Epilepsy & Behavior 153 (2024) 109723

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Bidirectional relationship between late-onset epilepsy (LOE) and dementia: A systematic review and meta-analysis of cohort studies

Zheng Tan [a,b], Fu-Yu Wang [c], Wen-Pei Wu [a,b], Liu-Zhen-Xiong Yu [a,b], Jun-Cang Wu [a,*], Long Wang [a,*]

[a] Department of Neurology, Hefei Hospital Affiliated to Anhui Medical University (The Second People's Hospital of Hefei), Hefei, Anhui 230011, China
[b] The Fifth Clinical Medical College of Anhui Medical University, Hefei, Anhui 230032, China
[c] Department of Pharmacy, The Second People's Hospital of Hefei, Hefei, Anhui 230011, China

ARTICLE INFO

Keywords:
Late-onset epilepsy (LOE)
Dementia
AD
Risk
Association

ABSTRACT

Objective: To explore the bidirectional relationship of late-onset epilepsy (LOE) with dementia and Alzheimer's disease (AD).

Methods: Using the common electronic databases, including PubMed, Cochrane Library databases and EMBASE, we systematically reviewed published cohort studies that assessed the risk of LOE in individuals comorbid with dementia or AD, and those with dementia or AD comorbid with LOE that had been published up to 31 March 2023. The data extraction process was carried out independently by two authors. The summary adjusted relative ratio (aRR) was calculated by employing Rev Man 5.3 for the inclusion of studies. To investigate the origins of heterogeneity, we conducted both subgroup and sensitivity analyses. In the presence of heterogeneity, a random-effects model was employed. To evaluate potential publication bias, we utilized the funnel plot and conducted Begg's and Egger's tests.

Results: We included 20 eligible studies in the final analysis after a rigorous screening process. Pooled results indicated that LOE was association with an increased risk of all-cause dementia (aRR: 1.34, 95% confidence interval [CI]: 1.13–1.59) and AD (aRR: 2.49, 95% CI: 1.16–5.32). In addition, the pooled effect size for LOE associated with baseline AD and all-cause dementia were 3.51 (95% CI: 3.47–3.56) and 2.53 (95% CI: 2.39–2.67), respectively. Both sensitivity and subgroup analyses showed that these positive correlations persisted. According to the results of the Egger's and Begg's tests, as well as visual inspection of funnel plots, none of the studies appeared to be biased by publication.

Conclusion: The findings suggested that LOE is a potential risk factor for dementia and AD, and vice versa, dementia and AD are both potential risk indicators for LOE. Since there is substantial heterogeneity among the cohorts analyzed and more cohort studies should be conducted to confirm the correlations found in the current study.

1. Introduction

Late-onset epilepsy (LOE), or epilepsy that begins in the middle-aged and elderly stages, now accounts for about half of all new cases of epilepsy, and along with dementia, is a growing threat to public health. Globally, there are approximately 1 in 1000 elderly person-years who live with LOE [1] and 50 million with dementia; numbers that are projected to triple in 2050 [2]. With the progressive aging of the global population, the number of patients with these two conditions is constantly growing, resulting in a serious burden on the social economy and family life [3,4]. Numerous studies have shown that LOE is highly comorbid with dementia, and particularly AD [5,6]. However, due to the lack of neuropathological features and biomarkers at dementia onset, there is only a causal association between LOE and dementia [7]. Interestingly, despite limited epidemiological data, it is suggested that dementia may explain 10 % of LOE cases [8]. Additionally, a proportion of LOE classified as cryptogenic has been relatively ignored, as has the correlation with dementia due to differences in research designs and

* Corresponding authors at: Department of Neurology, Hefei Hospital Affiliated to Anhui Medical University (The Second People's Hospital of Hefei), Hefei, Anhui 230011, China.
E-mail addresses: wujuncang126@126.com (J.-C. Wu), guxindao606@163.com (L. Wang).

https://doi.org/10.1016/j.yebeh.2024.109723
Received 29 November 2023; Received in revised form 23 February 2024; Accepted 25 February 2024
Available online 14 March 2024

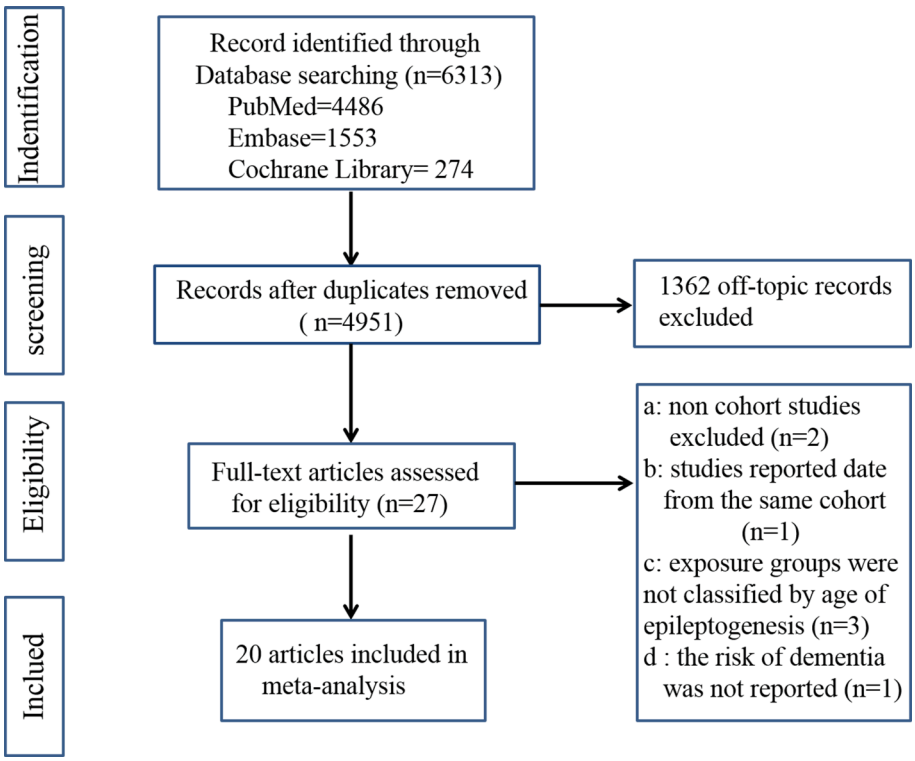


Fig. 1. Flow diagram of the study selection process.

methodologies of studies [9].

