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Late-Onset Epilepsy Predicts Stroke: Systematic Review and Meta-analysis

--Manuscript Draft--

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Abstract:	Objective Late-onset epilepsy (LOE) is closely associated with cerebrovascular disease, acting as both a marker of cerebrovascular disease (CVD) and occurring as a direct consequence. Despite this, our understanding of LOE as a cerebrovascular phenomenon is in its infancy. LOE also appears to be a harbinger of dementia. Methods A systematic review was performed to identify publications relating to LOE and identified observational studies, clinical studies and radiological studies. Results A meta-analysis of observational studies demonstrated that patients presenting with LOE experience an increased risk of subsequent stroke (weighted OR 3.88 (95% CI 2.76 - 5.46)). The additional studies demonstrated clinical and radiological evidence to support the premise that LOE is likely to reflect underlying cerebrovascular disease. Significance Cerebrovascular disease risk factors convey increased risk of LOE and LOE can precede stroke and dementia, acting as an early marker for cerebrovascular risk. This may represent a potential point for intervention. There are a number of suggested mechanisms relating LOE to stroke, however there is limited understanding of the natural history of LOE. Current data support the need for prospective research in order to understand the natural history of LOE and modify disease, in order to reduce the apparent sequelae of stroke and dementia.
Suggested Reviewers:	Laura Hamman Universitatsmedizin Greifswald laurahamann1412@web.de Previously published work on late-onset epilepsy
Response to Reviewers:	Dear Colleague, I am writing to re-submit our revised manuscript entitled "Late-Onset Epilepsy Predicts Stroke: Systematic Review and Meta-analysis" for consideration as an original research paper in Epilepsy and Behavior. This paper comprises systematic review of the existing literature, and meta-analysis of the studies to date observing risk of stroke after the onset of late-onset epilepsy. This meta-analysis supports the view that late-onset epilepsy can be a harbinger of subsequent increased stroke risk. This research forms the basis for considering change in clinical practice to address late-onset epilepsy as a potential intervention point for modification of cerebrovascular risk factors - including modification of high risk behaviors such as alcohol excess,

	smoking and drug use - and avoidance of future stroke risk. The specific comments made during editorial review were: "This is an interesting review on an important topic. The methodology is robust. However, a very similar systematic review (although including only population-based cohort studies) was published early on this year in the same journal (Epilepsy Behav. 2020 Mar;104(Pt B):106307). Apparently, this review included a few more studies than that under consideration. Hence, I suggest Authors to consider including results of the prior review into their own, to provide an even more comprehensive summary of the available evidence." Many thanks for these helpful comments. On review of the papers included in this review, (and excluding those pertaining to myocardial infarction), there were no additional papers which met the inclusion criteria for inclusion into meta-analysis, but where they contribute to the subject matter, they have been included to systematic review. With specific reference to the papers referenced, the paper by Olesen et al. 2011 does not directly compare epilepsy and non-epilepsy cohorts with reference to stroke, but rather directs investigation towards differences between anticonvulsants[1]. The role of anticonvulsants in stroke risk is an important and associated issue with regards to late-onset epilepsy, and an additional comment has been included to this effect. A second paper by Hsu et al., (2019)[2] uses Taiwanese national insurance data which overlaps with the data in an included paper, that of Chang et al. (2014)[3] and so the inclusion of these papers is mutually exclusive. On balance, given that the former paper focuses on the risk of complication during a stroke admission, a decision was made to remain with the inclusion of the original Chang et al. (2014) paper. Additionally, the review by Brigo et al. (2020)[4] has been itself included in systematic review as a valuable observation that patients with late-onset epilepsy not only experience increased risk of hypertension, diabetes and smoking as vascular risk factors, but also experience increased risk of myocardial infarction as a vascular outcome. I look forward to your response. Best Regards, Dr Jasmine Wall MBBChir MA MRCP(London) [1]Olesen JB, Abildstrøm SZ, Erdal J, Gislason GH, Weeke P, Andersson C, et al. Effects of epilepsy and selected antiepileptic drugs on risk of myocardial infarction, stroke, and death in patients with or without previous stroke: A nationwide cohort study. Pharmacoepidemiol Drug Saf 2011. https://doi.org/10.1002/pds.2186. [2]Hsu SPC, Yeh CC, Chou YC, Shih CC, Hu CJ, Cherng YG, et al. Stroke risk and outcomes in epilepsy patients: Two retrospective cohort studies based on National Health Insurance in Taiwan. Atherosclerosis 2019. https://doi.org/10.1016/j.atherosclerosis.2018.11.009. [3]Chang CS, Liao CH, Lin CC, Lane HY, Sung FC, Kao CH. Patients with epilepsy are at an increased risk of subsequent stroke: A population-based cohort study. Seizure 2014. https://doi.org/10.1016/j.seizure.2014.02.007. [4]Brigo F, Lochner P, Nardone R, Manganotti P, Lattanzi S. Increased risk of stroke and myocardial infarction in patients with epilepsy: A systematic review of population-based cohort studies. Epilepsy Behav 2020. https://doi.org/10.1016/j.yebeh.2019.05.005.

