National Institute for Health and Care Excellence

FINAL

Epilepsies in children, young people and adults: diagnosis and management

[2] Evidence review: Modifiable risk factors for a second seizure

NICE guideline NG217

Evidence review underpinning recommendations 1.1.1 to 1.1.9 in the NICE guideline

April 2022

FINAL

Developed by the National Guideline Centre

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN: 978-1-4731-4513-9

Contents

1 Modifiable risk factors for a further seizure after a first seizure

1.1 Review question

What are the modifiable risk factors for a further seizure after a first seizure, and what is the magnitude of risk of those factors?

1.1.1 Introduction

The likelihood of having a further seizure following a first seizure differs between individuals. Understanding and quantifying the magnitude or risk associated with different factors may help people to manage that risk and influence the impact on their lives as well as informing their shared decision to start long term antiseizure medication. This review area examines modifiable risk factors for a further seizure after a first seizure and what the magnitude of risk is for those factors.

Assessing modifiable risk factors for a second seizure is different from the prediction of a second seizure. Prediction is assessing if a tool can accurately predict a second seizure using all, or most of, the known risk factors for a second seizure. This will provide a risk score based on an individual's risk factors. So, this identifies who is at risk of a second seizure. In comparison, analysing potential modifiable risk factors looks for individual modifiable risk factors which may have an impact on second seizures. This informs us which risk factors may be modified in people who are identified to be at risk of a second seizure.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: People with a history of a single seizure (as determined by a specialist). Exclusion: New-born babies with acute symptomatic seizures
Risk factors under consideration	• Vascular disease • Blood pressure • Activity/exercise levels • Alcohol/ recreational drugs • Psychological factors / stress • Psychosocial factors • Sleep deprivation • AED use • Other drugs that reduce seizure thresholds • Tumours • Drugs affecting sleep • Systemic illness
Confounding factors	• No key confounders that have to be adjusted for have been identified
Outcomes	Second seizure (as determined by a specialist) Follow up: use all available but stratify: <6 months, 6-12 months, 1-5 years, >5 years
Study design	• Prospective and retrospective cohort studies

- Case-control studies will be considered if demonstrated to avoid bias arising from plausible potential confounders by appropriate methods

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Prognostic evidence: Included studies

Six cohort studies were found investigating the modifiable risk factors for a second seizure after having a first seizure and were included in the review. [2, 4, 5, 12, 31, 33]

Within the six studies included within the review, the risk factors considered were psychological factors, health conditions (e.g., diabetes and hypertension), infection or raised temperature and types of seizures. No evidence was found for the other risk factors considered:

- Blood pressure
- Activity/exercise levels
- Alcohol/ recreational drugs
- Psychosocial factors
- Sleep deprivation
- AED use
- Other drugs that reduce seizure thresholds
- Tumours
- Drugs affecting sleep

Of the included studies, two[2, 4] cohort studies investigated adult participants who were followed up from 1 – 5 years; one[31] study assessed adults, followed up for more than 5 years; and three[5, 12, 33] studies reviewed children (under 18) who were followed up for 1 – 5 years after their first seizure. No studies were found for other stratifications or those who had a mixed adult and child population.

Evidence from these studies is summarised in the clinical evidence summary below (Table 5).

See also the study selection flow chart in Appendix A, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.1 Excluded studies

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the prognostic evidence

Table 2: Summary of studies included in the evidence review – Adults >18 years (follow up 1 – 5 years)

