Human	**2347**
CINAHL	1. (MH "Epilepsy+") or (MH "Seizure") or (MH "Convulsions+")	15,866
	2. “epilep*” or “seizure*” or “convulsi*”	32,395
	3. 1 or 2	32,540
	4. (MH "Cognition Disorders") or (MH "Dementia+")	83,982
	5. “dementia*” or “Alzheimer*”	78,704
	6. 4 or 5	98,552
	7. (MH "Prospective Studies")	393,166
	8. (MH "Case Control Studies+")	74,077
	9. (MH "Correlational Studies")	23,184
	10. (MH "Nonconcurrent Prospective Studies")	215
	11. (MH "Cross Sectional Studies")	165,225
	12. “cohort” W0 “study or studies”	2,122,169
	13. “observational” W0 “study or studies”	2,122,169
	14. or/7-13	2,123,026
	15. 3 and 6 and 14	**557**

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

Country/region year, last name of the first author[a]	Taiwan 2015,[1] Cheng[R]	UK 1991,[2] Burns[R]	UK 2013,[3] Imfeld[R]	UK 2015,[4] Cook[R]	USA 2006,[5] Amatniek[P]	USA 2009,[6] Scarmeas[P]	USA 2017,[7] Beagle[R]
Recruiting sites[b]	National Health Insurance Research Database[P]	Camberwell Health Authority in South East London[H]	United Kingdom based General Practice Research Database[C]	Health Improvement Network Database[C]	Neurology Department Columbia University, Psychiatry Department Johns Hopkins University, Geriatric Neurobehavioral Center Massachusetts General Hospital[H]	Columbia University, The Johns Hopkins University, Massachusetts General Hospital Harvard University[H]	Memory and Aging Center[H]
Recruiting period	Jan 2000 to Dec 2010	Oct 1986 to Oct 1988	Jan 1998 to Sep 2008	Jan 1990 to Jul 2009	Since 1989	-	Jan 2007 to Dec 2013
Inclusion criteria	diagnosed with AD, AChEIs prescriptions ≥ 1, MMSE 10 to 26 or CDR 1 to 2	satisfying NINCDS/ADRDA AD criteria	≥ 65 years old with any of: 1) an AD diagnosis and ≥ 1 AD drug prescription, 2) dementia diagnosis and ≥ 2 AD drug prescriptions, 3) ≥ 2 records of AD, 4) AD diagnosis after a specific test, referral to a specialist, or neuroimaging, 5) AD diagnosis plus recorded symptoms (e.g., aphasia)	general practitioner recorded newly diagnosed AD, ≥ 50 years old, and a baseline period of ≥ 182 days prior to diagnosis to characterize the seizure populations	modified MMSE ≥ 30 (16 standard MMSE); no antipsychotic medication use ≥ one month, normal head MRI or CT, except for atrophy or small, silent subcortical lesions, willingness to be followed-up, English speaking or have an English-speaking advocate	mMMSE score ≥ 30/57, approximately equivalent to Folstein MMSE ≥ 16/30, data only for patients who were seizure free at the baseline assessment were used for seizure incidence calculation	meet AD diagnostic criteria at most recent clinical evaluation
Exclusion criteria	at least one image information (CT or MRI) to exclude stroke, history of seizure	-	< 3 years of recorded history prior to the AD or VD diagnosis; a history of HIV/AIDS, alcoholism, drug abuse, multiple sclerosis, motor neuron disease, Down syndrome; history of diagnosed epilepsy or seizures prior to the AD diagnosis, or > 3 prescriptions of anticonvulsant drugs	history of stroke or seizure	alcohol or drug dependency at study entry, CNS infection or non-AD caused dementia, evidence of cortical stroke, schizophrenia or schizoaffective disorder before intellectual decline, any ECT in the past 2 years or ≥ 10 ECT sessions during the lifetime, history of seizures	diagnosis of Parkinson disease or parkinsonism or schizophrenia or schizoaffective disorder prior to the onset of intellectual decline, clinical or historical evidence of stroke, history of alcohol abuse or dependence, ECT within 2 years of recruitment or overall ≥ 10 ECT sessions	seizure onset over 10 years prior to symptoms of neurodegenerative disease, previous seizures provoked by cortical lesions, acute metabolic disorders, or subdural hematomas, provoked myoclonus, those lacking sufficient records
Sample size, person-years of follow-up, age in years, number of males, number of seizure cases	937, 3697, 75.3 ± 8.2, 361, 44	127, 127, -, -,4	7086, 17178, 80.7 ± 6.7, 2198, 97	11042, 24754, 80, 3607, 219	233, 1374, -, -, 12	453, 1674, 74.4 ± 8.9, 181, 7	1320, 5773, -, 521, 56
AD diagnostic criteria	DSM-IV, NINCDS-ADRA	NINCDS-ADRDA	-	-	NINCDS-ADRA	DSM-III primary degenerative dementia of the Alzheimer type, NINCDS-ADRA	"probable AD", NINCDS-ADRA 1984 and 2011

Length of follow-up (years)	mean 4.02, maximum 10	1 year	approximately 2.42 years (calculated, person-years of follow-up / sample size)	approximately 2.24 years (calculated, person-years of follow-up / sample size)	median 5.99, range 0 to 8.95	mean 3.7, maximum 14	median 5.2, IQR 3.3 to 7.6
Incidence (per 1000 person-years) (95% CI)	11.9	31.5	5.6 (4.6 to 6.9)	8.8 (7.7 to 10.1)	8.7	4.18	9.7 (6.8 to 13.7)
Incidence (per 1000 person-years) by age group (95% CI)	-	-	6.2 (4.5 to 8.4) in 65 to 79, 5.3 (4.1 to 6.9) in over 80	21.7 (17.2 to 27.4) in 50 to 69 (n = 1034), 9.4 (6.7 to 13.1) in 70 to 74 (n = 1294), 8.2 (6.2 to 10.9) in 75 to 79 (n = 2363), 5.5 (4.0 to 7.8) in 80 to 84 (n = 2920), 5.4 (3.8 to 7.6) in over 85 (n = 3431)	42.6 (2/47) in 50 to 59, 15.5 (4/258) in 60 to 69, 5.7 (3/527) in 70 to 79, 5.5 (3/542) in 80+	-	-
EEG	-	-	-	-	available for 136 of the 233 AD patients, slow dominant rhythm and focal epileptiform findings recorded, but details not reported	184 AD patients: slow dominant rhythm 55, focal slowing 22, intermittent rhythmic slowing 10, other slowing 51, focal epileptiform 5, generalized epileptiform 2	48 out of 78 AD, DLB or FTD patients with seizures: normal 11, others diffuse or focal slowing, asymmetric, focal temporal, frontotemporal or generalized epileptiform
AD diagnosis to seizure onset (years)	3.6 ± 2.9	5.25 ± 3.55	for epilepsy or seizures occurring among AD, VD and no dementia 1.5 (IQR 0.5 to 3.0)	-	initial first seizure occurred at 1 year after enrolment, the last incident seizure occurred at 6.55 years of follow-up, median time to first seizure 4.06 years	8.2 ± 2.6, 5.1 to 11.8	-
A single seizure or recurrent seizures	not clear, only mentioned “seizures”	not clear, only mentioned “seizures”	not clear, only mentioned “seizures”	not clear, only mentioned “seizures”	not clear, only mentioned “seizures”	a single seizure (n = 4), ≥ 2 seizures (n = 3)	not clear, only mentioned “seizures”
Predictors tested (*significant in univariate analysis)	-	-	-	-	younger age*, focal epileptiform, race, severity, hypertension, depression, duration*, education, slow dominant rhythm	cohort, recruitment center, sex, younger age*, ethnicity, education, estimated duration of illness, baseline function, cognition, depression, comorbidities, use of cholinesterase inhibitors, neuroleptic agents	younger age*, MMSE, genetic risk variants

[a]Recruitment: P prospective, R retrospective

[b]Case selection: H hospital-based, C community-based, P population-based

AchEIs denotes acetylcholinesterase inhibitors, AD Alzheimer’s disease, CDR clinical dementia rating, CI confidence interval, CNS central nervous system, CT computed tomography, DLB dementia with Lewy bodies, DSM-III/-IV diagnostic and statistical manual of mental disorders (third/fourth edition), ECT electroconvulsive therapy, EEG electroencephalogram, FTD frontotemporal dementia, HIV/AIDS human immunodeficiency virus and acquired immunodeficiency syndrome, IQR interquartile range, LBD Lewy Body dementia, MMSE mini mental state examination, MRI magnetic resonance imaging, NINCDS-ADRA national institute of neurological and communicative disorders and stroke and the Alzheimer’s disease and related disorders association, UK United Kingdom, USA United States of America, VD vascular dementia