Recent in vivo studies have shown that cumulative amyloid-β (Aβ) deposition induced by chronic inflammation and neural network abnormalities have uncovered key pathophysiologic mechanisms underlying the bidirectional progression of LOE and dementia, especially AD [10,11]. Aβ has been demonstrated to accelerate neural network reintegration, resulting in hypersynchronization and seizures that in turn worsen neurodegeneration [12]. Epileptic discharge may occur in the early stages of AD [9], when Aβ-like pathological changes are in their initial stages and neurodegenerative manifestations have yet to be observed. Therefore, LOE itself may be a precursor to AD. Adults with unexplained epilepsy are more likely to develop dementia than the general population, and increased clinical epileptic activity is considered a marker of AD progression [13,14]. Meanwhile, the progression of AD is accompanied by an increase in seizure morbidity [15]. Moreover, a large body of cohort studies have shed new light on the bidirectional relationship between LOE and dementia, but the results are somewhat inconsistent [16–18]. Here, we explored the relationship between LOE and dementia to understand the strength of the risk between the two diseases. Consequently, we conducted a comprehensive and current cohort-based meta-analysis to quantitatively assess the bidirectional relationship between LOE with dementia and AD.

2. Methods

PRISMA guidelines were followed for conducting the systematic reviews and meta-analyses in accordance with preferred reporting items [19].

2.1. Search strategy

The EMBASE, PubMed, and Cochrane Library databases were extensively searched by two independent investigators (F-YW and Zheng Tan) from inception until March 31, 2023. A search was conducted using the MESH terms (“Late onset epilepsy” OR “Late onset epileptic” OR “Late onset epileptic seizures” OR “Late onset seizure” OR “Seizure” OR “Epilepsy”) AND (“Dementia” OR “Vascular Dementia” OR “AD” OR “Multi-Infarct Dementia” OR “Mixed Dementia” OR “Cognitive decline”).

2.2. Study selection

To determine the eligibility of articles for inclusion, we applied the following criteria: (1) selection of prospective and retrospective cohort studies; (2) inclusion of both the exposure group and control group (with dementia as the endpoint event; the exposure group and control groups were composed of LOE patients and non-LOE individuals matched in age and gender, respectively. Conversely, when LOE was considered as the endpoint event, the exposure and control groups were composed of dementia patients non-dementia individuals matched in gender and age, respectively); (3) age threshold for LOE at age 40 or older, without prior history of seizures earlier in life; (4) reporting of risk estimates, particularly the adjusted rate ratio (aRR), along with the 95 % confidence interval (CI), as the outcome measure; (5) inclusion of studies without any restrictions based on language of publication. In addition, we excluded reviews, case-control or cross-sectional studies, and studies with insufficient data.

2.3. Data extraction and quality assessment

Two authors (ZT and F-YW) extracted the following information independently: the first author’s name, publication year, geographical location, study design, number of participants, mean ages, diagnostic criteria for dementia and LOE, follow-up duration, adjustment, and study quality. Study quality was assessed using the Newcastle-Ottawa Scale (NOS) [20]. Reevaluation of divergent data was conducted in close consultation with a third author (W-PW) until a consensus was achieved. In the context of both case-control and cohort studies, the scoring spectrum spanned from 0 to 9. Studies that obtained scores below 3 were categorized as low quality, those within the range of 4 to 6 were considered moderate quality, and those with scores at or above 7 were classified as high quality.

Table 1
Characteristics of included cohort studies in this meta-analysis.

First authors, year	Country	Study design	Sample size	Age (years)	Follow-up duration (years)	Diagnostic method for LOE	Diagnostic method for dementia/AD	Outcome	Confounders adjusted	Study quality
LOE predicts all-cause dementia risk										
Cordonnier C, 2007	France	Prospective cohort study	169	73 average	3	ILAE	IQCODE	3.81 (1.13, 12.82)	Medical history, Stroke aetiology, location of the lesions, occurrence of seizures,	7
Carter MD, 2007	Canada	Prospective cohort study	5376	≥ 65	5	Clinical examination or SARF	3MS, MMS	1.56 (0.61, 3.96)	Age, sex, and baseline 3MS score	7
Kawakami O, 2018	Japan	Retrospective cohort study	481	62 average	7.3	Clinical information, scalp-recorded EEG, and MRI or CT	Clinical examination	4.08 (2.61, 6.38)	None	7
Johnson EL, 2020	USA	Prospective cohort study	8033	75 average	9	ICD-9/10	Neurocognitive assessment, interviews	2.11 (1.78, 2.50)	Age, sex, field center, race, education level, APOE ε4 allele status, hypertension, diabetes, smoking history, BMI, alcohol use, and stroke	9
Keret O, 2020	USA	Retrospective cohort study	292,262	73 average	6.1	ICD-9	ICD-9	1.89 (1.62, 2.20)	Age, sex, race, socioeconomic status, diabetes, hypertension, myocardial infarction, congestive heart failure, TBI, depression, and traumatic brain injury.	. 8
Tsai ZR, 2021	China	Retrospective cohort study	2700	≥ 50	13	ICD-9	ICD-9	2.87 (2.07, 3.99)	Age, sex, head injury, coronary artery disease, cancer, chronic obstructive pulmonary disease, hypertension, cerebrovascular disease, depression, liver disease, malnutrition, and autoimmune disease	8
LOE predicts AD risk										
Carter MD, 2007	Canada	Prospective cohort study	5376	≥ 65	5	3MS, MMS	Clinical examination or SARF	2.50 (0.60, 10.43)	Age, sex, and baseline 3MS score	7
Kawakami O, 2018	Japan	Retrospective cohort study	481	62 average	7.3	Clinical information, scalp-recorded EEG, and MRI or CT	DSM-IV	3.93 (2.51, 6.15)	NA	6
All-cause dementia predicts LOE risk										
Cordonnier C, 2005	France	Prospective cohort study	202	75 average	1.4	IQCODE	ILAE	4.66 (1.34, 16.21)	Age, sex, stroke, alcohol abuse, and neuroimaging	7
Hussain SA, 2006	USA	Prospective cohort study	1919	≥ 45	34.8	BIMC test	Self-report, medical records, EAS chart records, and telephone interview	1.96 (0.70, 5.48)	None	5
Pugh MJ, 2009	USA	Retrospective cohort study	1,025,219	≥ 65	1	ICD-9 and medical records	ICD-9 and new AED treatment	2.31 (1.91, 2.79)	Age, gender, race, stroke, hypertension, diabetes, alcohol	7