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Comments
Assis 2019[2]	N = 109 Patients aged ≥60 years who were consecutively admitted to Hospital São Rafael, a general tertiary teaching hospital with 356 beds in Salvador, Brazil, between November 2015 and April 2018.	Prospective, observational, single-centre study with multivariate analysis of the risk factors for early seizure recurrence	Sepsis Psychiatric Disorders	Comorbidities Neurological disorders Clinical disorders	Second Seizure	All factors significant within the univariate analysis were also used within the multivariate analysis but have not been clearly stated 22 out of the 103 patients over the age of 60 had a previous diagnosis of epilepsy at the time of hospital admission.
Baldin 2017[4]	N = 52 Patients were found through emergency department records who had an unprovoked seizure (seizure or multiple seizures) within a 24-hour period without an identified proximate precipitant	Retrospective cohort study with multivariable Cox regression	Lifetime generalized anxiety disorder Lifetime mood disorder	Age Gender Lifetime generalized anxiety disorder Lifetime mood disorder	Second Seizure	

Table 3: Summary of studies included in the evidence review – Adults > 18 (follow up > 5 years)

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Comments
Kim 2016[31]	N=124 Patients admitted to Ewha Woman's University Hospital between 2001 and 2012 due to cerebral infarction, 124 post-stroke seizure after ischemic stroke patients (PSSi) were included in this study.	Retrospective cohort study with multivariate logistic regression analysis	Status Epilepticus Partial Seizure type Diabetes Mellitus Hypertension Atrial Fibrillation Functional disability	Age Male gender Diabetes Mellitus Hypertension Atrial Fibrillation Lesion size Cortical involvement Haemorrhagic transformation Functional disability Status Epilepticus Relevant EEG findings Partial Seizure type	Second Seizure	

Table 4: Summary of studies included in the evidence review – Children <18 years (follow up 1 – 5 years)

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Comments
Berg 1998[5]	N=428 Only children with a first febrile seizure, a temperature of ≥101F, no evidence of intracranial infection, and no history of unprovoked seizures were eligible	Prospective cohort study with Cox regression model	Temperature Unprovoked seizures	Age Family history Duration of fever Temperature Unprovoked seizure	Second seizure	
Cheung 2015[12]	N=650 All children aged below 6 years presented with seizure attended A&E who required admissions to paediatric ward were included.	Retrospective cohort analysis with binomial logistic regression	Temperature in A&E (≥38oC)	Pre-hospital seizure duration between 5-15 minutes Pre-hospital seizure duration more than 15 minutes History of prematurity History of epilepsy Fever in A&E (≥38oC) Paracetamol taken within 4 hours on A&E arrival	Second Seizure	

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Comments
				History of brain insult		
Kumar 2019[33]	N=528 Children between 6 months and 5 years, presenting with seizure accompanied by fever, that is, a core body temperature (rectal temperature) of 100.4°F or 38°C, without central nervous system infection	Prospective cohort study with multiple logistic regression	Temperature (during seizure) per °F	Gender Age at first seizure Temperature Duration of fever Family history of febrile seizures Family history of epilepsy	Second Seizure	The outcome was compared to those without recurrent febrile seizures

See Appendix D for full evidence tables.

1.1.5.1 Summary of the prognostic evidence: Adults >18 years (follow up 1 – 5 years)

Table 5: Clinical evidence summary: Lifetime generalized anxiety disorder

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Second Seizure	No lifetime generalized anxiety disorder as reference		
	52 (1 study) 1-5 years	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	HR 2.48 (0.8 to 7.69)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias			

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
2 Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders 3 Downgraded by 1 increment if the confidence interval crossed the null line 4 Adjusted for age, gender, lifetime generalized anxiety disorder and lifetime mood disorder			

Table 6: Clinical evidence summary: Lifetime mood disorder

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Second Seizure	No lifetime mood disorder as reference		
	52 (1 study) 1-5 years	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	HR 1.90 (0.8 to 4.51)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders 3 Downgraded by 1 increment if the confidence interval crossed the null line 4 Adjusted for age, gender, lifetime generalized anxiety disorder and lifetime mood disorder			

Table 7: Clinical evidence summary: Psychiatric Disorders

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Second Seizure	No psychiatric disorders as reference		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
	109 (1 study) 1-5 years	⨁⨁⊖⊖ LOW1,2 due to risk of bias	OR 2.88 (1.07 to 7.75)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Adjusted for multiple comorbidities, neurological disorders and clinical disorders