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

#	Country/region year, last name of the first author[a]	Recruiting sites[b]	Recruiting period	Inclusion and exclusion criteria	AD diagnostic criteria	Seizure diagnostic criteria	Cognitive tests, mean ± SD, range, n (%)
1	Finland 2011,[8] Bell[R]	The Special Reimbursement Register maintained by the Social Insurance Institution of Finland[P]	Data extracted in Dec 2005	1) mild or moderate AD, 2) experienced decreased social capacity over three months, 3) had CT/MRI scan, 4) alternative diagnoses excluded, 5) confirmed diagnosis by neurologist or geriatrician	DSM-IV, NINCDS-ADRDA	1) examined by neurologists or at neurology clinics, 2) received relevant examinations (EEG, CT, MRI scan, relevant laboratory tests), 3) care plans	-
2	Finland 2018,[9] Rauramaa[R]	Geriatric department of Harjula Hospital in Kuopio[H]	1991 to 2001 (pathology)	probable or possible AD	NINCDS-ADRDA, CERAD (autopsy)	ILAE	-
3	Finland 2018,[10, 11] Taipale[R]	The Special Reimbursement Register (Finnish dataset) taken from nationwide Finnish registers covering all residents, and a longitudinal sample from a large German statutory health insurance[P]	2005 to 2011	clinically diagnosed AD identified from the Special Reimbursement Register, individuals with an observation time of less than three year before AD diagnosis were excluded from the German dataset	DSM-IV, NINCDS-ADRDA and ICD-10	ICD-10	-
4	France 2007,[12] Hommet[R]	Geriatric Internal Medicine Unit, University Hospital[H]	Aug 2000 to Aug 2005	hospitalized patients ≥ 65 years old with clinical AD, diagnosed by a neurologist or geriatrician	NINCDS-ADRDA	hospitalization for generalized or focal to bilateral tonic-clonic seizures, considered to have had seizures only if convulsive activity had been described by a physician or caregiver based on reliable history	MMSE 14
5	France 2016,[13] Zarea[R,P]	French ADEOAD cohort[H]	1993 to 2009	AD with a pathogenic mutation in PSEN1, PSEN2, APP, or duplication of APP, ≥ 5-year follow-up, excluded those with insufficient clinical and neurophysiologic data	-	ILAE	MMSE 8.2, 0 to 30, among those with seizures at onset of seizure
6	UK 1991,[2] Burns[R]	Camberwell Health Authority in South East London[H]	Oct 1986 to Oct 1988	satisfying NINCDS/ADRDA AD criteria	NINCDS-ADRDA	tonic-clonic seizures since the onset of dementia	CDR I n = 12, II n = 78 and III n = 85
7	UK 1992,[14] Forstl[R]	Camberwell Health Authority in South East London[H]	Oct 1986 to Oct 1988	autopsy verified AD	NINCDS-ADRDA, verified neuropathologically	tonic-clonic seizures since the onset of dementia; generalized motor seizures witnessed by clinical staff or if from patients` primary caregivers	MMSE 5.3, 0 to 21, CAMCOG 16.7, 0 to 66, memory subscore 2.1, 0 to 16, language subscore 7.6, 0 to 24, Praxis subscore 2.5, 0 to 11

#	Country/region year, last name of the first author[a]	Recruiting sites[b]	Recruiting period	Inclusion and exclusion criteria	AD diagnostic criteria	Seizure diagnostic criteria	Cognitive tests, mean ± SD, range, n (%)
8	Italy 2010,[15] Bernardi[R]	University Hospital in Rome[H]	Jan 2001 to Dec 2006	seen for the first time, underwent at least two clinical diagnostic assessments, a diagnosis of AD	ICD-9 codes, AD, 331.0x	commission on classification and terminology of ILAE, 1981; patients with seizures underwent EEG and MRI or CT brain scans to exclude symptomatic seizures	MMSE 19.9 ± 6.3 (3 to 27); CDR I 45 (31%), II 76 (52.4%), III 24 (16.6%)
9	Italy 2016,[16] Giorgi[R]	Electronic database, Dementia Center, Neurology Clinic of the University of Pisa[H]	Jan 2007 to Jan 2015	evaluated ≥ three times as outpatients, through ≥ two years	NINCDS-ADRDA	search for terms “epilepsy” or “seizures” in “diagnosis” field, and for AEDs (e.g.carbamazepine) in “treatment” field	-
10	Italy 2017,[17] DiFrancesco[R]	Unit for Alzheimer”s disease Assessment of the San Gerardo Hospital, Monza[H]	May 2000 to Jul 2016	affected by AD	NINCDS-ADRD, confirmed by neuropsychological data	≥ 1 unprovoked seizure(s), onset after 55 years old, before or after occurrence of cognitive symptoms; structural causes, e.g. CVD, tumor or trauma were investigated in all the patients with MRI or CT	-
11	Italy 2020,[18] Arnaldi[R]	University Hospital memory clinic[H]	Jan 1999 to Dec 2016	exclude seizure onset ≥ five years prior to cognitive symptoms and a history of stroke and/or a diagnosis of vascular dementia	1984 NINCDS-ADRDA for patients diagnosed between 1999 and 2011 and according to the 2011 NIA-AA criteria for patients diagnosed from 2011	not reported, but only included those with the presence of seizures under AEDs treatment before, after or concomitant with the diagnosis of dementia	TMT A and B, Stroop color-word test, digit span, symbol-digit, CDT MMSE 24.14 ± 4.36, 10 to 30 with seizures, 23.95 ± 3.64, 15 to 30 without seizures, RALVT and Corsi’s block design
12	Netherlands 1996,[19] Samson[R]	City of Rotterdam, four northern provinces[P]	1980 to 1987	AD diagnosed before 70 years old	NINCDS–ADRDA	-	-
13	Portugal 2019,[20] Tábuas-Pereira[R]	Dementia Outpatient Clinic of the Centro Hospitalar e Universitário de Coimbra[H]	-	patients with AD; exclude ischemic or hemorrhagic stroke, or tumor caused seizures, history of traumatic brain injury and seizures	full neuropsychological evaluation and cerebrospinal fluid biomarkers analysis	determined clinically, with the support of EEG, when considered necessary by patients’ physicians	MMSE 16.2 ± 6.4 with seizures 20.8 ± 7.4 without seizures
14	Sweden 2020,[21] Zelano[P]	SveDem, a national quality registry of dementia in Sweden[C]	2007	-	ICD-9 and -10	ILAE, ICD-10	MMSE
15	UK 1992,[22] McAreavey[R]	Dundee Psychiatric Inpatient Service[H]	Nov 1989	aged over 55 years old	ICD-9	brief and usually unprovoked stereotyped disturbances of behavior, emotion, motor function, or sensation result from an abnormal cortical neuronal electrical discharge diagnosed by the doctor in charge of the ward and confirmed by the authors; CT performed on younger patients or	MMSE

#	Country/region year, last name of the first author[a]	Recruiting sites[b]	Recruiting period	Inclusion and exclusion criteria	AD diagnostic criteria	Seizure diagnostic criteria	Cognitive tests, mean ± SD, range, n (%)
						those with a suggestion of focal lesions	
16	UK 2006,[23] Lozsadi[R]	A dedicated cognitive function clinic based at a regional neuroscience Center[H]	Jan 2000 to Dec 2005	-	NINCDS-ADRDA	ILAE	-
17	UK 2016,[24] Ryan[R]	Dementia Research Center at University College London's Institute of Neurology[H]	Jul 1987 to Oct 2015	ADAD due to APP or PSEN1 mutations, with detailed medical history and neurological examination findings available	-	-	-
18	UK 2019,[25, 26] Baker[P]	Memory clinic in Exeter, Devon[H]	Jan 2016 to Jun 2017	diagnosis of AD made at memory clinic assessment and consented to study	NIA-AA criteria	≥ 2 stereotyped episodes suggestive of epilepsy witnessed by a reliable informant	Addenbrooke"s Cognitive Examination version III
19	USA 1986,[27] Hauser[R]	2204 autopsies (dying at 9 state hospitals) done in Minnesota state hospitals, state nursing home with general autopsy[H,N]	1952 and 1972	from a larger autopsy-proven series of AD patients without other neuropathological findings, with medical records available	autopsy	convulsive activity clearly described in physicians" or nurses" notes	-
20	USA 1994,[28] Mendez[R]	Ramsey Foundation Alzheimer's Treatment and Research Center Brain Bank[C]	-	acquired, sustained, dysfunctional cognitive decline, neuropathological criteria for AD; excluded cases with non-AD lesions	age-adjusted, moderate-to-severe number of neurotic plaques in the neocortex similar to proposed criteria, moderate-to-severe neurofibrillary tangles in the hippocampus and lacked evidence of any other dementing illness	ILAE	-
21	USA 2010,[29] Jayadev[R]	Alzheimer"s disease Research Center[H]	"Over the past 25 years"	AD patients with mutation in PSEN2, with detailed medical records	-	-	-
22	USA 2013,[30] Vossel[R]	Memory and Aging Center at the University of California, San Francisco[H]	2007 and 2012	presented with cognitive decline and met NINCDS-ADRDA criteria for probable AD, excluded those with cortical strokes, cavernous hemangioma, meningioma, suspected brain tumor, subdural hematoma, history of alcohol abuse, amyloid angiopathy, enrollment in clinical treatment trials, and those with seizure onset during childhood or early adulthood (before 30 years)	NINCDS-ADRDA	ILAE: two or more unprovoked seizures or a first unprovoked seizure in the setting of a corroborating EEG showing epileptiform activity	MMSE