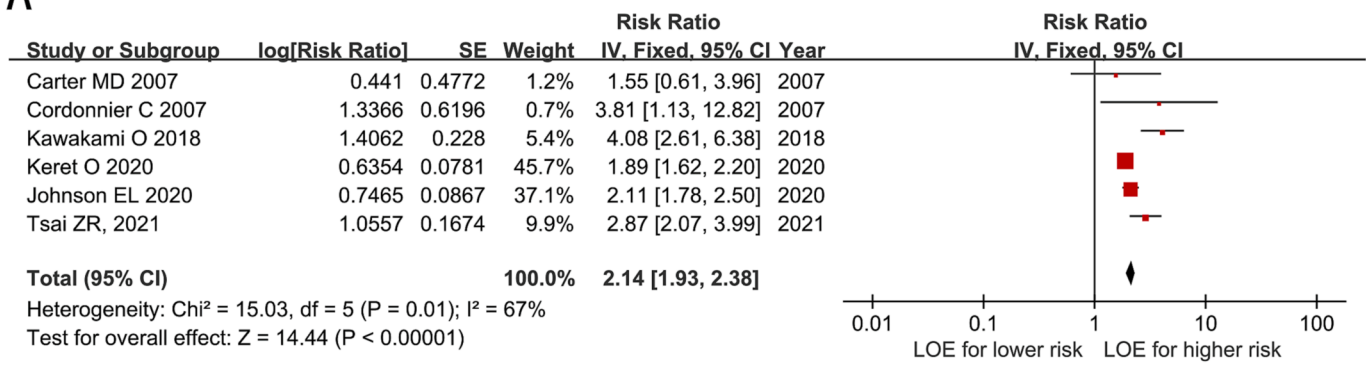
(*continued on next page*)

Table 1 (*continued*)

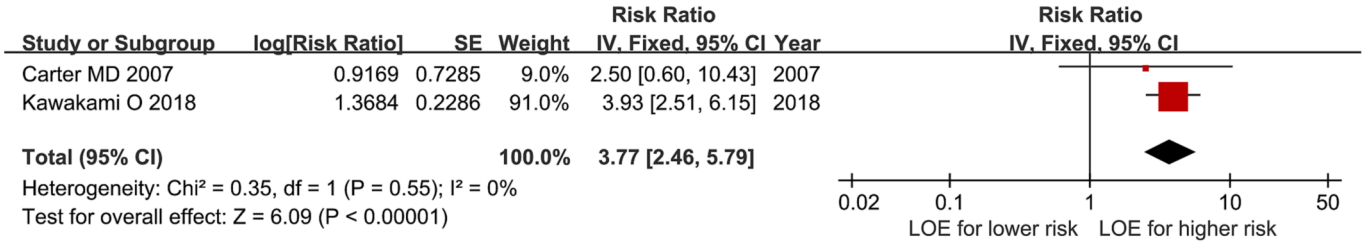
First authors, year	Country	Study design	Sample size	Age (years)	Follow-up duration (years)	Diagnostic method for LOE	Diagnostic method for dementia/AD	Outcome	Confounders adjusted	Study quality
									use, and several other diseases	
Martin RC, 2014	USA	Retrospective cohort study	1,195,188	≥ 65	5	ICD-9	ICD-9	2.42 (2.20, 2.66)	Age, sex, race, cerebrovascular disease, brain tumor, metastatic cancer, and traumatic brain injury	7
Johnson EL, 2018	USA	Prospective cohort study	15,792	55 average	25	Neurocognitive assessments	ICD-9	2.68 (2.19, 3.28)	Age, sex, stroke, APOE ε4 allele status, diabetes, hypertension, smoking status, education, exercise, alcohol use, and race	9
Zelano J, 2020	Sweden	Prospective cohort study	305,125	81 average	10	ICD-10	ICD-9/10	2.52 (2.31, 2.74)	Age, sex, stroke, head trauma, and brain tumor	8
Habeych ME, 2021	USA	Prospective cohort study	2,885,336	≥ 60	9	ICD-9	ICD-9	5.00 (4.80, 5.20)	Age, comorbid medical diagnostic categories, and the use of medications	8
AD predicts LOE risk										
Irizarry MC, 2012	Netherland	Retrospective cohort study	3078	≥ 75	15	MMSE	Medical records	2.79 (1.06, 7.33)	BMI, stroke/TIA, head injury, and current use of antidepressants or antipsychotics	5
Sherzai D, 2014	USA	Prospective cohort study	144,128,127	≥ 55	9	medical records	ICD-9, ICD-9-CM	4.00 (3.89, 4.10)	Age, gender, hispanic race	. 7
Cook M, 2015	UK	Retrospective cohort study	22,084	≥ 50	19	Medical records and validation with CPRD database	Medical records and validation with questionnaires	5.31 (3.97, 7.10)	Age, sex, BMI, smoking status, co-morbidities (asthma, brain tumor, brain injury, chronic obstructive pulmonary disease, depression, kidney failure, meningitis, antidepressants), and year of cohort entry	8
Chen CH, 2015	China	Retrospective cohort study	4816	75 average	10	DSM-IV or NINCDS-ADRDA criteria, MMSE score or CDR score, and CT or MRI	ICD-9	1.80 (1.20, 2.28)	Age, sex, diabetes, hypertension, coronary artery disease, heart failure, atrial fibrillation, dyslipidemia, cirrhosis, autoimmune disease, chronic kidney disease, malignancies, meningitis, and encephalitis	8
Lyou HJ, 2018	South Korea	Prospective cohort study	24,229	10	10		ICD-10 or AED use		None	7
Vöglein J, 2020	Germany	Prospective cohort study	20,745	≥ 70	11		Medical records and interview		None	7
				75 average		ICD-10 NINCDS/ ADRDA		2.77 (2.52, 3.06) 4.34 (3.01, 6.27)		
Blank LJ, 2021	USA	Retrospective cohort study	2,710,937	≥ 65	5	ICD-9	ICD-9	2.46 (2.39, 2.52)	Age, sex, race, and comorbid condition	. 9

Abbreviations: LOE, late-onset epilepsy; AD, Alzheimer's disease; AED, antiepileptic drug; BMI, body mass index; CDR, Clinical Dementia Rating; CPRD, Clinical Practice Research Datalink; CT, Computed Tomography; APOE, apolipoprotein E; BIMC, Blessed information-memory concentration; 3MS, Modified Mini-Mental State Examination; SARF, Self-Assessed Risk Factor; EEG, electroencephalogram; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ICD-9, International Classification of Disease, 9th Revision; ICD-10, International Classification of Disease, 10th Revision; MMSE, Mini-Mental Status Examination; MRI, magnetic resonance imaging; NINDS-ADRDA, National Institute of Neurological and Communicative Disease and Stroke-Alzheimer's Disease and Related Disorders Association; TIA, transient ischemic attack.