Table 8: Clinical evidence summary: Sepsis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Second Seizure	No sepsis as reference		
	109 (1 study) 1-5 years	⨁⨁⊖⊖ LOW1,2 due to risk of bias	OR 4.52 (1.42 to 14.39)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Adjusted for multiple comorbidities, neurological disorders and clinical disorders

1.1.5.2 Summary of the prognostic evidence: Adults >18 years (follow up >5 years)

Table 9: Clinical evidence summary: Partial seizures

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Second Seizure	No partial seizures as reference		
	124 (1 study) >5 years	⊕⊕⊖⊖ LOW1,2,3 due to indirectness, imprecision	OR 4.62 (0.55 to 39.08)
1 Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders 2 Downgraded by 1 increment if the confidence interval crossed the null line 3 Adjusted for age, male gender, diabetes mellitus, hypertension, atrial fibrillation, lesion size, cortical involvement, haemorrhagic transformation, functional disability, status epilepticus, relevant EEG findings, partial seizure type			

Table 10: Clinical evidence summary: Status Epilepticus

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Second Seizure	No status epilepticus as reference		
	124 (1 study) >5 years	⊕⊕⊖⊖ LOW1,2,3 due to indirectness, imprecision	OR 1.08 (0.15 to 7.68)
1 Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders 2 Downgraded by 1 increment if the confidence interval crossed the null line 3 Adjusted for age, male gender, diabetes mellitus, hypertension, atrial fibrillation, lesion size, cortical involvement, haemorrhagic transformation, functional disability, status epilepticus, relevant EEG findings, partial seizure type			

Table 11: Clinical evidence summary: Diabetes Mellitus

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Second Seizure	No diabetes mellitus as reference		
	116,608 (1 study) >5 years	⊕⊕⊖⊖ LOW1,2,3 due to indirectness, imprecision	OR 0.35 (0.04 to 3.15)

1 Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
2 Downgraded by 1 increment if the confidence interval crossed the null line
3 Adjusted for age, male gender, diabetes mellitus, hypertension, atrial fibrillation, lesion size, cortical involvement, haemorrhagic transformation, functional disability, status epilepticus, relevant EEG findings, partial seizure type

Table 12: Clinical evidence summary: Hypertension

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Second Seizure	No hypertension as reference		
	124 (1 study) >5 years	⊕⊕⊖⊖ LOW1,2,3 due to indirectness, imprecision	OR 0.35 (0.04 to 3.2)

1 Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
2 Downgraded by 1 increment if the confidence interval crossed the null line
3 Adjusted for age, male gender, diabetes mellitus, hypertension, atrial fibrillation, lesion size, cortical involvement, haemorrhagic transformation, functional disability, status epilepticus, relevant EEG findings, partial seizure type

Table 13: Clinical evidence summary: Atrial Fibrillation

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Second Seizure	No atrial fibrillation as reference		
	124 (1 study) >5 years	⊕⊕⊖⊖ LOW1,2,3 due to indirectness, imprecision	OR 10.45 (0.61 to 179.37)

1 Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
2 Downgraded by 1 increment if the confidence interval crossed the null line
3 Adjusted for age, male gender, diabetes mellitus, hypertension, atrial fibrillation, lesion size, cortical involvement, haemorrhagic transformation, functional disability, status epilepticus, relevant EEG findings, partial seizure type

Table 14: Clinical evidence summary: Functional disability – severe

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Second Seizure	No functional disability as reference		
	124 (1 study) >5 years	⊕⊕⊖⊖ LOW1,2,3 due to indirectness, imprecision	OR 3.52 (0.35 to 35.44)

1 Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
2 Downgraded by 1 increment if the confidence interval crossed the null line
3 Adjusted for age, male gender, diabetes mellitus, hypertension, atrial fibrillation, lesion size, cortical involvement, haemorrhagic transformation, functional disability, status epilepticus, relevant EEG findings, partial seizure type