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Highlights

Patients presenting with Late Onset Epilepsy have an increased risk of subsequent stroke.
There is also some evidence that late onset epilepsy can precede subsequent dementia.
Late Onset Epilepsy represents a potential intervention point to act: to identify treatable cerebrovascular risk factors such as smoking, diabetes and hypertension in order to reduce future stroke risk.

Figure 1

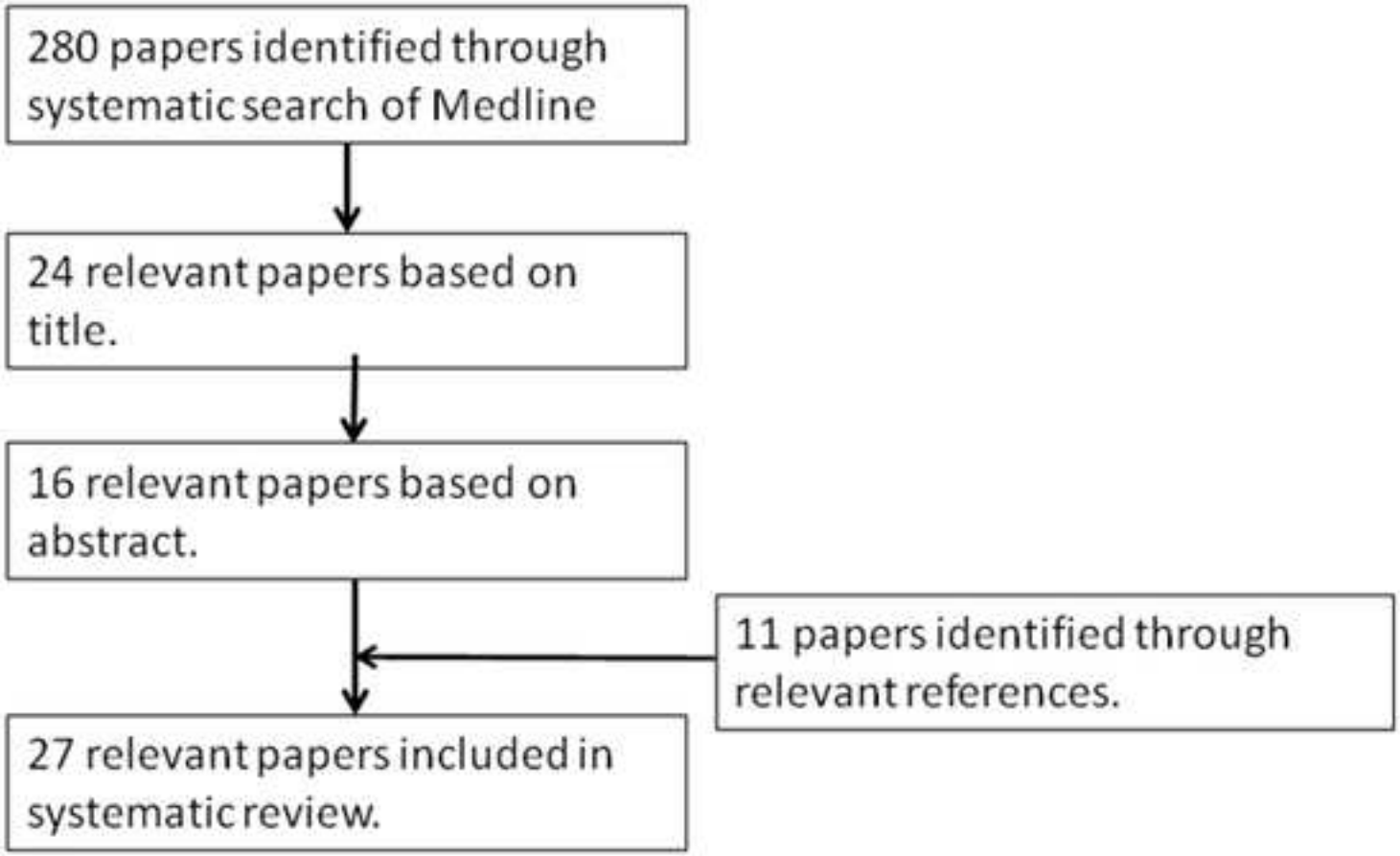
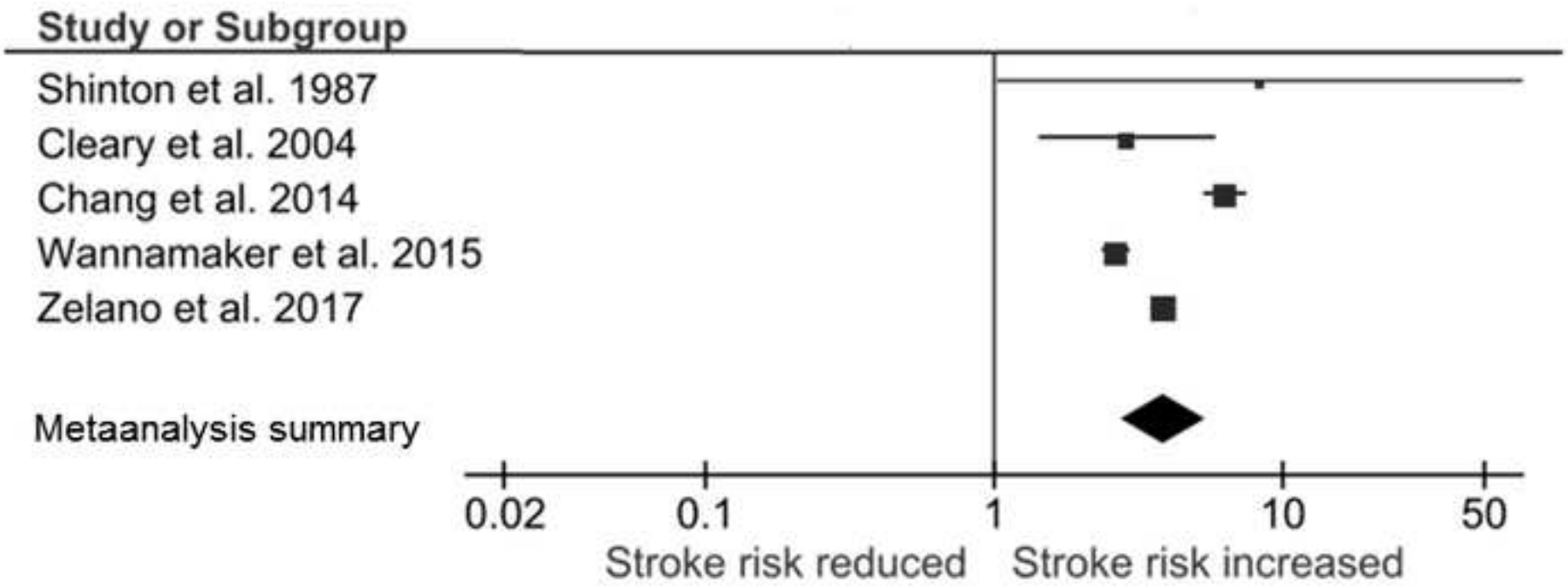