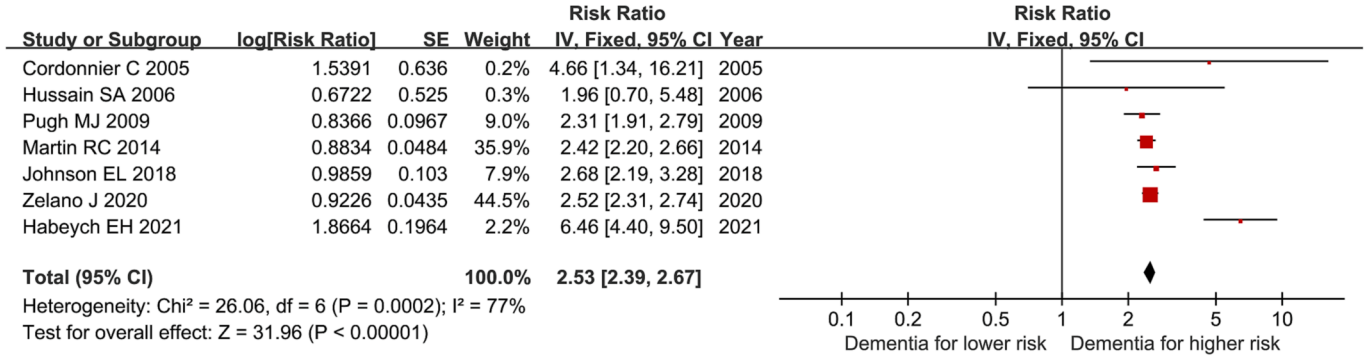
A



B



C



D

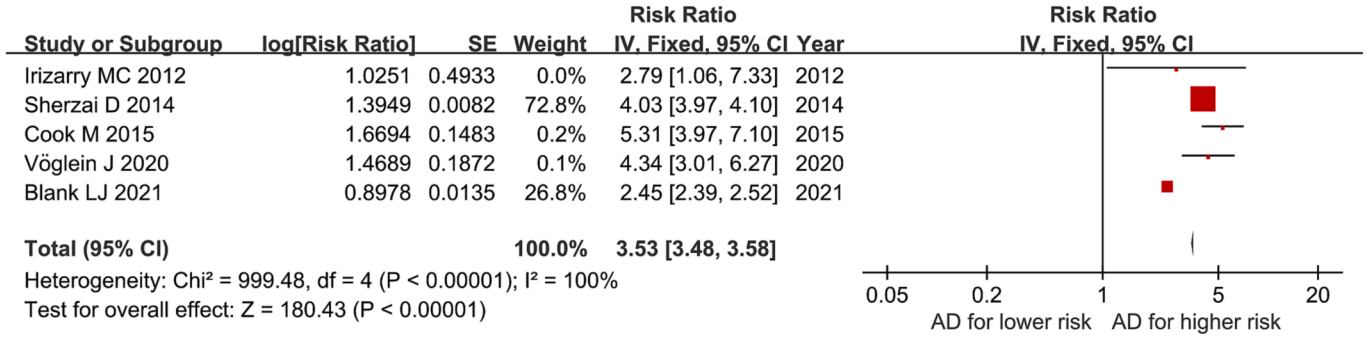


Fig. 2. Forest plot of the bidirectional relationship between LOE and dementia. (A) LOE and risk of all-cause dementia; (B) LOE and risk of AD; (C) All-cause dementia and risk of LOE; (D) AD and risk of LOE.

Table 2
Subgroup analysis for the risk ratio of all-cause dementia in LOE patients.

Subgroups	Included studies	RR(95 % CI)	Heterogeneity (I^2, Tau^2 and *P*-value)			P for subgroup difference
			I^2(%)	Tau^2	*P*-value	
Study design						0.76
prospective study	3	2.11 (1.79 ~ 2.49)	0	1.32	0.52	
retrospective study	3	4.05 (2.66 ~ 6.16)	85.0	13.67	0.01	
Follow-up						0.54
≥ 7	3	2.39 (2.07 ~ 2.76)	77.0	8.79	0.10	
< 7	3	1.84 (1.00 ~ 3.39)	0	1.44	0.51	
Regional distribution						0.21
Europe	4	1.99 (1.78 ~ 2.22)	0	2.27	0.52	
Asia	2	1.33 (1.22 ~ 1.46)	35.0	1.54	0.22	
Confounders adjusted						0.25
Yes	5	2.07 (1.86 ~ 2.30)	39.0	6.61	0.16	
No		-	-	-	-	

2.4. Data synthesis and analysis

Data analysis was carried out utilizing RevMan 5.3 and Stata 15.0 software. Using the aRR and the corresponding 95 % CI from each study, we assessed the bidirectional correlation between LOE and dementia. The Cochrane Q-statistic and the I^2-statistic were used meticulously to evaluate heterogeneity within the aRR across articles. Herein, I^2 values below 50 %, in the range of 50 % to 75 %, and exceeding 75 % signified low, medium, and high levels of homogeneity, respectively [21].

To investigate potential sources of heterogeneity, we performed subgroup and sensitivity analyses. Furthermore, to gauge the presence of publication bias, Egger's and Begg's tests were systematically performed. In our analyses, statistical significance was defined as a two-tailed P-value of less than 0.05.

3. Results

3.1. Identification of studies

As depicted in Fig. 1, our database search yielded a total of 6313 articles. After eliminating duplicates, the initial pool of articles was reduced to 4951. Subsequently, a further filtering process was conducted based on titles and abstracts, resulting in 27 articles being deemed eligible for full-text review. After a thorough assessment, seven articles were excluded, leaving a total of 20 research articles included in the final meta-analysis [22–41].