Table 15: Clinical evidence summary: Functional disability – moderate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Second Seizure	No functional disability as reference		
	124 (1 study) >5 years	⨁⨁⊖⊖ LOW1,2,3 due to indirectness, imprecision	OR 0.39 (0.01 to 9.93)
1 Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders 2 Downgraded by 1 increment if the confidence interval crossed the null line 3 Adjusted for age, male gender, diabetes mellitus, hypertension, atrial fibrillation, lesion size, cortical involvement, haemorrhagic transformation, functional disability, status epilepticus, relevant EEG findings, partial seizure type			

1.1.5.3 Summary of the prognostic evidence: Children <18 years (follow up 1-5 years)

Table 16: Clinical evidence summary: Unprovoked Seizures

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Second Seizure	No unprovoked seizures as reference		
	428 (1 study) 1 - 5 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness	RR 3.47 (1.61 to 7.48)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders 3 Adjusted for age, family history of epilepsy, duration of fever, temperature, unprovoked seizure			

Table 17: Clinical evidence summary: Temperature ≥38 degrees

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Second Seizure	Temperature <38 degrees as reference		
	650 (1 study) 1 - 5 years	⨁⨁⊖⊖ LOW1,2,3 due to risk of bias, indirectness	OR 2.07 (1.07 to 4.01)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
3 Adjusted for pre-hospital seizure duration between 5 – 15 minutes and more than 15 minutes, history of prematurity, history of epilepsy, fever in A&E(≥38ºC), paracetamol taken within 4 hours on A&E arrival, history of brain insult

Table 18: Clinical evidence summary: Temperature (per F increase)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Second Seizure	Higher temperature compared to lower temperature increase		
	650 (1 study) 1 - 5 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness	RR 0.79 (0.68 to 0.92)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
3 Adjusted for age, family history of epilepsy, duration of fever, temperature, unprovoked seizure

Table 19: Clinical evidence summary: Temperature (per F increase)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Second Seizure	Higher temperature compared to lower temperature increase		
	528 (1 study) 1 - 5 years	⨁⨁⊖⊖ LOW1,2,3 due to risk of bias, indirectness	OR 0.34 (0.15 to 0.77)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
3 Adjusted for age at first seizure, gender, temperature, duration of fever, family history of febrile seizures, family history of epilepsy

See Appendix F for full GRADE tables.

1.1.6 Economic evidence

1.1.7 Included studies

No health economic studies were included.

1.1.8 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.1.9 Economic model

This area was not prioritised for a new cost-effectiveness analysis.

1.1.10 Evidence statements

1.1.10.1 Clinical evidence statements

- None

1.1.10.2 Economic

- No relevant economic evaluations were identified.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1 The outcomes that matter most

The only outcome for this review question was a second seizure, as this review question was designed to evaluate the modifiable risk factors for second seizure in people who have had a first seizure.

1.1.11.2 The quality of the evidence

The evidence concerning the modifiable risk factors for second seizure was of low or very low quality. The main reasons were the risk of bias and indirectness. As all the studies were observational studies, they had to show adjustment was made for potential confounders, and one of the main reasons for downgrading was the failure of studies to adjust for at least two of the modifiable risk factors specified. Appropriate statistical adjustment for confounding variables should lead to the results that would be observed if the confounding variables are the same across the risk factor and no-risk factor groups, which should increase our confidence that the results are not confounded. Where the confidence interval of the odds, hazard or risk crosses the null line, this signifies that the result is consistent with the possibility of no effect from the risk factor in the population. The committee took note of these different elements in the quality assessment of the evidence in order to decide on recommendations.