Figure 2



Late-Onset Epilepsy Predicts Stroke: Systematic Review and Meta-analysis

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Reference count: 30
Tables: 2
Figures: 2

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ABSTRACT

Objective: Late-onset epilepsy (LOE) is closely associated with cerebrovascular disease, acting as both a marker of cerebrovascular disease (CVD) and occurring as a direct consequence. Despite this, our understanding of LOE as a cerebrovascular phenomenon is in its infancy. LOE also appears to be a harbinger of dementia.

Methods: A systematic review was performed to identify publications relating to LOE and identified observational studies, clinical studies and radiological studies.

Results: A meta-analysis of observational studies demonstrated that patients presenting with LOE experience an increased risk of subsequent stroke (weighted OR 3.88 (95% CI 2.76 - 5.46)). The additional studies demonstrated clinical and radiological evidence to support the premise that LOE is likely to reflect underlying cerebrovascular disease.

Significance: Cerebrovascular disease risk factors convey increased risk of LOE and LOE can precede stroke and dementia, acting as an early marker for cerebrovascular risk. This may represent a potential point for intervention. There are a number of suggested mechanisms relating LOE to stroke, however there is limited understanding of the natural history of LOE. Current data support the need for prospective research in order to understand the natural history of LOE and modify disease, in order to reduce the apparent sequelae of stroke and dementia.

KEYWORDS: late-onset epilepsy, late onset epilepsy, late onset seizure, white matter lesions, Alzheimer's dementia, vascular dementia

1. INTRODUCTION

There is no clear consensus as to the age from which new onset epilepsy indicates increased cerebrovascular disease risk, but studies have shown a relationship from the fourth decade onwards[1]. Above the age of fifty, incidence of new onset epilepsy is approximately 400/100,000 person years. Of individuals with a new diagnosis of seizure or epilepsy after age 50, 9.8-11.9% will have a stroke in the subsequent decade, equivalent to a population pre-stroke epilepsy rate of 25-55/100,000 person years[2]. The relationship between cerebrovascular disease (CVD)[1] and epilepsy is bidirectional, and the most common cause of new onset seizures in adulthood is post-stroke epilepsy.

LOE patients have an increased risk of subsequent stroke, and observations on this topic date back from Hippocrates (circa. 400 BC) to Barolin (1970s)[3]. Yet consideration of LOE as a cerebrovascular phenomenon is in its infancy and there is only patchy evidence to explain the underlying mechanisms of disease. Despite the evidence of increased stroke risk after LOE, LOE is managed primarily symptomatically in order to achieve seizure control.