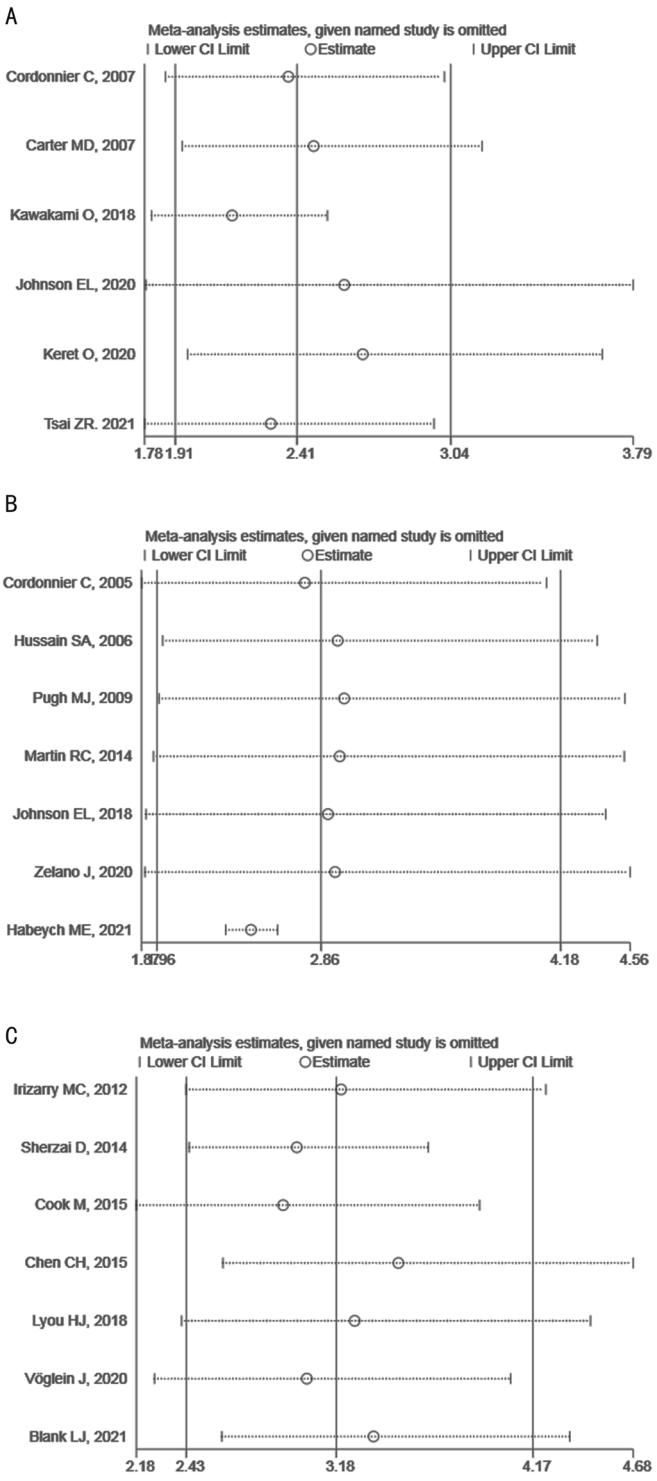


Fig. 3. Sensitivity analysis graph for excluding one study each time. (A) Studies in which LOE predicting the risk of all-cause dementia. (B) Studies in which all-cause dementia predicting the risk of LOE. (C) Studies in which AD predicting the risk of LOE.

3.2. Study characteristics

The details of the included studies are presented in Table 1. Among the studies, six were conducted in Europe [22,28,31,34,38,39], ten in North America [23,25,26,29,30,32,33,36,40,41], and four in Asia [24,27,35,37]. Six studies predicted the impact of LOE on dementia or AD [22–27], and 14 studies predicted the impact of dementia or AD on

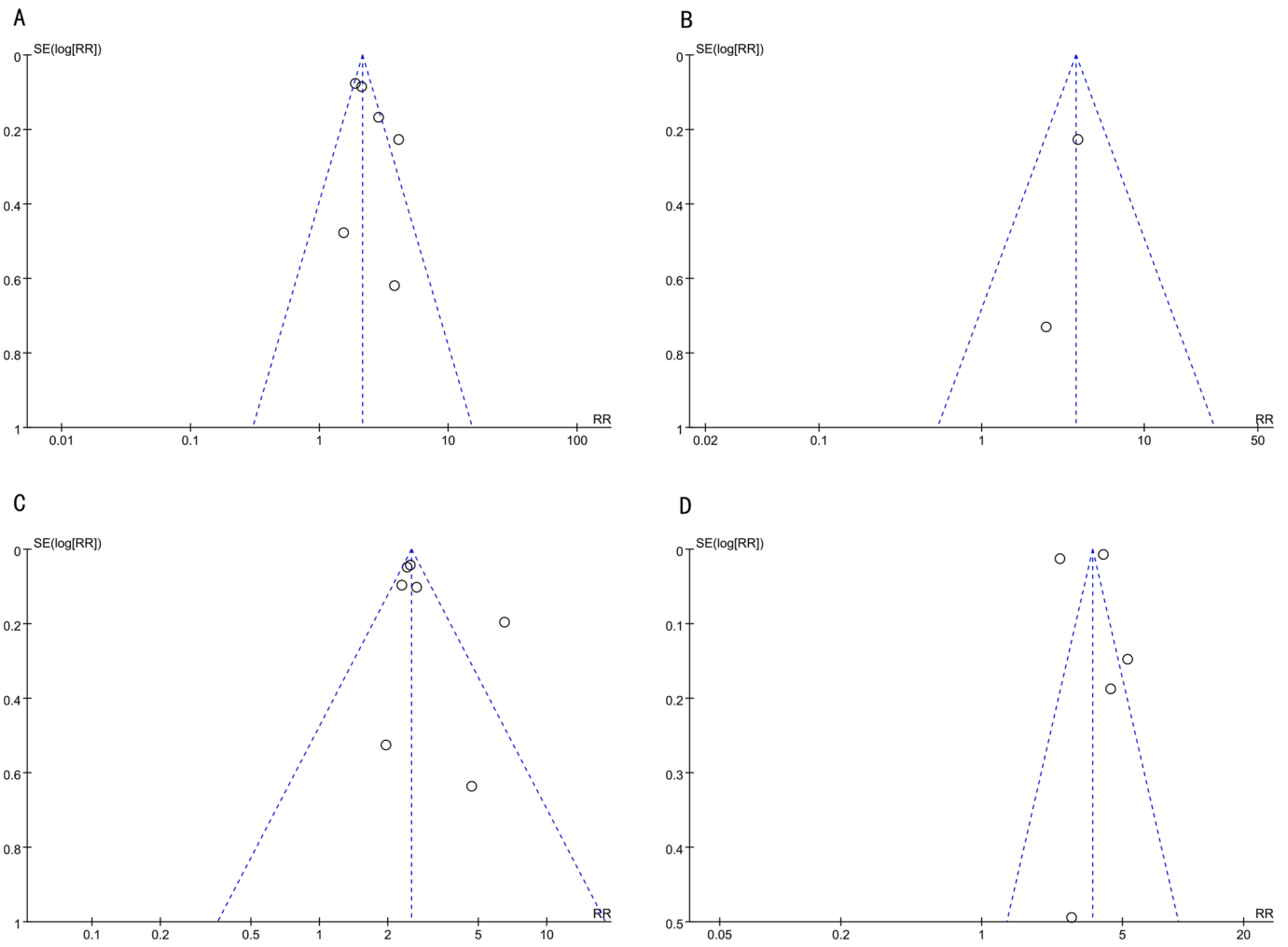


Fig. 4. Funnel plot of the bidirectional relationship between LOE and dementia. (A) LOE and risk of all-cause dementia; (B) LOE and risk of AD. (C) All-cause dementia and risk of LOE; (D) AD and risk of LOE.

LOE risk [28–41]. Two other studies examined the impact of LOE on dementia and the impact of AD on LOE [23,24]. Among the included studies, the sample sizes of 11 studies exceeded 15,000 [25,30,32–34,36–41], while the remaining nine were less than 10,000 [22–24,26–29,31,35]. Nine studies were followed up lasting longer than 10 years [27,29,31,34–39], while 11 studies had a follow-up duration of less than 10 years [22–26,28,30,32,33,40,41]. It is worth noting that, with the exception of three studies, which were of moderate quality (NOS scores of 5, 5 and 6, respectively) [24,29,31], all others were deemed to be of high quality, with a NOS score of 7 or higher (Tables S1–4).