1.1.11.3 Benefits and harms

The evidence showed that in adults who are followed up between one to five years, the presence of psychiatric disorders leads to almost three times the odds of a second seizure as no psychiatric disorders. In addition, people with sepsis have an odds of a second seizure

that is almost five times greater than the odds in people who do not have sepsis. In adults followed up for over five years, vascular risk factors such as diabetes, hypertension and atrial fibrillation do not show significant effects in relation to a second seizure. However, the committee noted that vascular risk factors can predispose to late onset epilepsy. The committee, therefore, considered it good practice to assess these areas of a person's health when they are assessed following a seizure.

The evidence showed that in children followed up for one to five years, unprovoked seizures result in 3.5 times the risk of a second seizure as no unprovoked seizures. One study showed that a temperature of over 38 degrees carries an odds of a second seizure that is double the odds observed with a temperature below 38 degrees. However, two studies also showed that a higher temperature can be a protective factor against premature mortality. They showed that people with higher temperatures have 0.3 to 0.8 times the risk of a second seizure, compared to lower temperatures.

No evidence was found in relation to other factors that the committee considered modifiable risk factors such as alcohol and recreational drug use and sleep deprivation. There are good pathophysiological reasons why these may cause seizures, and this is seen in clinical practice.

The committee agreed to emphasize that a comprehensive assessment of potential psychological, biological, and social risk factors should be carried out after a person's first seizure and that these risks, and advice on how they may be modified, should be discussed with the person, their family, or carers.

1.1.11.4 Cost effectiveness and resource use

No economic evidence was identified for this review question.

The committee discussed the clinical evidence noting the low quality of the evidence presented for determining risk factors of a second seizure for both adults and a paediatric population. The committee noted that in adults, underlying psychiatric disorders and sepsis are non-modifiable risk factors that may increase a person's risk of a second seizure. Therefore, the committee made a recommendation to assess the presence of these risk factors when presenting with an initial seizure.

The committee also discussed the clinical evidence presented for children, noting that children presenting with an initial afebrile seizure may be at increased risk of a second seizure.

The committee agreed that the recommendations made for adults are current best practice, but noted current practice varies. The committee estimated that only 25% of people presenting with an initial seizure are fully assessed for modifiable risk factors. In addition, the committee acknowledged that in current practice, biological risk factors are more likely to be reviewed than psychosocial risk factors.

The committee also acknowledged that in current practice, children presenting with an initial seizure will always be assessed to try and determine if they experienced an afebrile seizure. The committee noted that for those children presenting with an afebrile seizure, appropriate safety advice will be provided to the child's parent or carer, and urgent referral advice will be provided, which can be used if a child experiences a second seizure.

The committee noted that if people are not appropriately assessed for risk of a second seizure, this could have a negative impact on a person's quality of life in the long-term for those people who experience a second seizure. A first seizure may significantly impact a person's life (for example, through social interactions or driving privileges), but the committee also noted experiencing a second seizure can result in a more severe negative impact on a

person's QoL compared to those people only experiencing one initial seizure. The committee also noted people who were appropriately assessed for risk of a second seizure are less likely to experience such a significant impact on their overall QoL if they experience a second seizure compared to those who were not assessed. This is because making people aware of the risks of second seizure enables them to understand these risks and manage the future impact seizures may have on their lives. Conversely, people who are not aware of these risks may be unaware they are at risk of a second seizure. In addition, people who experience a second seizure and have not been informed of these risks may feel annoyed they were not appropriately informed when they presented with an initial seizure. An epilepsy diagnosis can significantly impact a person's daily living (for example, driving restrictions). Therefore, some people may perceive not being fully informed at the early stages of diagnosis pathway as 'lost time' in coming to terms with their diagnosis if they are later diagnosed with epilepsy.

The committee also acknowledged that not appropriately assessing a person's risk factors when presenting with initial seizure may result in some people experiencing increased anxiety. For example, a person presenting with an initial seizure may be at low risk of a second seizure but if this is not appropriately assessed and conveyed to the person presenting with an initial seizure, they may seek information on the internet that does not necessarily apply to them.