#	Country/region year, last name of the first author[a]	Recruiting sites[b]	Recruiting period	Inclusion and exclusion criteria	AD diagnostic criteria	Seizure diagnostic criteria	Cognitive tests, mean ± SD, range, n (%)
23	USA 2017,[31] Birnbaum[R]	Any Medicare/Medicaid certified nursing home[N]	15 July, 2003 to 2007	all residents	ICD-9 codes AD, 331.0x	Minimum Data Set 2.0 item I.1.aa (seizure disorder) or ICD-9 code 345.xx or 780.39 in item I.3	-
24	USA, Europe, and Australia, 2016,[32] Tang[P]	Study Centers in the USA, Europe, and Australia[C]	Feb 2008 to Jul 2014	members of families of mutation carriers (APP, PSEN1, or PSEN2) known to cause ADAD	CDR scale > 0	-	CDR 1.05 ± 0.79, MMSE 20·98 ± 10·92
25	USA, Netherlands, Australia 1991,[33] Breteler[R]	Re-analysis of case-control studies (four studies all meet our inclusion criteria)	-	epilepsy over one year prior to onset of AD; exclude studies without specified age of epilepsy onset	DSM-III and NINCDS-ADRDA (USA), slow progressive decline of intellectual function, a CDR scale score of over 0.5, a Short Portable Mental Status Questionnaire score of < 20 (out of 30), a Hachinski scale score < 7 (out of 18), and no evidence for abnormalities on CT other than cerebral atrophy, and no evidence for focal dysfunction in the EEG (Netherlands) NINCDS-ADRDA (Australia)	-	-

[a]Recruitment: P prospective, R retrospective

[b]Case selection: H hospital-based, N nursing home based, C community-based, P population-based

AD denotes Alzheimer's disease, ADAD autosomal dominant familial Alzheimer's disease, ADEOAD autosomal dominant early onset Alzheimer disease, AEDs antiepileptic drugs, APP amyloid β precursor protein gene, CAMCOG Cambridge cognitive examination, CDR clinical dementia rating scale, CDT clock drawing test, CERAD consortium to establish a registry for Alzheimer's disease, CT computed tomography, CVD cardiovascular diseases, DSM-V diagnostic and statistical manual (fifth edition), ECT electroconvulsive therapy, EEG electroencephalography, ICD-9/10 international classification of diseases (ninth/tenth edition), ILAE international league against epilepsy, MMSE mini mental state examination, MRI magnetic resonance imaging, NIA-AA national institute on aging-Alzheimer's association, NINCDS-ADRDA national institute of neurological and communicative disorders and stroke and the Alzheimer's disease and related disorders association, PSEN1 presenilin-1, PSEN2 presenilin-2, RALVT Rey auditory learning verbal test, SD standard deviation, TMT trail-making test, UK United Kingdom, USA United States of America.

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

#	Country/region year, last name of the first author	Sample size, number of males, mean age in years (range)	Number of participants with seizures, prevalence	Seizure type and EEG findings	A single seizure or recurrent seizures	Disease duration in years, mean ± SD	Treated with AEDs	Predictors tested (*significant in univariate analyses)
1	Finland 2011,[8] Bell	28089, 9045, 80 (42 to 101)	590, 2.1%	-	Not reported, term "epilepsy" used	-	-	-
2	Finland 2018,[9] Rauramaa	64, 6, 70.6 ± 7 with seizures 78.3 ± 10 without seizures	11, 17.2%	4 generalized, 2 focal, EEG (n = 10): 7 generalized, 2 focal finding and discharges, 1 generalized and a focal finding	not reported, term "epilepsy" used	between AD diagnosis and seizures 2.5 ± 1.2 SE	phenytoin 3, carbamazepine 3, data unavailable 4, no AEDs 1, diazepam "all subjects". Age starting AEDs 75 ± 6.9 (range 66 to 82, n = 5)	younger age at AD diagnosis*, younger age at the time of hospitalization*, longer duration of AD*, age at death, brain weight, vascular lesions, neuropathological diagnosis, apolipoprotein E genotype
3	Finland 2018,[10, 11] Taipale	70718, 24602, 78.1 ± 7.1	1140, 1.6%	-	not reported, term "epilepsy" used	-	-	-
4	France 2007,[12] Hommet	197, 47, 83	3, 1.5%	2 focal (EEG, CT scan signs), 1 isolated unprovoked seizures	not reported, terms "seizures" and "epilepsy" used	-	valproate acid 2, not mentioned 1	-
5	France 2016,[13] Zarea	132, 114, 44.8 (24 to 63) age of onset	55, 41.7%	all seizures (n = 63, including 8 cases of acute symptomatic seizures): 82% generalized, 8% focal to generalization, 8% focal (impaired awareness), 2% focal (aware); interictal EEG in 54 of 63 patients, abnormal in 17: spike-waves 4, spikes 4, rapid slow waves 2, seizure 1, polyspikes 1, pseudoperiodic spikes 1, unspecified 4	a single seizure (n = 24) recurrent seizures (n = 31)	between cognitive symptoms and seizures 5.8	valproic acid 36%, phenobarbital 22%, levetiracetam 11%, carbamazepine 8%, lamotrigine 6%, gabapentin 4%, phenytoin 3%, pregabalin 1%, topiramate 1%	APP duplication increased seizure risk*
6	UK 1991,[2] Burns	178, 38, 80.4 ± 6.6 (56 to 99)	5/176, 2.8%	5 tonic/clonic seizures	not reported, term "epileptic fits - the occurrence of tonic/clonic seizures" used	AD duration 5.25 ± 3.55	-	-
7	UK1992,[14] Forstl	56, 13, 83.1 ± 6.2 (67 to 96)	6 generalized motor seizures, 10.7%	6 generalized motor seizures	not reported, term "generalized motor seizures" used	AD duration 7.7 ± 4.6	-	-
8	Italy 2010,[15] Bernardi	145, 56, 78.0 ± 7.2 (51 to 91)	14, 9.7%	13 focal (impaired awareness) to generalization, 1 generalized, 21 out of 145 AD patients had EEG, all patients with seizures had an EEG	recurrent seizures (n = 10)	cognitive symptoms to recruitment: 5.3 ± 2.2, 2 to 14, no seizures before cognitive symptoms, between AD diagnosis and seizures 3.6 ± 1.6	all treated with AEDs	age, male sex*, education, disease duration, dementia severity, hypertension, no diabetes*, dislipidemia, neuroimaging findings, anti-dementia or antidepressant therapy, antipsychotic therapy

9	Italy 2016,[16] Giorgi	1223, -, 69.6 ± 8.5 age was “age at AD diagnosis”	30, 2.5%	In 20 cases with concomitant brain lesions: all focal seizures, secondary generalization in 4. In 10 cases without any concomitant brain lesion: 5 generalized tonic-clonic, 4 focal (impaired awareness) and 1 focal to generalization; EEG (n = 13): focal interictal abnormalities in 2 with concomitant brain lesions and in 1 without any concomitant brain lesion	not reported, but during the two-year follow-up, no clear epileptic seizures had been reported (n = 23), whereas generalized seizures (n = 4), focal seizures (n = 2), or focal (impaired awareness) seizures (n = 1) were reported	seizures onset after cognitive symptoms 3.03 ± 5.2 years	all treated with AEDs	-
10	Italy 2017,[17] DiFrancesco	1371, 521, 75 ± 7, age was “age at cognitive decline”	39 (23 before, 16 following cognitive symptoms), 2.8%	11 generalized, 5 focal, 7 undetermined (among 23 before cognitive symptoms); EEG (n = 8): normal 2, focal or generalized epileptiform abnormalities 4, unspecific interictal abnormalities 2	not reported, terms “seizures” and “epilepsy” used	between seizures and cognitive symptoms 4.6 (median 2, IQR 0.5 to 6, range 0.5 to 29), between cognitive symptoms and seizures 5	good control of seizures with a single AED among 23 before cognitive symptoms	-
11	Italy 2020,[18] Arnaldi	1,645,-,-	30, 1.8%	15 generalized, 10 focal, 5 unknown; interictal epileptiform discharges were more likely found in AD patients with seizures than those without	not reported, terms “seizures” and “epilepsy” “requiring AEDs treatment” used	seizures after AD (n = 15), seizures before AD (n = 5), concomitant with AD (n = 7), unknown (n = 3)	all treated with AEDs, 23 seizure-free after treatment	age, gender, education, EEG measures, MMSE, GDS, AChEIs, hypertension, diabetes, heart disease, hypercholesterolemia, TMT A and B, symbol-digit, Stroop color/color-word, Corsi’s span, digit-span, RALVT immediate/delayed, CDT, figure copying, verbal fluency
12	Netherlands 1996,[19] Samson	190, -, 61 (male 37 to 70, female 47 to 69) age was age at AD diagnosis	94, 49.5%	-	not reported, term “seizures” used	follow-up time after AD diagnosis 6 (2 to 15)	-	-
13	Portugal 2019,[20] Tábuas-Pereira	292, 107, 63.8 ± 8.9 age was “age at onset”	52, 17.8%	-	not reported, term “seizures” used	-	-	age at first seizure, younger age at AD onset*, baseline MMSE*, CSF T-tau*, gender, age at lumbar puncture, duration of follow-up, education, CSF Aβ42, no history of hypertension*, apolipoprotein E, memantine, history of infection, diabetes, renal failure, stroke, mortality
14	Sweden 2020,[21] Zelano	25,626, -, -	625, 2.4%	-	not reported, term “epilepsy” used, “a single seizure and status epilepticus” listed separately	between seizures and dementia (not just AD) ≥7300 days, between dementia and seizures maximum 3650 days	-	-