Recent data also indicate that LOE can herald dementia, with significant intersection between Alzheimer's disease (AD), CVD and LOE[4]. Additionally, there is overlap in

[1] Abbreviations:
CVD = cerebrovascular disease
LOE = late onset epilepsy
AD = Alzheimer's disease
MRI = magnetic resonance imaging
ICH = intracerebral haemorrhage
WML = white matter lesions
APOE = apolipoprotein E
MMSE = mini mental state exam
ARIC = Atherosclerosis Risk In Communities (Study)
OR = odds ratio

the pathophysiology of CVD and vascular dementia[5]. However, the nature of the relationship between dementia, CVD and LOE remains poorly defined.

A systematic review in 2014 identified several observational studies examining the relationship between LOE and CVD, whilst identifying a paucity of radiological studies[6]. Brigo *et al.*[6] used the term 'heraldic seizure' to refer to idiopathic new onset epilepsy occurring in patients over the age of 60, 'heralding' increased probability of subsequent stroke. This echoes earlier terminology such as ‘vascular precursor epilepsy’ coined by Barolin[3]. Since then, contemporary access to high quality magnetic resonance imaging (MRI) and operationalisation of large epidemiological level digital databases, have provided further insights into the risk of stroke following the onset of LOE, and the mechanisms through which this might occur. Studies employing these two approaches, alongside others using observational clinical data, have been used to investigate the relationship between LOE and CVD in the current study.

2. METHODS

A systematic review was performed using PubMed to search the MedLine database for papers published from 2014 to August 2019, using the previous systematic review in 2014 and references from the identified paper set to identify papers of interest from before this point. Search terms were set out as below:

(((((("late onset epilepsy"[All Fields] OR "late onset epileptic"[All Fields]) OR "late onset epileptic seizures"[All Fields]) OR "late onset seizures"[All Fields]) OR "late onset seizure"[All Fields]) AND "2014/08/24"[PDat] : "2019/08/22"[PDat])

OR ((("seizures"[All Fields] OR "epilepsy"[All Fields]) AND "late onset"[All Fields]) AND "2014/08/24"[PDat] : "2019/08/22"[PDat])

A similar search strategy was performed over a longer period of 15 years in order to confirm that this timeframe was suitably inclusive; no additional papers were found that had not already been identified.

Articles were filtered by hand based on relevance of the title and abstract. Relevant references from these papers were added to the pool (Figure 1). These have been included where they represent seminal work, or contribute to meta-analysis. Inclusion criteria encompassed studies involving adult onset epilepsy, and also adult onset seizures. Exclusion criteria included post-stroke seizure and studies involving paediatric subjects. PRISMA guidelines were adhered to as detailed in Table 2.

Of all studies, 5 constituted retrospective quantitative studies, examining odds of stroke in patients with late-onset seizure(s) and/or LOE patients, compared to a control population (Table 1). Meta-analysis to provide a combined odds ratio was performed using a random-effects model using RevMan systematic review software[7].

Ideally, papers would use the International League Against Epilepsy definition of epilepsy i.e. "a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome"[8]. Most papers have used a 'pragmatic' definition in order to operationalise large data-sets, such as newly coded epileptic diagnosis, or

commencement of anticonvulsants in the context of a new diagnosis of 'seizure' or 'epilepsy', as described in Table 1.

3. RESULTS

3.1 Observational studies

Five case-control or cohort studies were identified comparing incidence of stroke in LOE to a control population; their properties are summarised in Table 1. Meta-analysis demonstrated that patients presenting with LOE experience an increased risk of subsequent stroke ((weighted odds ratio 3.88 (95% CI 2.76 - 5.46)) as shown in Figure 2 and Table 3.

This odds ratio appears to be stable across a range of follow up intervals and across geographically disparate populations. This effect was preserved when defining age of "late-onset" as early as 30 in the study by Chang *et al*[1].

Although several of these studies did not differentiate between ischaemic stroke and ICH in the reporting of stroke, where they were differentiated, there was a disproportionately high incidence of ICH [1].

4. Systematic Review

4.1 Systematic Review

LOE emerges from the literature as a distinct phenotype of epilepsy. Josephson *et al*.[9]identified key characteristics of LOE, including an absence of learning disorders or mental health issues, higher prevalence of focal seizures, and a lower prevalence of generalised tonic-clonic seizures. Although this phenotype is more common with increasing age, it first emerges in the 30s, with an increasing prevalence in the 40s and peak incidence in 60s and 70s[9]. Furthermore, there is evidence that LOE associated

with white matter lesions (WMLs) more frequently exhibits a phenotype of temporal lobe onset; whereas post-stroke seizures are more commonly associated with a frontal lobe focus[10]. The existence of a distinct LOE phenotype suggests that LOE is a different phenomenon to post-stroke epilepsy, or to younger onset epilepsy.