Overall, the committee concluded there will likely be a change in clinical practice for how a large proportion of adults are managed after their first seizure resulting in additional costs for the NHS. However, the recommendations are not expected to lead to a substantial resource impact because the assessment of risk factors does not take long and can be discussed and assessed with the clinician when a person presents with an initial seizure. This will not constitute an additional visit with a health care professional but may require some additional time with a clinician assessing the person who has presented with an initial seizure. The additional costs incurred by the NHS observed in the form of additional staff time will likely be offset by the QoL gains observed from providing people with the appropriate information regarding their individualised risk of a second seizure.

There is not expected to be a substantial resource impact associated with the recommendation made for children as this recommendation reflects current practice.

1.1.11.5 Other factors the committee took into account

The committee agreed it was important to highlight that modifying risk factors to prevent second seizures is a multifactorial process. This is because the exact reason why some of these risk factors have a direct impact on seizure occurrence is not completely understood.

The committee discussed that after a person has had a seizure it is important to provide information to the person, and their families or carers on how to recognise a further seizure and to give advice on first aid and any measures they could take to reduce their risk of another seizure, as well as who they should contact if they experience a further seizure before their first appointment with the epilepsy service.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.1 to 1.1.9 in the NICE guideline.

References

1. Arboix A, Garcia-Eroles L, Massons JB, Oliveres M, Comes E. Predictive factors of early seizures after acute cerebrovascular disease. Stroke. 1997; 28(8):1590-1594
2. Assis T, Bacellar A, Costa G, Pires E, Nascimento O. Predictors of early seizure recurrence among elderly inpatients admitted to a tertiary center: A prospective cohort study. Epilepsy & Behavior. 2019; 98(Pt A):145-152
3. Assis TM, Bacellar A, Costa G, Nascimento OJ. Mortality predictors of epilepsy and epileptic seizures among hospitalized elderly. Arquivos de Neuro-Psiquiatria. 2015; 73(6):510-515
4. Baldin E, Hauser WA, Pack A, Hesdorffer DC. Stress is associated with an increased risk of recurrent seizures in adults. Epilepsia. 2017; 58(6):1037-1046
5. Berg AT, Darefsky AS, Holford TR, Shinnar S. Seizures with fever after unprovoked seizures: an analysis in children followed from the time of a first febrile seizure. Epilepsia. 1998; 39(1):77-80
6. Berg AT, Shinnar S, Shapiro ED, Salomon ME, Crain EF, Hauser WA. Risk factors for a first febrile seizure: a matched case-control study. Epilepsia. 1995; 36(4):334-341
7. Bethune P, Gordon K, Dooley J, Camfield C, Camfield P. Which child will have a febrile seizure? American Journal of Diseases of Children. 1993; 147(1):35-39
8. Bhatia D, Mikulich-Gilbertson SK, Sakai JT. Prescription opioid misuse and risky adolescent behavior. Pediatrics. 2020; 145(2):e20192470
9. Bleich S, Degner D, Bandelow B, von Ahsen N, Ruther E, Kornhuber J. Plasma homocysteine is a predictor of alcohol withdrawal seizures. Neuroreport. 2000; 11(12):2749-2752
10. Chang TR, Kowalski RG, Carhuapoma JR, Tamargo RJ, Naval NS. Cocaine use as an independent predictor of seizures after aneurysmal subarachnoid hemorrhage. Journal of Neurosurgery. 2016; 124(3):730-735
11. Chen WC, Magill ST, Englot DJ, Baal JD, Wagle S, Rick JW et al. Factors associated with pre- and postoperative seizures in 1033 patients undergoing supratentorial meningioma resection. Neurosurgery. 2017; 81(2):297-306
12. Cheung ACK. Predictors of recurrent seizure before admission in children presented with seizure to emergency department. Hong Kong Journal of Emergency Medicine. 2015; 22(5):297-302
13. Chopra DA, Shah AB, Vadhariya AH, Painter JT. The risk of varenicline-induced seizure among those who have attempted to quit smoking using pharmacotherapy. Epilepsy & Behavior. 2019; 97:169-173
14. Chou IJ, Kuo CF, Tanasescu R, Tench CR, Tiley CG, Constantinescu CS et al. Epilepsy and associated mortality in patients with multiple sclerosis. European Journal of Neurology. 2019; 26(2):342-e323
15. Christensen J, Pedersen HS, Fenger-Gron M, Fann JR, Jones NC, Vestergaard M. Selective serotonin reuptake inhibitors and risk of epilepsy after traumatic brain injury - A population based cohort study. PloS One. 2019; 14(7):e0219137
16. Dayan PS, Lillis K, Bennett J, Conners G, Bailey P, Callahan J et al. Prevalence of and risk factors for intracranial abnormalities in unprovoked seizures. Pediatrics. 2015; 136(2):e351-360
17. De Herdt V, Dumont F, Henon H, Derambure P, Vonck K, Leys D et al. Early seizures in intracerebral hemorrhage: incidence, associated factors, and outcome. Neurology. 2011; 77(20):1794-1800
18. Delpisheh A, Veisani Y, Sayehmiri K, Fayyazi A. Febrile seizures: etiology, prevalence, and geographical variation. Iranian Journal of Child Neurology. 2014; 8(3):30-37
19. Dhakar MB, Sivakumar S, Bhattacharya P, Shah A, Basha MM. A retrospective cross-sectional study of the prevalence of generalized convulsive status epilepticus in traumatic brain injury: United States 2002-2010. Seizure. 2015; 32:16-22