15	UK 1992,[22] McAreavey	168, -, -	16, 9.5%	-	not reported, terms “seizures” and “epilepsy” used	-	-	-
16	UK 2006,[23] Lozsadi	177, 86, (49 to 84)	12, 6.8%	9 focal seizures including 3 with secondary generalization, 3 generalized	not reported, term “seizures” and “epilepsy” used	seizures ≥ 10 years before AD diagnosis (n = 5), seizures onset at around the time of AD diagnosis (n = 7)	carbamazepine 6, including one switched from topiramate to carbamazepine	-
17	UK 2016,[24] Ryan	121 (85 PSEN1, 36 APP), -, 46.2 ± 5.9 (PSEN1 atypical cognitive presentations) 42·0 ± 7·4 (typical amnestic), 50.4 ± 5.2 APP, age was “age of onset”	APP 9, 25%: 3 early, 3 late, 3 uncertain; PSEN1 20, 24%	-	not reported, term “seizures” used	-	-	In both genetic groups, individuals with myoclonus were more likely to develop seizures than were those without myoclonus*
18	UK 2019,[25, 26] Baker	102, 51, 78.53 ± 6.47	13, 12.7%	mainly altered responsiveness, amnesia on waking or motor automatisms, 2 generalized	all had ≥ 2 stereotyped episodes suggestive of epilepsy witnessed by a reliable informant	childhood onset seizure (n = 1), seizures and memory onset 8 years (n = 1), memory onset to seizure 6 months to 3 years (n = 11)	lamotrigine 2, levetiracetam 2, sodium valproate 1, phenobarbitone 1 (among those with AD, VD, LBD and MCI)	-
19	USA 1986,[27] Hauser	83, -, 69.1 ± 8.6 with seizures, age was “age of AD onset”	10, 12%	10 generalized	seizures after cognitive symptoms (n = 8): a single seizure (n = 3) recurrent seizures (n = 5)	generalized before cognitive symptoms (n = 2), seizures after cognitive symptoms (n = 8), 6.5 (1 to 15)	-	-
20	USA 1994,[28] Mendez	446, -, 67.1 ± 9.1 without seizures 64.1 ± 8.8 with seizures, age was “age of onset”	77, 17.3%	69 generalized tonic-clonic seizures, 8 focal (aware or impaired awareness); EEG within a few days of seizures in 52 patients: focal or generalized slowing 39, slowing with sharp waves 4, periodic complexes 2, spike waves and epileptiform changes 2, normal activity 5	a single seizure (n = 24) recurrent seizures (n = 55)	between AD diagnosis and seizures 6.8	AEDs were used in 65: phenytoin 63, carbamazepine 1, phenobarbital 4 (2 AEDs in 3 patients)	younger age of onset of AD*, familial dementia, hypertension, heart or cerebrovascular diseases, pulmonary diseases, alcohol abuse, diabetes, head trauma, other medical illnesses
21	USA 2010,[29] Jayadev	64, -, -	20, 31%	-	not reported, but term “seizures” used	-	-	-
22	USA 2013, [30]Vossel	1004, 428, 74.5 ± 10.3 without seizures 69.1 ± 9.0 with seizures	35, 3.5%	16 focal (impaired awareness, 5 developed bilateral convulsive seizures), 13 generalized, 6 focal (aware); EEG in 29 patients: normal 6	two or more unprovoked seizures, unless a corroborating EEG showing epileptiform activity	before cognitive symptoms (n = 3), at the onset of cognitive symptoms (n = 7), 1 to 10 years after cognitive symptoms (n = 24), 13 years after cognitive symptoms (n = 1)	lamotrigine 14, levetiracetam 8, valproic acid 2, clonazepam 2, no AEDs 2, lamotrigine and levetiracetam 1, and other AEDs 6, all seizure free or partial response	-

23	USA 2017,[31] Birnbaum	247730, -, -	17386, 7%	-	not reported, but terms “seizures” and “epilepsy” used	-	-	-
24	USA, Europe, and Australia, 2016,[32] Tang	107, 47, 42.9 ± 8.17, age was “age of AD onset”	3, 2.8%	-	not reported, but term “seizures” used	follow-up time after AD onset 3.93 ± 3.18	-	PSEN1 mutations before versus after codon 200
25	USA, Netherlands, Australia 1991, Breteler[33]	851, -, -	17, 2%	-	not reported, but term “epilepsy” used	seizures occurred over 1 year prior to AD onset	-	familial versus sporadic, sex, onset of epilepsy before AD (≤10 years versus 10 years)

AD denotes Alzheimer’s disease, AChEIs acetylcholinesterase inhibitors, AEDs antiepileptic drugs, APP amyloid β precursor protein gene, CAMCOG Cambridge cognitive examination, CDT clock drawing test, CSF cerebrospinal fluid, CT computed tomography, EEG electroencephalography, GDS geriatric depression scale, IQR Interquartile range, LBD Lewy Body dementia, MCI mild cognitive impairment, MMSE mini mental state examination, MRI magnetic resonance imaging, PSEN1 presenilin-1, RALVT Rey auditory learning verbal test, SD standard deviation, SE standard error, TMT trail-making test, UK United Kingdom, USA United States of America, VD vascular dementia.

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

Country/region year, last name of the first author[a]	Brazil 2015,[34, 35] Assis[R]	Ireland 2002,[36] Timmons[R]	Japan 2014,[37] Ishigaki[R]	Japan 2018,[38] Kawakami[R]	Sweden 1997,[39] Forsgren[R]	UK 2004,[40] Gaitatzis[R]	USA 1996,[41] Hesdorffer[R]	USA 2014,[42] Sherzai[R]
Recruiting sites[b]	a tertiary center[H]	Hospital Inpatient Enquiry system[H]	Department of Neurology, Showa University School of Medicine	The Anjo Kosei Hospital, a major community hospital serving a population of a million people of the West Mikawa Southern Medical Area, Aichi Prefecture[H]	The region of study was the catchment area of the Umeh health authorities, cases through official Swedish Population Register (SPAR-DAFA)[P]	UK General Practice Database[P]	Records linkage system of the Rochester Epidemiology Project[P]	The NIS is designed to approximate a stratified 20% sample of all non-federal, short-term, general, and specialty hospitals serving adults in the United States[H]
Recruiting period	Jan 2009 to Dec 2010	Jan 1995 to Dec 1998	Jan 2007 to Dec 2012	May 2002 to Nov 2015	Mar 1992 to Dec 1994	Jan 1995 to Dec 1998	1955 and 1984	1999 to 2008
Inclusion and exclusion criteria	epilepsy or seizures onset ≥ 60 years, excluded those with no information on age of seizure onset	new onset epilepsy, seizures or other similar codes identified, at the time of hospital discharge or death; excluded previous seizures, miscoded age or diagnosis, charts unavailable	admitted patients with epilepsy, excluding acute symptomatic seizure	adult onset epilepsy over 40 years old, of unknown etiology, no structural, genetic, infectious, metabolic, immune etiologies	adult residents of the study region with an initial diagnosis of epileptic seizures, excluded previously diagnosed seizures, living outside catchment area	alive and permanently registered at the practice for the last 6 months of each analysis year from 1995 to 1998, excluded children < 16 years old	Rochester residents, incident unprovoked seizure ≥ 55 years old, excluded seizures preceded by clinically detected vascular insults to the brain, CNS infection, TBI causing ≥ 30 minutes unconsciousness or post-traumatic amnesia, brain surgery, CNS tumor, mental retardation, or cerebral palsy	all discharges from hospitals Whites, African Americans and Hispanics, age ≥ 50 years old
Seizures diagnostic criteria	ILAE Classification and Terminology 1981	-	-	ILAE Classification and Terminology 2017	an epileptic seizure defined as a sudden and transitory event of motor, sensory, autonomic, or psychic nature assumed to be the result of transient excessive discharge of a excitable population of neurons in the brain	ICD-9, 345	ILAE Classification and Terminology 1981	ICD-9 epilepsy and convulsions 345.xx and 780.3x
AD diagnostic criteria	-	-	-	probable AD based on clinical criteria NIA-AA, NINCDS-ADRDA criteria prior to 2011	NINCDS-ADRDA criteria	diagnosis of dementia and AD based on entries by the GP, informed by specialists, investigations, and hospital admissions if available	previous normal and irreversibly declined intellectual and social function, predominant dementia symptoms, memory impairment, two of: disorientation, personality or behavior decline, dyscalculia, apraxia or agnosia, language problems, impairment in judgment or abstract thinking, for six months if without autopsy, plus insidious onset, slow progression and other dementia causes ruled out for clinical AD	discharge codes for AD