3.3. LOE and risk of all-cause dementia or AD

The pooled results indicated that individuals with LOE had a significantly higher likelihood of developing all-cause dementia (aRR = 2.14, 95 % CI: 1.93–2.38; Fig. 2A) and AD (aRR = 3.77, 95 % CI: 2.46–5.79; Fig. 2B). Moderate heterogeneity was indicated for dementia (I^2 = 67 %, P = 0.01), whereas no heterogeneity was found for AD (I^2 = 0.0 %, P = 0.55). In the subgroup analysis examining the aRR of all-cause dementia among patients with LOE, consistent results were observed across various factors, including study design, follow-up duration, country, and confounder adjustment. The P-values for subgroup differences were all greater than 0.05, indicating no significant variation in the results (Table 2). A sensitivity analysis was conducted to further evaluate the heterogeneity of the results. Analysis revealed that no single study had a higher impact on the pooled aRR for all-cause dementia (Fig. 3A). The overall meta-analysis of LOE predicting an increased risk of all-cause dementia indicated no evidence of publication bias by Egger's test (P = 0.240), Begg's tests (P = 0.452), or a visual inspection of the funnel (Fig. 4A-B).

Finally, publication bias in the relationship between LOE and AD was difficult to identify in two studies.

3.4. All-cause dementia or AD and risk of LOE

We identified seven studies that examined the risk of LOE associated with all-cause dementia. After pooling the data, we found that the aRR of LOE associated with all-cause dementia was 2.53 (95 % CI: 2.39–2.67), but with the moderate heterogeneity (I^2 = 77 %, P < 0.001; Fig. 2C). In the subgroup analysis for the aRR of dementia in LOE patients, results were consistent across stratifications based on study design, location, duration of follow-up, and adjustment for confounding factors (Table 3). Heterogeneity was almost absent in the subgroups of retrospective study, North America, and shorter follow-up (<10 years). Sensitivity analysis indicated that none of individual studies significantly affected the pooled-effect (Fig. 3B). Moreover, the funnel plot seemed symmetrical by visual inspection (Fig. 4C). Both the Egger's test (P = 0.184) and Begg's test (P = 0.230) confirmed no potential selection bias.

Seven studies examined AD predicting impact of LOE. The overall aRR of LOE comorbid with AD was 3.51 (95 % CI: 3.47–3.56), but with

Table 3
Subgroup analysis for the risk ratio of LOE in dementia patients.

Subgroups	Included studies	RR(95 % CI)	Heterogeneity (I^2, Tau^2 and *P*-value)			P for subgroup difference
			I^2(%)	Tau^2	*P*-value	
Study design						0.73
prospective study	5	2.64 (2.44 ~ 2.85)	83.0	23.17	0.001	
retrospective study	2	2.40 (2.20 ~ 2.61)	0	0.19	0.67	
Follow-up						0.77
≥ 10	3	2.54 (2.35 ~ 2.74)	0	0.56	0.75	
< 10	4	2.52 (2.32 ~ 2.73)	88.0	25.48	< 0.001	
Regional distribution						0.74
North America	2	2.52 (2.32 ~ 2.75)	0	0.94	0.33	
Europe	5	2.53 (2.34 ~ 2.73)	84.0	25.13	< 0.001	
Confounders adjusted						0.66
Yes	6	2.53 (2.39 ~ 2.68)	81.0	25.83	< 0.001	
No	1	1.96 (0.70 ~ 5.48)	-	-	-	

Table 4
Subgroup analysis for the risk ratio of LOE in AD patients.

Subgroups	Included studies	RR (95 % CI)	Heterogeneity (I^2, Tau^2 and *P*-value)			P for subgroup difference
			I^2(%)	Tau^2	*P*-value	
Study design						0.81
prospective study	3	4.00 (3.93 ~ 4.06)	96.0	55.64	< 0.001	
retrospective study	4	2.47 (2.40 ~ 2.53)	90.0	29.24	< 0.001	
Follow-up						0.85
≥ 10	5	2.96 (2.71 ~ 3.23)	85.0	27.18	< 0.001	
< 10	2	3.53 (3.48 ~ 3.58)	100.0	990.45	< 0.001	
Regional distribution						0.46
Europe	3	4.77 (3.82 ~ 5.95)	0	1.96	0.38	
Asia	2	2.71 (2.47 ~ 2.98)	76.0	4.15	0.04	
North America	2	3.53 (3.48 ~ 3.58)	100	990.45	< 0.001	
Confounders adjusted						0.73
Yes	5	3.53 (3.48 ~ 3.58)	100	1008.85	< 0.001	
No	2	2.86 (2.60 ~ 3.14)	81	5.34	0.02	

the high heterogeneity (I^2 = 99 %, P < 0.001; Fig. 2D). The subgroup analysis based on study design and follow-up duration did not provide an explanation for the higher heterogeneity. Nevertheless, when considering location as a subgroup, it was found that European studies had a lower level of heterogeneity (I^2 = 0 %). This indicated that follow-up duration was the origin of the heterogeneity (Table 4). Further sensitivity analysis indicated stable results (Fig. 3C). Upon visual inspection, the funnel plot displayed a symmetrical pattern (Fig. 4D), indicating a low likelihood of publication bias. Furthermore, both the Egger's test (P = 0.986) and Begg's test (P = 0.881) identified no significant evidence of potential selection bias.

4. Discussion

In this meta-analysis of cohort studies, we comprehensively evaluated the relationship between LOE and dementia. The results showed that LOE was associated with 2.14-fold and 3.77-fold higher aRRs of all-cause dementia and AD, respectively; whereas all-cause dementia and AD were associated with 2.53-fold and 3.51-fold higher aRRs of LOE, respectively. Additionally, that relationship was not affected by subgroup or sensitivity analyses.

Despite a recent review of longitudinal design studies investigating the relationship between epilepsy and dementia [42], no subgroup analysis by age stratification of epilepsy onset was conducted. It remains unclear whether LOE and dementia have a bidirectional relationship. Furthermore, the incorrect inclusion of a study about epilepsy and migraine [43]in that meta-analysis may affect the statistical accuracy. In the current meta-analysis, we specifically summarized studies of cohort design, then conducted a systematic assessment of the aRR for the bidirectional relationship between LOE and dementia or AD.

Recent studies suggested that continuous overexpression of Aβ and Tau are a key factor involved in the bidirectional deterioration of LOE and AD [44–46]. Aβ has been demonstrated to cause synaptic damage, neurotransmitter system and synaptic plasticity impairment, and altered synergistic network activity alteration [47]. Seizures trigger a process of Aβ expression and tau hyperphosphorylation in the hippocampus, which is also thought to be a pre-epileptic variant of AD [48,49]. In addition, a study published in the issue of NEUROLOGY showed that a decrease in serum Aβ42/Aβ40 from mid to later life was related with an increased risk of LOE [50]. Interestingly, this potential link may be related to the rapid accumulation of pathological amyloid, rather than the total amount, which could explain why only a portion of individuals with AD develop LOE [50]. As a result of these findings, amyloidosis may play an interrelationship with LOE that can lead to cognitive decline.