20. Duncan R, Oto M. Predictors of antecedent factors in psychogenic nonepileptic attacks: multivariate analysis. Neurology. 2008; 71(13):1000-1005
21. Dworetzky BA, Bromfield EB, Townsend MK, Kang JH. A prospective study of smoking, caffeine, and alcohol as risk factors for seizures or epilepsy in young adult women: data from the Nurses' Health Study II. Epilepsia. 2010; 51(2):198-205
22. Eyer F, Schuster T, Felgenhauer N, Pfab R, Strubel T, Saugel B et al. Risk assessment of moderate to severe alcohol withdrawal--predictors for seizures and delirium tremens in the course of withdrawal. Alcohol and Alcoholism. 2011; 46(4):427-433
23. Hamerle M, Ghaeni L, Kowski A, Weissinger F, Holtkamp M. Alcohol use and alcohol-related seizures in patients with epilepsy. Frontiers in Neurology. 2018; 9:401
24. Huang CC, Wang ST, Chang YC, Huang MC, Chi YC, Tsai JJ. Risk factors for a first febrile convulsion in children: a population study in southern Taiwan. Epilepsia. 1999; 40(6):719-725
25. Hundozi Z, Shala A, Boshnjaku D, Bytyqi S, Rrustemi J, Rama M et al. Hypertension on admission is associated with a lower risk of early seizures after stroke. Seizure. 2016; 36:40-43
26. Hwang K, Joo JD, Kim YH, Han JH, Oh CW, Yun CH et al. Risk factors for preoperative and late postoperative seizures in primary supratentorial meningiomas. Clinical Neurology and Neurosurgery. 2019; 180:34-39
27. Hwang SL, Lin CL, Lee KS, Lieu AS, Kuo TH, Chang CZ et al. Factors influencing seizures in adult patients with supratentorial astrocytic tumors. Acta Neurochirurgica. 2004; 146(6):589-594
28. Jeon SM, Park S, Kim D, Kwon JW. Risk of seizures associated with antipsychotic treatment in pediatrics with psychiatric disorders: a nested case-control study in Korea. European Child and Adolescent Psychiatry. 2021; 30(3):391-399
29. 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 Neurology. 2018; 75(11):1375-1382
30. Kantamalee W, Katanyuwong K, Louthrenoo O. Clinical characteristics of febrile seizures and risk factors of its recurrence in chiang mai university hospital. Neurology Asia. 2017; 22(3):203-208
31. Kim HJ, Park KD, Choi KG, Lee HW. Clinical predictors of seizure recurrence after the first post-ischemic stroke seizure. BMC Neurology. 2016; 16(1):212
32. Kotsopoulos I, de Krom M, Kessels F, Lodder J, Troost J, Twellaar M et al. Incidence of epilepsy and predictive factors of epileptic and non-epileptic seizures. Seizure. 2005; 14(3):175-182
33. Kumar N, Midha T, Rao YK. Risk factors of recurrence of febrile seizures in children in a tertiary care hospital in kanpur: A one year follow up study. Annals of Indian Academy of Neurology. 2019; 22(1):31-36
34. Kumari PL, Nair MK, Nair SM, Kailas L, Geetha S. Iron deficiency as a risk factor for simple febrile seizures--a case control study. Indian Pediatrics. 2012; 49(1):17-19
35. Labovitz DL, Hauser WA, Sacco RL. Prevalence and predictors of early seizure and status epilepticus after first stroke. Neurology. 2001; 57(2):200-206
36. Li X, Breteler MM, de Bruyne MC, Meinardi H, Hauser WA, Hofman A. Vascular determinants of epilepsy: the Rotterdam Study. Epilepsia. 1997; 38(11):1216-1220
37. Mehta A, Zusman BE, Choxi R, Shutter LA, Yassin A, Antony A et al. Seizures after intracerebral hemorrhage: Incidence, risk factors, and impact on mortality and morbidity. World Neurosurgery. 2018; 112:e385-e392
38. Morais NM, Ranzan J, Riesgo RS. Predictors of epilepsy in children with cerebrovascular disease. Journal of Child Neurology. 2013; 28(11):1387-1391
39. Murray BP, Carpenter JE, Dunkley CA, Moran TP, Alfaifi M, Alsukaiti WS et al. Seizures in tramadol overdoses reported in the ToxIC registry: predisposing factors and the role of naloxone. Clinical Toxicology: The Official Journal of the American