People with LOE are more likely to have risk factors for CVD. The Atherosclerosis Risk in Communities (ARIC) Study constituted a large, prospective, observational study of people at high risk of cardiovascular events. Through retrospective subset analysis, it was demonstrated that a number of CVD risk factors, including APOE ε4 allele, diabetes, hypertension and smoking, independently conveyed increased risk of developing LOE[11]. By contrast, exercise and low alcohol intake conveyed reduced risk of subsequent LOE[11]. Hypertension has previously been recognised to convey increased epilepsy risk[12]. One possible mechanism for this might be cerebral microangiopathy, although other direct mechanisms have been proposed, such as modulation of the renin-angiotensin-aldosterone axis[13]. Addtionally, patients with LOE appear to have an increased risk of myocardial infarction, a disease which is associated with similar atherosclerotic risk factors[14]. The risk of LOE conveyed by CVD risk factors suggests a role for LOE as a marker of CVD.

Additionally, LOE may predict dementia. Costa *et al*.[15] studied prospectively the progression to dementia in a small cohort of 40 patients aged >55 years presenting with LOE. They observed a significantly increased rate of conversion to Alzheimer's Disease (AD) in the 3.5 years following onset of seizures, with a rate of 17.5% conversion to dementia (46% AD) compared to 0% in the control population, despite similar MMSE scores in case and control cohorts at the start of the study. Although seizures are often

a feature of late AD, there is previous work recognising that epilepsy can be a feature of mild-moderate AD[16]. Costa *et al.*[15] hypothesise that parenchymal beta-amyloid may be pro-epileptogenic; but this mechanism alone would not explain the excess cases of non-Alzheimer's dementia in LOE.

4.2 Radiological studies

Early studies did not identify reliable evidence of structural disease in LOE[17]. As MRI technique and interpretation has developed, there are several reports of structural brain changes in the context of LOE.

Observational studies show that LOE patients have an increased volume of white matter lesions (WML), which is recognised to reflect cerebral small vessel disease in the absence of another disease process[18]. This remains a robust finding across a number of validated scoring systems including Cardiovascular Health Study White Matter Grade and the Age Related White Matter Changes rating[19][20].

The highest grade of evidence is from the ARIC study[11,19]. Not only did ARIC demonstrate an association between a higher burden of WMLs on MRI and increased likelihood of later development of LOE, but regression analysis demonstrated that this effect persisted after adjusting for demographics and vascular risk factors even after censoring at the time of stroke or dementia. Lower total cortical volumes (as a proportion of total intracranial volume) in LOE patients were also observed in ARIC[19]. Furthermore, LOE was significantly associated with low individual volumes of the frontal, parietal or occipital regions in a cross-sectional sample population. As imaging

was only available for 28 cases, it is difficult to comment on the comparative volume loss in these cortical areas.

Imaging studies immediately following seizure provide valuable insight into the natural history of seizure on the microvasculature. Imaging 24-48 hours after seizure has been linked to MRI evidence of microhaemorrhage[21]. It is a question for further research whether seizures may prompt a vicious cycle, whereby areas of cerebrovascular damage continue to be disrupted by further seizure, through damage to the microvasculature. There is separate exploratory work using arterial spin labelling to examine microvascular perfusion in patients presenting with LOE[18], and also evidence that diffusion maybe altered in the frontotemporal areas, the brainstem and internal capsule in adult onset temporal lobe epilepsy[22]. These avenues of investigation may yield non-invasive methods of exploring the immediate sequelae of seizures.

5. DISCUSSION

We have performed the first meta-analysis of observational studies of stroke risk after the development of LOE and have found an increased risk of subsequent stroke (weighted OR 3.88 (95% CI 2.76 to 5.46)). Our systematic review has identified clinical and radiological evidence to support the premise that LOE is likely to reflect underlying cerebrovascular disease.

Whilst we have been able to calculate a weighted odds ratio for the relative risk of stroke after the onset of LOE, the determination of absolute stroke risk is more problematic. The study providing the best available estimate is based on the *Rikkstroke*

register[2], which estimates that between 9.8% and 11.9% of individuals with a new seizure or epilepsy diagnosis after 50 years of age will have a stroke in the subsequent decade. This apparent absolute risk of 10% or greater of stroke after a diagnosis of LOE should signal the need for greater attention to be paid to this issue. Not least, considerable efforts are still required to ensure optimal clinical recognition and diagnosis of LOE, which is notoriously challenging because of the nature of its presentation, which differs from younger onset epilepsy phenotypes, as identified above.

Currently, the focus in clinical practice is very much on symptomatic seizure control, rather than modifying the potential stroke risk. Before change in practice can be recommended, such as the widespread use of antiplatelet medication, important gaps in knowledge about LOE, its pathophysiology and natural history need to be addressed. Most studies did not for instance discriminate the pathological subtypes of incident stroke after LOE onset. One study described a disproportionately increased risk of ICH compared to ischaemic stroke [1]. Little is known, for instance, about the potential contribution of cerebral amyloid angiopathy (CAA); it is interesting that in the ARIC study[14] the APOE ε4 allele was found to be independently associated with increased LOE risk. The APOE ε4 allele is also associated with both CAA and AD.