							diagnosis, abundant neurotic plaques and/or neurofibrillary tangles in cortical region other than hippocampus for pathologic AD diagnosis	
Sample size, number of males, age in years	111, 54, 75 ± 9.1 (number of males and age were for 120 participants, including 9 with acute symptomatic seizure)	68, 41, male 77 (range 66 to 88) female 79 (range 69 to 90)	153, -, ≥ 65 years old	145, 77, 62 ± 11.4	122, 64, ≥ 40 (160, 78, ≥ 17)	5834 (aged 16 to 64 years old n = 4659, aged ≥ 64 years old n = 1175), 2854, -	145, 62, -	725527, 341723, 68.20 ± 0.1
Number of participants with AD, prevalence	8, 7.2%	5, 7.4%	20, 13.1%	26, 17.9%	11, 6.9% among those ≥ 17, 9% among those ≥ 40	8, 0.2%, (aged 16 to 64 years old); 32, 2.7% (aged ≥ 64 years old); 40, 0.7% (overall)	17, 11.7%	50061, 6.9%
Etiology	-	cerebrovascular lesion (clinical or CT finding, n = 26), idiopathic (n = 23), medication related (n = 15) alcohol excess (n = 6), hyponatremia (n = 5), AD (n = 5), febrile (n = 2) and hypoglycemia (n = 1), one participant could have multiple etiologies	-	-	Remote symptomatic (n = 86), idiopathic (n = 36) among those ≥ 40 years old (n = 122)	-	-	-
Seizure type	45 generalized, 30 focal (7 with secondary generalization, 45 unclassified	35 generalized tonic-clonic, including one with an EEG focal discharge, 28 focal (1/3 aware, 2/3 secondary generalization), 5 absence seizures. 46% presented after a single seizure (mainly tonic-clonic), 29% after a second seizure, 13% after ≥ 4 seizures, mean of 5 seizures before AD diagnosis	-	-	108 focal, 25 generalized, 20 start unknown and 7 unclassifiable among those ≥ 17 (n = 160)	-	67 generalized, 78 focal onset, 6 focal onset and 11 generalized among those 17 participants with AD, 94 (64.8%) second unprovoked seizure occurred by December 31, 1984	-
MRI CT, EEG	-	CT performed in 94%, MRI in 2%, EEG (n = 29): focal discharge 6, generalized slowing 2	-	MRI and/or CT findings collected, EEG: normal, temporal, frontal, occipital or other focal spikes,	CT performed in 80%, MRI in 58%, EEG (awake and/or asleep) performed in 84%	-	-	-

				generalized spike, and other abnormal patterns, epileptiform discharges most often detected in the temporal area				
Duration between AD and seizures in years, mean (range)	-	AD developed after seizures	-	AD developed after seizures	AD and seizures: 6.7 (1.5 to 12)	-	AD and seizures: median 3.3 (0.4 to 9.3)	-
Cognitive tests	-	-	-	HDS-R < 20/30, MMSE < 23/30, CDR ≥ 1.0, Logical Memory (WMS-R), ADAS	-	-	-	-
Predictors tested (*significant in univariate analyses)	-	-	-	older age*, sex, 12-months seizure free, single AED, seizure type and years of education	-	-	-	-

[a]Recruitment: P prospective, R retrospective

[b]Case selection: H hospital-based, P population-based

AD denotes Alzheimer's disease, ADAS Alzheimer's disease assessment scale, AEDs antiepileptic drugs, CAMCOG Cambridge cognitive examination, CDR clinical dementia rating scale, CT computed tomography, ECT electroconvulsive therapy, EEG electroencephalography, GP general practitioner, HDS-R Hasegawa dementia scale revised version, ICD-9 international classification of diseases (ninth edition), ILAE international league against epilepsy, IQR interquartile range, MMSE mini mental state examination, MRI magnetic resonance imaging, NIA-AA national institute on aging-Alzheimer's association, NINCDS-ADRA national institute of neurological and communicative disorders and stroke and the Alzheimer's disease and related disorders association, TBI traumatic brain injury, WMS-R Wechsler memory scale-revised.

Supplementary Table S5a Quality assessment

Comments, last Name of the first author[a]	Taiwan 2015,[1] Cheng	UK 1991,[2] Burns	UK 2013,[3] Imfeld	UK 2015,[4] Cook
1.Was the study's target population a close representation of the national population with epileptic seizures or Alzheimer's Disease in relation to relevant variables, e.g. age, sex?	High Risk (diagnosed with Alzheimer's Disease, acetylcholinesterase inhibitors prescriptions ≥ 1, MMSE 10 to 26 or CDR 1 to 2)	Low Risk (satisfying national institute of neurological and communicative disorders and stroke and the Alzheimer's disease and related disorders association, Alzheimer's Disease criteria)	High Risk (≥65 years old, exclude <3 years of records prior to the Alzheimer's Disease or Vascular Dementia, alcoholism, drug abuse, multiple sclerosis, motor neuron disease, Down syndrome, epilepsy prior to Alzheimer's Disease diagnosis, or>3 anticonvulsant drugs prescriptions)	High Risk (exclude those with history of stroke, because this study also reported the stroke incidence. After stroke, symptomatic seizures risk increased, and this study may have underestimated seizure occurrence due to the exclusion of people with a history of stroke)
2.Was the sampling frame a true or close representation of the target population?	Low Risk (National Health Insurance Research Database(NHIRD), contained all original claims of 1 million beneficiaries randomly sampled from 25.68 million individuals in registry)	High Risk (two psychiatric hospitals)	Low Risk (United Kingdom based General Practice Research Database)	Low Risk (Health Improvement Network Database, - nationally representative)
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low Risk (a total of 981 diagnosed AD patients and 3835 propensity score-matching controls were identified from the 1000,000 randomly sampled cohort dataset of the Taiwan NHIRD)	High risk (all patients are part of a longitudinal study investigating the natural history of Alzheimer's Disease and correlating clinical and neuropathological findings, - unclear how the sample formed)	Low Risk (all potential cases)	Low Risk (all Alzheimer's Disease cases)
4.Was the likelihood of non-response bias minimal?	Low Risk (record review, database covers majority of population)	High Risk (unclear about the non-response bias)	Low Risk (consent not required)	Low Risk (>400 general practitioners in the United Kingdom, consent is not required for participants)

5.Were data collected directly from the subjects or their proxy?	High Risk (records database)	Low Risk (each patient examined personally by the first author at entry to the study)	Low Risk (medical database)	Low Risk (medical database)
6.Was an acceptable case definition used in the study?	Low Risk ("all data from primary outpatient departments and inpatient hospital care settings after 2000 are included in this database")	High Risk (Unclear how “seizures” were defined)	High Risk (Unclear how “seizures” were defined)	High Risk (Unclear diagnostic criteria for seizures)
7.Was the application of the study instrument that measured the parameter of interest (i.e. incidence and prevalence of epileptic seizures and AD) shown to have reliability and validity?	High Risk (only codes taken, cases not independently reviewed/centrally adjudicated)	High Risk (cases not independently reviewed/centrally adjudicated)	Low Risk (general practitioners who took data were all trained in collection of data for research purposes, medical record manually reviewed)	Low Risk (a positive predictive value of over 89%, diagnostic codes recorded by general practitioners were shown to be accurate for seizure (Gao et al. 2008))
8.Was same mode of data collection used?	Low Risk	Low Risk	Low Risk	Low Risk
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	High Risk (did not report person-years of follow-up, or confidence interval of the incidence rate)	Low Risk	Low Risk	Low Risk
Summary LOW RISK 0 to 3 items with "High Risk", MODERATE RISK 4 to 6 items with "High Risk", HIGH RISK 7 to 9 items with "High Risk"	MODERATE RISK	MODERATE RISK	LOW RISK	LOW RISK

[a]Refer to Supplementary Text S3 for references

Supplementary Table S5b Quality assessment

Comments, last Name of the first author[a]	USA 2006,[5] Amatniek	USA 2009,[6] Scarmeas	USA 2017,[7] Beagle	Finland 2011,[8] Bell
1.Was the study's target population a close representation of the national population with epileptic seizures or Alzheimer's Disease in relation to relevant variables, e.g. age, sex?	High Risk (exclude alcohol or drug dependency, central nervous system infection, evidence of cortical stroke, schizophrenia or schizoaffective disorder before intellectual decline, any electroconvulsive therapy in past 2 years or ≥ 10 electroconvulsive therapy sessions)	High Risk (exclude Parkinson disease, Parkinsonism, Schizophrenia or schizoaffective disorder prior to intellectual decline, evidence of stroke, alcohol abuse, electroconvulsive within 2 years of recruitment or ≥ 10 electroconvulsive sessions)	Low Risk (meet Alzheimer disease diagnostic criteria at most recent clinical evaluation)	High Risk (mild or moderate Alzheimer disease, experienced decreased social capacity over three months, had CT/MRI scan, confirmed diagnosis by neurologist or geriatrician)
2.Was the sampling frame a true or close representation of the target population?	High Risk (Neurology Department Columbia University, Psychiatry Department Johns Hopkins University, Geriatric Neurobehavioral Centre Massachusetts General Hospital)	High Risk (Columbia University, The Johns Hopkins University, Massachusetts General Hospital Harvard University)	High Risk (Memory and aging center)	Low Risk (the Special Reimbursement Register maintained by the Social Insurance Institution of Finland, population-based)
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low Risk (consecutively)	Low Risk (Individuals from 2 Predictors Study cohorts, "consecutive" mentioned there)	High Risk (Unclear how the sample generated)	Low Risk (contains records of all reimbursed drug purchases made by all 5.3 million Finnish residents in non-institutional settings)
4.Was the likelihood of non-response bias minimal?	High risk (unclear how many did not consent to study)	High Risk (unclear about the non-response bias)	High Risk (unclear about the non-response bias)	Low Risk (consent not required)
5.Were data collected directly from the subjects or their proxy?	Low Risk (medical records)	Low Risk (neurologic, other clinical, and mental status examinations conducted at study enrollment and at 6-month intervals thereafter)	Low Risk (medical records)	Low Risk (written documentary evidence must be provided to the SII by that person's physician, - physician can only make diagnosis based on history taken and examination)