It is widely acknowledged that conditions such as stroke, traumatic brain injury, and cerebral tumors are prevalent comorbidities among the elderly population, which are frequently associated with dementia and LOE. Theoretically, the coexistence of these risk factors may render patients more susceptible to seizures and new-onset dementia

[49,51,52]. However, the results of the meticulous subgroup analysis revealed a notable correlation between LOE and an elevated risk of developing AD, as well as between dementia and an increased propensity for LOE, even after adjustment for confounding variables.

Furthermore, in our statistical modeling for predicting the risk of LOE within AD populations, our subgroup analysis indicated that the sources of heterogeneity may stem from regional variations. Consequently, further investigations encompassing larger sample sizes and diverse regional cohorts are needed to elucidate the bidirectional association between LOE and AD.

Moreover, our subgroup analysis indicated that the strength of the relevance between LOE and risk of AD was marginally greater than that observed for the risk of all-cause dementia. However, it is essential to acknowledge that this finding may be subject to potential overestimation by reason of the restricted number of available studies.

To our knowledge, this study is the first comprehensive meta-analysis of cohort studies exploring the relationship between LOE and dementia or AD. Nonetheless, it is imperative to acknowledge certain limitations. First, as mentioned, the restricted number of available studies assessing the impact of LOE on AD diminishes the accuracy of the aggregated estimation. Second, variations in clinical diagnostic criteria for dementia and epilepsy among the studies may influence the robustness of the findings. Third, antecedent investigations have suggested a positive correlation with the daily use of oral anti-seizure medications, notably first-generation drugs, and dementia [53]. Given that several studies did not incorporate adjustments for anti-seizure medications use in their statistical analyses, there is potential for an overestimation of dementia risk in LOE patients. Fourth, both LOE and dementia were mostly diagnosed using International Classification of Diseases (ICD) codes, or at least half of the included literature also adopted ICD codes as validation for their outcomes, which may have lead to potential risk of misclassification. Lastly, it should be noted that while most of the studies included in this analysis took extensive measures to adjust for potential confounding factors, there still remains the possibility of residual confounding from unmeasured variables. This is an inherent limitation of clinical research that should be acknowledged.

Conclusively, our findings indicate a positive and bidirectional association between LOE and both dementia and AD. This correlation may prove valuable in the early clinical assessment of cognitive function and electroencephalography analysis of patients, facilitating the formulation of relevant diagnostic and therapeutic strategies.

Funding

This work was supported by the Natural Science Research Project of Anhui Universities, (Grant/Award Number: KJ2021A0349) and Health Applied Medicine Project of Hefei (Grant/Award Number: Hwk2023zd022).

CRediT authorship contribution statement

Zheng Tan: Writing – original draft, Resources. **Fu-Yu Wang:** Investigation. **Wen-Pei Wu:** Methodology. **Liu-Zhen-Xiong Yu:** Software. **Jun-Cang Wu:** Writing – review & editing. **Long Wang:** Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2024.109723.

References

[1] Sarkis RA, Willment KC, Pennell PB, Marshall G. Late-onset unexplained epilepsy: What are we missing? Epilepsy Behav : E&B 2019;99:106478.
[2] Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chetelat G, Teunissen CE, et al. Alzheimer's disease. Lancet 2021;397(10284):1577–90.
[3] Deuschl G, Beghi E, Fazekas F, Varga T, Christoforidi KA, Sipido E, et al. The burden of neurological diseases in Europe: an analysis for the Global Burden of Disease Study 2017. Lancet Public Health 2020;5(10):e551–67.
[4] Abraira L, Gramegna LL, Quintana M, Santamarina E, Salas-Puig J, Sarria S, et al. Cerebrovascular disease burden in late-onset non-lesional focal epilepsy. Seizure 2019;66:31–5.
[5] Punia V. Late-onset epilepsy: A distinct entity that begins and ends with the associated comorbidities. Epilepsy Curr 2022;22(1):43–5.
[6] Zhang D, Chen S, Xu S, Wu J, Zhuang Y, Cao W, et al. The clinical correlation between Alzheimer's disease and epilepsy. Front Neurol 2022;13:922535.
[7] Neri S, Mastroianni G, Gardella E, Aguglia U, Rubboli G. Epilepsy in neurodegenerative diseases. Epileptic Disorders : Int Epilepsy J Videotape 2022;24(2):249–73.
[8] Liu S, Yu W, Lu Y. The causes of new-onset epilepsy and seizures in the elderly. Neuropsychiatr Dis Treat 2016;12:1425–34.
[9] Nardi Cesarini E, Babiloni C, Salvadori N, Farotti L, Del Percio C, Pascarelli MT, et al. Late-onset epilepsy with unknown etiology: A pilot study on neuropsychological profile, cerebrospinal fluid biomarkers, and quantitative EEG characteristics. Front Neurol 2020;11:199.
[10] Paudel YN, Angelopoulou E, Jones NC, O'Brien TJ, Kwan P, Piperi C, et al. Tau related pathways as a connecting link between epilepsy and Alzheimer's disease. ACS Chem Nerosci 2019;10(10):4199–212.
[11] Carmo D, Silva B, Alzheimer's Disease Neuroimaging I, Yasuda C, Rittner L, Lotufo R: Hippocampus segmentation on epilepsy and Alzheimer's disease studies with multiple convolutional neural networks. *Heliyon* 2021, 7(2):e06226.
[12] Kazim SF, Seo JH, Bianchi R, Larson CS, Sharma A, Wong RKS, et al. Neuronal network excitability in Alzheimer's disease: The puzzle of similar versus divergent roles of amyloid beta and Tau. eNeuro 2021;8(2).
[13] Ophir K, Ran B, Felix B, Amir G. Ten year cumulative incidence of dementia after late onset epilepsy of unknown etiology. J Clin Neurosci : Off J Neurosurg Soc Australasia 2021;86:247–51.
[14] Csernus EA, Werber T, Kamondi A, Horvath AA. The significance of subclinical epileptiform activity in Alzheimer's disease: A review. Front Neurol 2022;13:856500.
[15] Yeh WC, Hsu CY, Li KY, Chien CF, Huang LC, Yang YH. Association between subclinical epileptiform discharge and the severity of cognitive decline in Alzheimer's disease: A longitudinal cohort study. J Alzheimers Dis 2022;90(1):305–12.
[16] Nagino N, Kubota Y, Nakamoto H, Miyao S, Kodama T, Ito S, et al. Non-lesional late-onset epilepsy in the elderly Japanese patients: Presenting characteristics and seizure outcomes with regard to comorbid dementia. J Clin Neurosci : Off J Neurosurg Soc Australasia 2022;103:100–6.
[17] Cvetkovska E, Babunovska M, Boskovski B, Kuzmanovski I, Tanovska N, Trencevska GK. Prevalence of various risk factors associated with new-onset epilepsy after the age of 50: a retrospective population-based study. Epileptic Disorders : Int Epilepsy J Videotape 2022;24(1):95–101.
[18] Johnson EL, Krauss GL, Kucharska-Newton A, Lam AD, Sarkis R, Gottesman RF. Mortality in patients with late-onset epilepsy: Results from the atherosclerosis risk in communities study. Neurology 2021;97(11):e1132–40.
[19] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Bmj* 2009, 339:b2535.
[20] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25(9):603–5.
[21] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557–60.
[22] 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):514–6.
[23] Carter MD, Weaver DF, Joudrey HR, Carter AO, Rockwood K. Epilepsy and antiepileptic drug use in elderly people as risk factors for dementia. J Neurol Sci 2007;252(2):169–72.
[24] Kawakami O, Koike Y, Ando T, Sugiura M, Kato H, Hiraga K, et al. Incidence of dementia in patients with adult-onset epilepsy of unknown causes. J Neurol Sci 2018;395:71–6.
[25] Keret O, Hoang TD, Xia F, Rosen HJ, Yaffe K. Association of late-onset unprovoked seizures of unknown etiology with the risk of developing dementia in older veterans. JAMA Neurol 2020;77(6):710–5.
[26] Johnson EL, Krauss GL, Walker KA, Brandt J, Kucharska-Newton A, Mosley Jr TH, et al. Late-onset epilepsy and 25-year cognitive change: The Atherosclerosis Risk in Communities (ARIC) study. Epilepsia 2020;61(8):1764–73.
[27] Tsai ZR, Zhang HW, Tseng CH, Peng HC, Kok VC, Li GP, et al. Late-onset epilepsy and subsequent increased risk of dementia. Aging 2021;13(3):3573–87.
[28] 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):1649–53.
[29] 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.