It is important to note that the risk of subsequent disease after LOE is not confined to stroke: there are also convincing data emerging that there is also significantly increased risk of dementia. Furthermore, there is important evidence emerging that the risk of stroke, and possibly also dementia, is not confined to the population developing LOE in later life. More recent data indicate that there is significantly increased risk conferred by LOE, perhaps better termed "adult onset epilepsy", even from the third or fourth

decades of life. For example, in one study, the effect size, in terms of the risk of stroke, was most pronounced in those developing epilepsy below the age of 39 (HR 8.88, 95% CI 5.71 to 13.82)[1]. In future it will be necessary to consider whether the concept of 'late-onset epilepsy' might need to be replaced by 'adult-onset epilepsy' for the purpose of considering risk of subsequent disease.

There is however considerable heterogeneity in the design of the included studies. LOE, for example, is variably defined, with ‘late-onset’ varying between 30 and 60 years of age. Additionally, the period of observation varied from 1 to 8 years. However, where outcomes have been documented at several time intervals, the hazard ratio remains stable across a range of observation periods[1]. Considerable variation between studies is also evidenced by the high I^2 index which indicates between-study variability in odds ratio and standard deviation of outcomes. Several studies employ epidemiological data derived from insurance records, or clinical coding.[1,23,24]. However, clinically coded data is dependent on the correct interpretation of clinical records, which can be variable and can undermine the integrity of subsequent analysis (particularly if stroke mimics are miscoded, e.g. postictal paresis miscoded as stroke)[25]. A weakness of the broadly defined ‘late-onset epilepsy’ is that some studies have included all adult onset seizures, including single seizures due to a variety of aetiologies encompassing acute symptomatic, alcohol related, and other causes. This exemplifies the challenges of utilising retrospectively collected data and again emphasises the need for prospectively collected dedicated data for the purpose of research into LOE. Nonetheless, evidence of a real relationship between LOE and stroke is all the stronger given its persistence despite the ‘noise’ of such heterogeneous studies and data sources.

Conventionally, epilepsy is regarded as arising from cortical regions. However, it is believed that disruption of networks, including as a result of subcortical changes as seen in cerebrovascular small vessel disease, may contribute to epileptogenesis. A number of qualitative studies have failed to demonstrate a significant difference in subcortical cerebrovascular disease as defined radiologically by white matter lesions (WMLs)[25]. However, when analysed quantitatively, there is evidence of increased WML burden in patients with LOE compared to controls[18]. Differences between findings might be partly due to the use of semi-quantitative WML measures (Fazekas and Scheltens scales), which may be insufficiently robust for reliable statistical analysis by comparison with quantitative measures. The role of WMLs is however still debated[26]. Some radiological studies suggest that LOE is associated with lower cortical volumes[19]. There is however insufficient evidence because of a lack of longitudinal imaging studies to comment on the temporal relationship, or the extent of causation, between subcortical cerebrovascular disease and cortical atrophy in LOE.

Abraira *et al.* present evidence which would support the hypothesis that specific areas of the brain may be involved in epileptogenesis in LOE. They report a greater degree of hippocampal atrophy among patients with LOE by comparison with healthy controls. It is clearly necessary for future work to investigate the relationships between cerebrovascular disease, global and regional atrophy, and LOE. Other areas needing to be addressed in future work include the proposed role of antiepileptic drugs and their effects on cerebrovascular risk[27][28].

6. CONCLUSION

LOE signals risk of stroke and dementia. In the young population, cerebral insults leading to epilepsy are arguably better defined than in LOE, where the phenotype and aetiology are different. A 'late-onset phenotype' appears to emerge from the third or fourth decade and increases in incidence thereafter. Aging is associated with a shift towards a greater burden of cerebrovascular and neurodegenerative pathology, and this is accompanied by LOE. LOE may represent a point of intervention to modify the risk of stroke and dementia, but considerable advances in knowledge of natural history and pathophysiology are needed, through prospective studies.

7. AREAS FOR FUTURE RESEARCH

A standardised and evidence-based definition for LOE, including age of onset, is clearly needed. Further research is needed to explore the underlying mechanisms of LOE due to CVD. The apparent excess of ICH in one study needs validation, and the potential for a relationship between CAA and LOE needs to be explored.

LEGEND

Figure 1: Flowchart of systematic review methodology.

Figure 2: Forest Plot of Meta-analysis of risk of stroke following late-onset epilepsy compared to control populations.

CONFLICTS OF INTEREST

Declaration of interest: none.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. JW is the guarantor. JW developed the search strategy. HE provided clinical expertise on late onset epilepsy. JK provided statistical expertise. All authors read, provided feedback and approved the final manuscript. This work was completed and funded as part of an NIHR clinical academic fellowship. No sponsors were involved in the development of this review.

REFERENCES

[1] Chang CS, Liao CH, Lin CC, Lane HY, Sung FC, Kao CH. Patients with epilepsy are at an increased risk of subsequent stroke: A population-based cohort study. Seizure 2014. https://doi.org/10.1016/j.seizure.2014.02.007.

[2] Zelano J, Larsson D, Kumlien E, Åsberg S. Pre-stroke seizures: A nationwide register-based investigation. Seizure 2017. https://doi.org/10.1016/j.seizure.2017.05.010.