6.Was an acceptable case definition used in the study?	Low Risk (asked if they had been diagnosed/treated for seizures or had a seizure; also reviewed original questionnaires and medical records and then had neurologists review information)	High Risk (unclear diagnostic criteria for seizures)	Low Risk (International League against Epilepsy criteria)	Low Risk (examined by neurologists or at neurology clinics, received relevant examinations (electroencephalography, computed tomography, magnetic resonance imaging scan, relevant laboratory tests), care plans)
7.Was the application of the study instrument that measured the parameter of interest (i.e. incidence and prevalence of epileptic seizures and AD) shown to have reliability and validity?	Low Risk (two neurologists independently evaluated the study charts and medical records from the date of the event, reaching consensus if the two opinions varied on seizure likelihood)	Low Risk (two epileptologists (H.C. and J.C.) independently reviewed the original questionnaires and all available medical records)	High Risk (no central adjudication for new-onset seizures)	Low Risk (the Special Reimbursement Register considered to have good validity in relation to diagnoses of epilepsy)
8.Was same mode of data collection used?	Low Risk	Low Risk	Low Risk	Low Risk
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low Risk	Low Risk	High Risk (did not report person-years of follow up)	High Risk (prevalence in % but did not actually give the numerator (n with epilepsy)
Summary LOW RISK 0 to 3 items with "High Risk", MODERATE RISK 4 to 6 items with "High Risk", HIGH RISK 7 to 9 items with "High Risk"	LOW RISK	MODERATE RISK	MODERATE RISK	LOW RISK

2 [a]Refer to Supplementary Text S3 for references

3

Supplementary Table S5c Quality assessment

Comments, last Name of the first author[a]	Finland 2018,[9] Rauramaa	Finland 2018,[10, 11] Taipale	France 2007,[12] Hommet	France 2016,[13] Zarea
1.Was the study's target population a close representation of the national population with epileptic seizures or Alzheimer's Disease in relation to relevant variables, e.g. age, sex?	High Risk (64 neuropathologically confirmed Alzheimer`s disease patients, - externally not all the Alzheimer disease patients are neuropathologically confirmed)	Low Risk (no inclusion and exclusion criteria on age and sex or cognitive performance. Although the German database only included those ≥ 65 years old, we did not use the German data due to data only available for dementia without detailed reports on Alzheimer`s disease)	High Risk (hospitalized patients ≥ 65 years old with clinical Alzheimer`s disease)	High Risk (only autosomal dominant early onset Alzheimer`s disease)
2.Was the sampling frame a true or close representation of the target population?	High Risk (Geriatric department of Harjula Hospital in Kuopio)	Low Risk (Finnish dataset (the Special Reimbursement Register) taken from nationwide Finnish registers covering all residents)	High Risk (Geriatric Internal Medicine Unit, University Hospital)	Low Risk (national multicentric study was performed on the French Autosomal Dominant Early Onset Alzheimer`s Disease cohort)
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	High risk (unclear how 64 Alzheimer disease patients were identified from a longitudinal follow-up study of patients with dementia of Alzheimer's type from the geriatric department of Harjula Hospital)	Low Risk (age-stratified 2.2 % random sample)	Low Risk (consecutively)	Low Risk (consecutively)
4.Was the likelihood of non-response bias minimal?	High Risk (unclear about the non-response bias)	Low Risk (consent not required)	High Risk (unclear about the non-response bias)	High Risk (unclear about the non-response bias)

5.Were data collected directly from the subjects or their proxy?	Low Risk (medical records)	High Risk (registry databases)	Low Risk (considered to have seizures only if convulsive activity had been clearly described by a physician or caregiver based on reliable history)	Low Risk (medical records)
6.Was an acceptable case definition used in the study?	Low Risk (International League Against Epilepsy criteria)	Low Risk (International Classification of Diseases-10)	Low Risk (hospitalization for generalized or focal to generalized tonic-clonic seizures)	Low Risk (International League against Epilepsy criteria)
7.Was the application of the study instrument that measured the parameter of interest (i.e. incidence and prevalence of epileptic seizures and AD) shown to have reliability and validity?	High Risk (no central adjudication of seizures)	High Risk ("seizures" not centrally adjudicated)	High Risk ("seizures" not centrally adjudicated)	Low Risk (A.Z. and D.W. reviewed each case to ascertain the presence and type of seizure)
8.Was same mode of data collection used?	Low Risk	Low Risk	Low Risk	High Risk (mixed prospective and retrospective)
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	High Risk (prevalence rate was not reported)	Low Risk	High Risk (prevalence rate was not reported)	High Risk (prevalence rate was not reported)
Summary LOW RISK 0 to 3 items with "High Risk", MODERATE RISK 4 to 6 items with "High Risk", HIGH RISK 7 to 9 items with "High Risk"	MODERATE RISK	LOW RISK	MODERATE RISK	MODERATE RISK

[a]Refer to Supplementary Text S3 for references

Supplementary Table S5d Quality assessment

Comments, last Name of the first author[a]	UK 1992,[14] Forstl	Italy 2010,[15] Bernardi	Italy 2016,[16] Giorgi	Italy 2017,[17] DiFrancesco
1.Was the study's target population a close representation of the national population with epileptic seizures or Alzheimer's Disease in relation to relevant variables, e.g. age, sex?	High Risk (autopsy verified Alzheimer`s disease)	Low Risk	High Risk (evaluated ≥ 3 times as outpatients, through ≥ 2 years)	Low Risk
2.Was the sampling frame a true or close representation of the target population?	High Risk (two psychiatric hospitals)	High Risk (University Hospital in Rome)	High Risk (electronic database, Dementia Centre, Neurology Clinic of the University of Pisa)	High Risk (unit for Alzheimer's disease Assessment of the San Gerardo Hospital, Monza University Hospital memory clinic)
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	High Risk (first 56 patients who came to postmortem examination from a larger longitudinal study - convenience sampling)	Low Risk ("all" patients referred to the cognitive function clinic, and 583 patients seen for the first time who underwent at least two clinical diagnostic assessments between January 2001 and December 2006)	High risk (sampling method unclear)	Low Risk (all the patients referred to the Unit)
4.Was the likelihood of non-response bias minimal?	High Risk (unclear about the non-response bias)	High Risk (unclear about the non-response bias)	High Risk (unclear about the non-response bias)	High Risk (unclear about the non-response bias)

5.Were data collected directly from the subjects or their proxy?	Low Risk (all patients undergone regular clinical examinations, last administered within 12 months before death, seizures witnessed by clinical staff or patients` primary caregivers)	Low Risk (medical records)	Low Risk (medical records)	Low Risk (medical records)
6.Was an acceptable case definition used in the study?	Low Risk (tonic-clonic seizures since the onset of dementia, generalized motor seizures)	Low Risk (International League against Epilepsy criteria)	High Risk (search for terms “epilepsy” or “seizures” in “diagnosis” field, and for antiepileptic drugs (e.g. carbamazepine) in “treatment” field)	Low Risk (≥ 1 unprovoked seizures, onset after 55 years old, before or after occurrence of cognitive symptoms)
7.Was the application of the study instrument that measured the parameter of interest (i.e. incidence and prevalence of epileptic seizures and AD) shown to have reliability and validity?	Low Risk (independent examinations)	Low Risk (epilepsy data collected by neurologists and reviewed by study physician)	High Risk (not centrally adjudicated)	Low Risk (clinical and instrumental data of patients with epilepsy were deeply reviewed)
8.Was same mode of data collection used?	Low Risk	Low Risk	Low Risk	Low Risk
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	High Risk (prevalence rate was not reported)	Low Risk	High Risk (prevalence rate was not reported)	High Risk (prevalence rate was not reported)
Summary LOW RISK 0 to 3 items with "High Risk", MODERATE RISK 4 to 6 items with "High Risk", HIGH RISK 7 to 9 items with "High Risk"	MODERATE RISK	LOW RISK	HIGH RISK	LOW RISK

[a]Refer to Supplementary Text S3 for references

9 **Supplementary Table S5e Quality assessment**

Comments, last Name of the first author[a]	Italy 2020,[18] Arnaldi	Netherlands 1996,[19] Samson	Portugal 2019,[20] Tábuas-Pereira	Sweden 2020,[21] Zelano
1.Was the study's target population a close representation of the national population with epileptic seizures or Alzheimer's Disease in relation to relevant variables, e.g. age, sex?	High Risk (exclude seizure onset ≥ 5 years prior to cognitive symptoms and a history of stroke and/or a diagnosis of vascular dementia)	High Risk (Alzheimer`s disease diagnosed before 70 years old)	High Risk (exclude history of traumatic brain injury and seizures)	Low Risk
2.Was the sampling frame a true or close representation of the target population?	High Risk (University Hospital memory clinic)	Low Risk (population-based)	High Risk (Dementia Outpatient Clinic of the Centro Hospitalar e Universitário de Coimbra)	Low Risk (a national quality registry of dementia in Sweden)
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low Risk (consecutive)	Low Risk (all patients with Alzheimer's disease living in two areas of the Netherlands in whom the disease was diagnosed before the age of 70)	High Risk (sampling methods unclear, these patients are part of a prospectively evaluated cohort at our center)	Low Risk (all)
4.Was the likelihood of non-response bias minimal?	High Risk (unclear about the non-response bias)	High Risk (unclear about the non-response bias)	High Risk (unclear about the non-response bias)	Low Risk (consent not required)
5.Were data collected directly from the subjects or their proxy?	Low Risk (medical records)	Low Risk (next of kin of the patient)	Low Risk (medical records)	Low Risk (Diagnostic codes, which "contains information on all diagnoses from inpatient hospital visits from 1987 and hospital-based outpatient visits since 2000)