[30] 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):237–42.
[31] Irizarry MC, Jin S, He F, Emond JA, Raman R, Thomas RG, et al. Incidence of new-onset seizures in mild to moderate Alzheimer disease. Arch Neurol 2012;69(3):368–72.
[32] Sherzai D, Losey T, Vega S, Sherzai A. Seizures and dementia in the elderly: Nationwide Inpatient Sample 1999–2008. Epilepsy Behav : E&B 2014;36:53–6.
[33] Martin RC, Faught E, Richman J, Funkhouser E, Kim Y, Clements K, 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):1120–7.
[34] Cook M, Baker N, Lanes S, Bullock R, Wentworth C, Arrighi HM. Incidence of stroke and seizure in Alzheimer's disease dementia. Age Ageing 2015;44(4):695–9.
[35] 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;115:63–6.
[36] Johnson EL, Krauss GL, Lee AK, Schneider ALC, Dearborn JL, Kucharska-Newton AM, et al. Association between midlife risk factors and late-onset epilepsy: Results from the atherosclerosis risk in communities study. JAMA Neurol 2018;75(11):1375–82.
[37] Lyou HJ, Seo KD, Lee JE, Pak HY, Lee JH. Association of Alzheimer's disease with the risk of developing epilepsy: A 10-year nationwide cohort study. Dementia Neurocognitive Disorders 2018;17(4):156–62.
[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):129–35.
[39] Voglein J, Ricard I, Noachtar S, Kukull WA, Dieterich M, Levin J, et al. Seizures in Alzheimer's disease are highly recurrent and associated with a poor disease course. J Neurol 2020;267(10):2941–8.
[40] Habeych ME, Falcone T, Dagar A, Ford L, Castilla-Puentes R. Dementia, subtype of seizures, and the risk of new onset seizures: A cohort study. J Alzheimers Dis 2021;81(3):973–80.
[41] Blank LJ, Acton EK, Thibault D, Willis AW. Neurodegenerative disease is associated with increased incidence of epilepsy: a population based study of older adults. Age Ageing 2021;50(1):205–12.
[42] Dun C, Zhang Y, Yin J, Su B, Peng X, Liu L. Bi-directional associations of epilepsy with dementia and Alzheimer's disease: a systematic review and meta-analysis of longitudinal studies. Age Ageing 2022;51(3).
[43] Harnod T, Wang YC, Kao CH. High risk of developing subsequent epilepsy in young adults with migraine: a nationwide population-based cohort study in Taiwan. QJM 2015;108(6):449–55.
[44] Romoli M, Sen A, Parnetti L, Calabresi P, Costa C. Amyloid-beta: a potential link between epilepsy and cognitive decline. Nat Rev Neurol 2021;17(8):469–85.
[45] Fernandes M, Manfredi N, Aluisantonio L, Franchini F, Chiaravalloti A, Izzi F, et al. Cognitive functioning, cerebrospinal fluid Alzheimer's disease biomarkers and cerebral glucose metabolism in late-onset epilepsy of unknown aetiology: A prospective study. Eur J Neurosci 2022;56(9):5384–96.
[46] Costa C, Romoli M, Liguori C, Farotti L, Eusebi P, Bedetti C, et al. Alzheimer's disease and late-onset epilepsy of unknown origin: two faces of beta amyloid pathology. Neurobiol Aging 2019;73:61–7.
[47] Sanchez MP, Garcia-Cabrero AM, Sanchez-Elexpuru G, Burgos DF, Serratosa JM. Tau-induced pathology in epilepsy and dementia: Notions from patients and animal models. Int J Mol Sci 2018;19(4).
[48] Canet G, Zub E, Zussy C, Hernandez C, Blaquiere M, Garcia V, et al. Seizure activity triggers tau hyperphosphorylation and amyloidogenic pathways. Epilepsia 2022;63(4):919–35.
[49] DiFrancesco JC, Labate A, Romoli M, Chipi E, Salvadori N, Galimberti CA, et al. Clinical and instrumental characterization of patients with late-onset epilepsy. Front Neurol 2022;13:851897.
[50] Johnson EL, Sullivan KJ, Schneider ALC, Simino J, Mosley TH, Kucharska-Newton A, et al. Association of plasma Abeta(42)/Abeta(40) ratio and late-onset epilepsy: Results from the atherosclerosis risk in communities study. Neurology 2023;101(13):e1319–27.
[51] Gardner RC, Barnes DE, Li Y, Boscardin J, Peltz C, Yaffe K. Medical and psychiatric risk factors for dementia in veterans with and without Traumatic Brain Injury (TBI): A nationwide cohort study. J Prev Alzheimers Dis 2023;10(2):244–50.
[52] 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):139–44.
[53] Taipale H, Gomm W, Broich K, Maier W, Tolppanen AM, Tanskanen A, et al. Use of antiepileptic drugs and dementia risk-an analysis of finnish health register and German health insurance data. J Am Geriatr Soc 2018;66(6):1123–9.