[3] Trinka E, Krämer G, Werhahn K. Epilepsy & Behavior. Epilepsy Behav 2015;48:103–4. https://doi.org/10.1016/j.yebeh.2015.03.026.

[4] Sen A, Capelli V, Husain M. Cognition and dementia in older patients with epilepsy. Brain 2018. https://doi.org/10.1093/brain/awy022.

[5] Shi Y, Wardlaw JM. Update on cerebral small vessel disease: A dynamic whole-brain disease. Stroke Vasc Neurol 2016. https://doi.org/10.1136/svn-2016-000035.

[6] Brigo F, Tezzon F, Nardone R. Late-onset seizures and risk of subsequent stroke: A systematic review. Epilepsy Behav 2014. https://doi.org/10.1016/j.yebeh.2013.11.003.

[7] The Nordic Cochrane Centre. Review Manager (RevMan). Cochrane Collab 2014.

[8] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE Official Report: A practical clinical definition of epilepsy. Epilepsia 2014. https://doi.org/10.1111/epi.12550.

[9] Josephson CB, Engbers JDT, Sajobi TT, Jette N, Agha-Khani Y, Federico P, et al. Towards a clinically informed, data-driven definition of elderly onset epilepsy. Epilepsia 2016. https://doi.org/10.1111/epi.13266.

[10] Gasparini S, Ferlazzo E, Beghi E, Sofia V, Mumoli L, Labate A, et al. Epilepsy associated with Leukoaraiosis mainly affects temporal lobe: a casual or causal relationship? Epilepsy Res 2015. https://doi.org/10.1016/j.eplepsyres.2014.10.012.

[11] Koubeissi M. Seize the Day for a Day With No Seizures: Modifiable Midlife Risk Factors Identified. Epilepsy Curr 2019. https://doi.org/10.1177/1535759718822041.

[12] Ng SKC, Hauser WA, Brust JCM, Susser M. Hypertension and the risk of new-onset unprovoked seizures. Neurology 1993. https://doi.org/10.1212/wnl.43.2.425.

[13] Gasparini S, Ferlazzo E, Sueri C, Cianci V, Ascoli M, Cavalli SM, et al. Hypertension, seizures, and epilepsy: a review on pathophysiology and management. Neurol Sci 2019. https://doi.org/10.1007/s10072-019-03913-4.

[14] Brigo F, Lochner P, Nardone R, Manganotti P, Lattanzi S. Increased risk of stroke and myocardial infarction in patients with epilepsy: A systematic review of population-based cohort studies. Epilepsy Behav 2020. https://doi.org/10.1016/j.yebeh.2019.05.005.

[15] 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. https://doi.org/10.1016/j.neurobiolaging.2018.09.006.

[16] 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. https://doi.org/10.1001/archneurol.2011.830.

[17] Kilpatrick CJ, Tress BM, O'Donnell C, Rossiter SC, Hopper JL. Magnetic Resonance Imaging and Late Onset Epilepsy. Epilepsia 1991. https://doi.org/10.1111/j.1528-1157.1991.tb04664.x.

[18] Emsley HCA, Parkes LM. Seizures in the context of occult cerebrovascular disease. Epilepsy Behav 2019. https://doi.org/10.1016/j.yebeh.2019.06.039.

[19] Johnson EL, Krauss GL, Lee AK, Schneider ALC, Kucharska-Newton AM, Huang J, et al. Association between white matter hyperintensities, cortical volumes, and late-onset epilepsy. Neurology 2019;92:E988–95. https://doi.org/10.1212/WNL.0000000000007010.

[20] Maxwell H, Hanby M, Parkes LM, Gibson LM, Coutinho C, Emsley HCA. Prevalence and subtypes of radiological cerebrovascular disease in late-onset isolated seizures and epilepsy. Clin Neurol Neurosurg 2013. https://doi.org/10.1016/j.clineuro.2012.07.009.

[21] Izutsu N, Fujimoto Y, Yamada N, Kajikawa R, Yoshimura K, Nagashima M, et al. Small Hyperintensities in the Area of the Perforating Arteries in Patients with Seizure. Eur Neurol 2018. https://doi.org/10.1159/000488673.

[22] Sone D, Sato N, Kimura Y, Watanabe Y, Okazaki M, Matsuda H. Brain morphological and microstructural features in cryptogenic late-onset temporal lobe epilepsy: a structural and diffusion MRI study. Neuroradiology 2018. https://doi.org/10.1007/s00234-018-2019-z.

[23] Cleary P, Shorvon S, Tallis R. Late-onset seizures as a predictor of subsequent stroke. Lancet 2004. https://doi.org/10.1016/S0140-6736(04)15946-1.

[24] Wannamaker BB, Wilson DA, Malek AM, Selassie AW. Stroke after adult-onset epilepsy: A population-based retrospective cohort study. Epilepsy Behav 2015. https://doi.org/10.1016/j.yebeh.2014.11.028.