6.Was an acceptable case definition used in the study?	Low Risk (presence of seizures under antiepileptic drugs treatment)	High Risk (unclear how seizures were diagnosed)	Low Risk (determined clinically, with the support of electroencephalography, when considered necessary by patients' physicians)	Low Risk (International League against Epilepsy criteria, International Classification of Diseases-10)
7.Was the application of the study instrument that measured the parameter of interest (i.e. incidence and prevalence of epileptic seizures and AD) shown to have reliability and validity?	High Risk (not centrally adjudicated)	High Risk (not centrally adjudicated)	Low Risk (the file consultation/examination of other supporting indications (e.g. EEG) suggests that the researchers evaluated this independently)	Low Risk (positive predictive value of an epilepsy diagnosis in national Patient Register is approximately 90%)
8.Was same mode of data collection used?	Low Risk	Low Risk	Low Risk	Low Risk
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low Risk	High Risk (the reported prevalence rate did not match calculation using numerator/denominator)	Low Risk	High Risk (prevalence rate was not reported)
Summary LOW RISK 0 to 3 items with "High Risk", MODERATE RISK 4 to 6 items with "High Risk", HIGH RISK 7 to 9 items with "High Risk"	MODERATE RISK	MODERATE RISK	MODERATE RISK	LOW RISK

[a]Refer to Supplementary Text S3 for references

12 **Supplementary Table S5f Quality assessment**

Comments, last Name of the first author[a]	UK 1992,[22] McAreavey	UK 2006,[23] Lozsadi	UK 2016,[24] Ryan	UK 2019,[25, 26] Baker
1.Was the study's target population a close representation of the national population with epileptic seizures or Alzheimer's Disease in relation to relevant variables, e.g. age, sex?	High Risk (aged >55 years)	Low Risk (no specific exclusion criteria)	High Risk (autosomal dominant Alzheimer`s disease)	Low Risk
2.Was the sampling frame a true or close representation of the target population?	High Risk (Dundee Psychiatric Inpatient Service, single site)	High Risk (a dedicated cognitive function clinic based at a regional neuroscience center, seen by one neurologist is not nationally representative)	Low Risk (Dementia Research Centre at University College London's Institute of Neurology)	High Risk (the Memory clinic in Exeter, Devon)
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low Risk (Dementia was diagnosed in 208 patients aged >55 years by the responsible consultant psychiatrist)	Low Risk (all)	Low Risk (all individuals with autosomal dominant Alzheimer's disease due to amyloid β precursor protein gene or presenilin-1 mutations seen at the Dementia Research Centre)	Low Risk (all)
4.Was the likelihood of non-response bias minimal?	Low Risk (consent not required)	Low Risk (retrospective file review of all cases, consent not required)	High risk (only 121/213 had clinical histories and neurological examination available)	High Risk (156 patients initially contacted but did not take part in the study)
5.Were data collected directly from the subjects or their proxy?	Low Risk (ward nursing and medical staff were also asked about the occurrence of epileptic attacks in their inpatient populations)	Low Risk (cases were seen in a dedicated cognitive function clinicbased at a regional neuroscience center)	Low Risk (noticed by someone who knew the patient well)	Low Risk (data collected from the participants in the presence of the same informant who was in attendance for the initial interview)

6.Was an acceptable case definition used in the study?	Low Risk (brief and usually unprovoked stereotyped disturbances of behavior, emotion, motor function, or sensation result from an abnormal cortical neuronal electrical discharge)	Low Risk (International League against Epilepsy criteria)	High Risk (seizure diagnostic criteria not clear)	Low Risk (≥ 2 stereotyped episodes suggestive of epilepsy witnessed by a reliable informant)
7.Was the application of the study instrument that measured the parameter of interest (i.e. incidence and prevalence of epileptic seizures and AD) shown to have reliability and validity?	Low Risk (seizures diagnosed by the doctor in charge of the ward and confirmed by the authors)	High Risk (no central adjudication of seizures)	High Risk (no central adjudication of seizures)	High Risk (no central adjudication of seizures)
8.Was same mode of data collection used?	Low Risk	Low Risk	Low Risk	Low Risk
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	High Risk (prevalence rate was not reported)	Low Risk	Low Risk	Low Risk
Summary LOW RISK 0 to 3 items with "High Risk", MODERATE RISK 4 to 6 items with "High Risk", HIGH RISK 7 to 9 items with "High Risk"	LOW RISK	LOW RISK	MODERATE RISK	LOW RISK

[a]Refer to Supplementary Text S3 for references

Supplementary Table S5g Quality assessment

Comments, last Name of the first author[a]	USA 1986,[27] Hauser	USA 1994,[28] Mendez	USA 2010,[29] Jayadev	USA 2013,[30] Vossel
1.Was the study's target population a close representation of the national population with epileptic seizures or Alzheimer's Disease in relation to relevant variables, e.g. age, sex?	High Risk (autopsy-proven Alzheimer's Disease and with medical records available)	High Risk (neuropathological criteria for Alzheimer's Disease, exclude cases with non-Alzheimer's Disease lesions)	High Risk (autosomal dominant Alzheimer's disease)	High Risk (exclude cortical strokes, cavernous hemangioma, meningioma, suspected brain tumor, subdural hematoma, history of alcohol abuse, amyloid angiopathy, enrollment in clinical treatment trials, and those with seizure onset during childhood or early adulthood)
2.Was the sampling frame a true or close representation of the target population?	Low Risk (2204 autopsies dying at 9 state hospitals done in Minnesota state hospitals, state nursing home with general autopsy, - mainly these are where autopsies could be conducted)	Low Risk (Ramsey Foundation Alzheimer's Treatment and Research Centre Brain Bank)	High Risk (Alzheimer's disease Research Centre)	High Risk (Memory and Aging Center at the University of California, San Francisco)
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low Risk (though selected from a larger autopsy-proven series of AD patients, no differences in course, severity, or family history were identified when these 83 cases were compared with the larger group)	High Risk (autopsies were requested by families for research participation and confirmation of the dementia diagnosis)	High Risk (101 affected persons in these 11 families from a total of 184 families)	Low Risk (searched the database for all patients who presented with cognitive decline and met National Institute of Neurological and Communicative Disorders and Stroke Alzheimer's Disease and Related Disorders Association criteria for probable Alzheimer's Disease)
4.Was the likelihood of non-response bias minimal?	High Risk (unclear about the non-response bias)	High Risk (unclear about the non-response bias)	High Risk (data available on 64/101 affected persons - from which seizure prevalence determined)	Low Risk (not required to re-consent for this analysis)

5.Were data collected directly from the subjects or their proxy?	Low Risk (Patients were considered to have seizures or myoclonus only if convulsive activity was clearly described in physicians' or nurses' notes)	Low Risk (seizure history obtained from the accompanying physician and nursing home records, and from a detailed medical history questionnaire administered to family members)	Low Risk (medical records)	Low Risk (medical records)
6.Was an acceptable case definition used in the study?	High Risk (unclear the diagnostic criteria for seizure)	Low Risk (International League against Epilepsy criteria)	High Risk (unclear the diagnostic criteria for seizures)	Low Risk (International League against Epilepsy criteria)
7.Was the application of the study instrument that measured the parameter of interest (i.e. incidence and prevalence of epileptic seizures and AD) shown to have reliability and validity?	High Risk (no central adjudication of seizures)	Low Risk (seizure history obtained from the accompanying physician and nursing home records, and from a detailed medical history questionnaire administered to family members, medical records reviewed for the accuracy of their seizure diagnoses and to exclude acute, symptomatic causes for seizures)	High Risk (no central adjudication of seizures)	Low Risk (diagnosis made by a multidisciplinary team consisting of behavioral neurologists, epileptologists, neuropsychologists, and psychiatrists, who performed extensive behavioral, neuropsychological, neurophysiological, and neuroimaging assessments)
8.Was same mode of data collection used?	Low Risk	Low Risk	Low Risk	Low Risk
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	High Risk (prevalence rate was not reported)	Low Risk	Low Risk	Low Risk
Summary LOW RISK 0 to 3 items with "High Risk", MODERATE RISK 4 to 6 items with "High Risk", HIGH RISK 7 to 9 items with "High Risk"	MODERATE RISK	LOW RISK	MODERATE RISK	LOW RISK