[25] Li L, Rothwell PM. Biases in detection of apparent "weekend effect" on outcome with administrative coding data: Population based study of stroke. BMJ 2016. https://doi.org/10.1136/bmj.i2648.

[26] 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. https://doi.org/10.1016/j.seizure.2019.02.004.

[27] Katsiki N, Mikhailidis DP, Nair DR. The effects of antiepileptic drugs on vascular risk factors: A narrative review. Seizure 2014. https://doi.org/10.1016/j.seizure.2014.05.011.

[28] Olesen JB, Abildstrøm SZ, Erdal J, Gislason GH, Weeke P, Andersson C, et al. Effects of epilepsy and selected antiepileptic drugs on risk of myocardial infarction, stroke, and death in patients with or without previous stroke: A nationwide cohort study. Pharmacoepidemiol Drug Saf 2011. https://doi.org/10.1002/pds.2186.

[29] Shinton RA, Zezulka A V., Gill JS, Beevers DG. THE FREQUENCY OF EPILEPSY PRECEDING STROKE. Case-control Study in 230 Patients. Lancet 1987. https://doi.org/10.1016/S0140-6736(87)90701-X.

[30] Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009. https://doi.org/10.1371/journal.pmed.1000097.

Table 1: Properties of observational studies of stroke risk after late-onset epilepsy. Key: ICH - intracranial haemorrhage; SAH - subarachnoid haemorrhage.

	Study design	**N**	**Control population**	**Case finding**	**Age of onset (year)**	**Years follow up**	**Type of stroke included**	**Inclusion Criteria**	**Sources of Bias**	**Exclusion criteria**
Shinton *et al.* 1987 [29]	Case control retrospective	352	Non stroke admissions	Serial admissions with stroke	18+	Ever	SAH, ischaemic stroke, ICH	Newly commenced anticonvulsants with seizures, or recurrent witnessed seizure		Alcohol excess, metastatic cancer, previous stroke
Cleary *et al.* 2004[23]	Cohort study retrospective	9418	Randomly selected	Population study from GP records	60+	Median 3 years. 14 yrs max	Ischaemic stroke, ICH	First seizure or newly commenced anticonvulsant with epilepsy diagnosis	Using clinically coded GP data	Cerebrovascular disease, alcohol or drug misuse, dementia, acquired brain injury
Chang *et al.* 2014[1]	Case control retrospective	4087	All eligible from population data	Population study from national insurance data	20+	11 yrs max (8 year data used)	Ischaemic, ICH	Newly diagnosed epilepsy or newly commenced anticonvulsants	High case: control ratio (1:4) Using clinically coded Insurance data	Did not remove epilepsy of clear aetiology
Wannamaker *et al.* 2015 [24]	Cohort study retrospective	37671	Uncomplicated lower limb fracture	Serial epilepsy from ED, outpatients and inpatient discharges	35-60	10 yrs	Using ICD: any	Coded with new diagnosis of 'epilepsy' or 'seizures'	Incidence of epilepsy with preceding stroke particularly striking in the age bracket 35 to 45 at first epilepsy diagnosis compared with controls in the same age group (20.7% vs. 8.0%, respectively)	brain cancer or traumatic brain injury, conditions known to lead to either epilepsy or seizures, and controls with concomitant injuries to other parts of the body were excluded
Zelano *et al.* 2017[2]	Case control retrospective	3507613	Population level data ICD-10	National stroke registry	60+	3 days - 10 yrs prior	Ischaemic, ICH	Coded with first seizure or new epilepsy diagnosis		Did not exclude epilepsy of clear aetiology High case:control ratio

Table 2: Prisma Checklist for systematic review and meta-analysis[30].

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	na
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	11

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	na
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	13 (fig1)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	20 (table 1)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	20
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	20
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	32 (table 2)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	20
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	na
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

Table 2: Summary of meta-analysis of stroke risk in late-onset epilepsy.

Study or subgroup	**Log (Odds Ratio)**	**SE**	**Late-onset Epilepsy (n)**	**Control (n)**	**Weight**	**Odds Ratio (95% CI)**
Shinton *et al.* 1987	2.12	1.07	176	176	2.4%	8.33 (1.02,67.84)
Cleary *et al.* 2004	1.06	0.36	4709	4709	13.0%	2.89 (1.43,5.85)
Chang *et al.* 2014	1.84	0.088	709	3378	27.2%	6.30 (5.30, 7.48)
Wannamaker *et al*. 2015	0.97	0.057	21035	16636	28.4%	2.64 (2.36, 2.95)
Zelano *et al.* 2017	1.351	0.031	13948	3493665	29.0%	3.86 (3.63, 4.10)
Total (95% CI)			**40677**	**3518564**	**100%**	**3.88 (2.76, 5.46)**
Heterogeneity: $Tau^2 = 0.10$, $Chi^2 = 74.64$, df=4 ($P < 0.00001$), $I^2 = 95\%$ Test for overall effect: $Z = 7.80$ ($P < 0.00001$)						

Late-Onset Epilepsy Predicts Stroke: Systematic Review and Meta-analysis

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