[a]Refer to Supplementary Text S3 for references

Supplementary Table S5h Quality assessment

Comments, last Name of the first author[a]	USA 2017,[31] Birnbaum	USA, Europe, and Australia, 2016,[32] Tang	USA, Netherlands, Australia 1991,[33] Breteler	Brazil 2015,[34, 35] Assis
1.Was the study's target population a close representation of the national population with epileptic seizures or Alzheimer's Disease in relation to relevant variables, e.g. age, sex?	High Risk (nursing home residents)	High Risk (autosomal dominant Alzheimer's disease)	High Risk (exclude epilepsy over one year prior to onset of Alzheimer's Disease, exclude studies without specified age of epilepsy onset)	High Risk (epilepsy or seizures onset ≥ 60 years, excluded those with no information on age of seizure onset)
2.Was the sampling frame a true or close representation of the target population?	Low Risk (any Medicare/Medicaid certified nursing home, and 98% of NHs in the United States have Medicare/Medicaid certification)	Low Risk (Study centers in the USA, Europe, and Australia)	High Risk (consecutive new referrals to dementia clinics in Sydney conducted at the Repatriation General Hospital Concord (RGHC) and Lidcombe Hospital, Australia, Geriatric Research, Education, and Clinical Center at the Edith N. Rogers Memorial Veterans Hospital in Bedford, MA, USA)	High Risk (a tertiary center)
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low Risk (all)	Low Risk	Low Risk (all)	Low Risk (consecutively)
4.Was the likelihood of non-response bias minimal?	Low Risk (consent not required)	Low Risk (retrospective, so all identified "cases" were included)	High Risk (unclear about the non-response bias)	Low Risk (all 120 patients meeting inclusion criteria were included in the study)
5.Were data collected directly from the subjects or their proxy?	Low Risk (medical records)	Low Risk (interview)	High Risk (unclear)	Low risk (hospitalized patients - medical records and telephone calls)

6.Was an acceptable case definition used in the study?	Low Risk (Minimum Data Set 2.0 item I.1.aa (seizure disorder) or International Classification of Diseases-9 code 345.xx or 780.39 in item I.3)	Low Risk (the National Alzheimer's Coordinating Center's Uniform Data Set, A5)	High Risk (unclear the diagnostic criteria for seizure)	High Risk (unclear the diagnostic criteria for Alzheimer's Disease)
7.Was the application of the study instrument that measured the parameter of interest (i.e. incidence and prevalence of epileptic seizures and AD) shown to have reliability and validity?	High Risk (case not adjudicated)	High Risk (not centrally adjudicated)	High Risk (case not adjudicated)	High Risk (case not adjudicated)
8.Was same mode of data collection used?	Low Risk	Low Risk	High Risk (four samples)	Low Risk
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low Risk	Low Risk	High Risk (prevalence rate was not reported)	High Risk (number of cases and prevalence rate were not reported)
Summary LOW RISK 0 to 3 items with "High Risk", MODERATE RISK 4 to 6 items with "High Risk", HIGH RISK 7 to 9 items with "High Risk"	LOW RISK	LOW RISK	HIGH RISK	MODERATE RISK

17 [a]Refer to Supplementary Text S3 for references

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19 **Supplementary Table S5i Quality assessment**

Comments, last Name of the first author[a]	Ireland 2002,[36] Timmons	Japan 2014,[37] Ishigaki	Japan 2018,[38] Kawakami	Sweden 1997,[39] Forsgren
1.Was the study's target population a close representation of the national population with epileptic seizures or Alzheimer's Disease in relation to relevant variables, e.g. age, sex?	High Risk (new onset epilepsy, seizures or other similar codes identified, at the time of hospital discharge or death, exclude previous seizures, miscoded age or diagnosis, charts unavailable)	High risk, as discussed by the authors "children with epilepsy might admit the pediatrics in Showa University School of Medicine and might not enrolled in this study"	High Risk (adult onset epilepsy over 40 years old, of unknown etiology, no structural, genetic, infectious, metabolic, immune etiologies)	High Risk (exclude previously diagnosed seizures)
2.Was the sampling frame a true or close representation of the target population?	High Risk (Hospital Inpatient Enquiry system at a tertiary referral center)	High risk (single center hospital-based)	High Risk (The Anjo Kosei Hospital, a major community hospital serving a population of a million people of the West Mikawa Southern Medical Area, Aichi Prefecture)	Low Risk (region of study: catchment area of the Umeh health authorities, cases through official Swedish Population Register)
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low Risk	Low Risk ("consecutive")	Low Risk (all)	Low Risk (all)
4.Was the likelihood of non-response bias minimal?	Low Risk (consent not required)	Low Risk (consent not required)	Low Risk (retrospective, so all identified cases/eligible participants included)	Low Risk (consent not required, interviewed only if medical records insufficient)
5.Were data collected directly from the subjects or their proxy?	Low Risk (a telephone call to their General Practitioner or, if they were resident in a Nursing Home, the matron of the Nursing Home)	Low Risk (medical records)	Low Risk (electronic medical records)	Low Risk (medical records)

6.Was an acceptable case definition used in the study?	High Risk (unclear the diagnostic criteria for Alzheimer's Disease)	High risk (no related information reported)	Low Risk (probable Alzheimer's Disease based on national institute on aging-Alzheimer's association, national institute of neurological and communicative disorders and stroke and the Alzheimer's disease and related disorders association criteria prior to 2011)	Low Risk (national institute of neurological and communicative disorders and stroke and the Alzheimer's disease and related disorders association criteria)
7.Was the application of the study instrument that measured the parameter of interest (i.e. incidence and prevalence of epileptic seizures and AD) shown to have reliability and validity?	High Risk (case not adjudicated)	High risk (not adjudicated)	Low Risk (patients underwent magnetic resonance imaging and/or single-photon emission computed tomography and/or 123-metaiodobenzylguanidine scintigraphy if necessary)	High Risk (case not adjudicated)
8.Was same mode of data collection used?	Low Risk	Low risk	Low Risk	Low Risk
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low Risk	High risk (number of cases and appropriate prevalence rate were not reported)	High Risk (prevalence rate was not reported)	High Risk (prevalence rate was not reported)
Summary LOW RISK 0 to 3 items with "High Risk", MODERATE RISK 4 to 6 items with "High Risk", HIGH RISK 7 to 9 items with "High Risk"	MODERATE RISK	MODERATE RISK	LOW RISK	LOW RISK

[a]Refer to Supplementary Text S3 for references

Supplementary Table S5j Quality assessment

Comments, last Name of the first author[a]	UK 2004,[40] Gaitatzis	USA 1996,[41] Hesdorffer	USA 2014,[42] Sherzai	Number of studies with "High Risk" (n)
1.Was the study's target population a close representation of the national population with epileptic seizures or Alzheimer's Disease in relation to relevant variables, e.g. age, sex?	High Risk (permanently registered at the practice for the last 6 months of each analysis year from 1995 to 1998)	High Risk (include unprovoked seizure ≥ 55 years old, exclude seizures preceded by clinically detected vascular insults to the brain, central nervous system infection, traumatic brain injury causing ≥ 30 minutes unconsciousness or post-traumatic amnesia, brain surgery, central nervous system tumor, mental retardation, or cerebral palsy)	High Risk (Whites, African Americans and Hispanics, age ≥ 50 years old)	31
2.Was the sampling frame a true or close representation of the target population?	Low Risk (UK General Practice Database)	Low Risk (Records linkage system of the Rochester Epidemiology Project)	Low Risk (a stratified 20% sample of all non-federal, short-term, general, and specialty hospitals serving adults in the United States)	22
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low Risk (all)	Low Risk (all)	Low Risk (sampling strategy: selects hospitals nationwide from the State Inpatient Database according to defined strata based on ownership, bed size, teaching status, urban or rural location, and region)	8
4.Was the likelihood of non-response bias minimal?	Low Risk (consent not required)	Low Risk (consent not required)	Low Risk (consent not required)	20
5.Were data collected directly from the subjects or their proxy?	Low Risk (diagnosis of dementia and AD based on entries by the General Practitioner, informed by specialists, investigations, and hospital admissions if available)	Low Risk (medical records)	Low Risk (medical records)	3

6.Was an acceptable case definition used in the study?	Low Risk (International Classification of Diseases-9)	Low Risk (previous normal and irreversibly declined intellectual and social function, predominant dementia symptoms, memory impairment, two of: disorientation, personality or behavior decline, dyscalculia, apraxia or agnosia, language problems, impairment in judgment or abstract thinking, for six months if without autopsy, plus insidious onset, slow progression and other dementia causes ruled out for clinical AD diagnosis, abundant neurotic plaques and/or neurofibrillary tangles in cortical region other than hippocampus for pathologic Alzheimer's Disease diagnosis)	Low Risk (discharge codes for Alzheimer's Disease)	13
7.Was the application of the study instrument that measured the parameter of interest (i.e. incidence and prevalence of epileptic seizures and AD) shown to have reliability and validity?	High Risk (case not adjudicated)	Low Risk (all subjects with suspected dementia reviewed by a neurologist (E.K.))	Low Risk (validated in previous publications)	22
8.Was same mode of data collection used?	Low Risk	Low Risk	Low Risk	2
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	High Risk (prevalence rate was not reported)	High Risk (prevalence rate was not reported)	High Risk (number of cases was not reported)	21
Summary LOW RISK 0 to 3 items with "High Risk", MODERATE RISK 4 to 6 items with "High Risk", HIGH RISK 7 to 9 items with "High Risk"	LOW RISK	LOW RISK	LOW RISK	

23 [a]Refer to Supplementary Text S3 for references