Academy of Clinical Toxicology & European Association of Poisons Centres & Clinical Toxicologists. 2019; 57(8):692-696
40. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated October 2020]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview
41. Parmontree P, Tunthanathip T, Doungngern T, Rojpitbulstit M, Kulviwat W, Ratanalert S. Predictive risk factors for early seizures in traumatic brain injury. Journal of Neurosciences in Rural Practice. 2019; 10(4):582-587
42. Phabphal K, Geater A, Limapichat K, Sathirapanya P, Setthawatcharawanich S. Risk factors of recurrent seizure, co-morbidities, and mortality in new onset seizure in elderly. Seizure. 2013; 22(7):577-580
43. Pugh MJ, Knoefel JE, Mortensen EM, Amuan ME, Berlowitz DR, Van Cott AC. New-onset epilepsy risk factors in older veterans. Journal of the American Geriatrics Society. 2009; 57(2):237-242
44. Rantala H, Uhari M. Risk factors for recurrences of febrile convulsions. Acta Neurologica Scandinavica. 1994; 90(3):207-210
45. Reith J, Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Seizures in acute stroke: predictors and prognostic significance. The Copenhagen Stroke Study. Stroke. 1997; 28(8):1585-1589
46. Shinnar S, Berg AT, Moshe SL, O'Dell C, Alemany M, Newstein D et al. The risk of seizure recurrence after a first unprovoked afebrile seizure in childhood: an extended follow-up. Pediatrics. 1996; 98(2 Pt 1):216-225
47. Sittichanbuncha Y, Chomrak C, Naksensin W, Sawanyawisuth K. Seizures at the emergency department in thailand and risk factors for recurrent seizures. Neurology Asia. 2015; 20(2):139-142
48. Skardelly M, Brendle E, Noell S, Behling F, Wuttke TV, Schittenhelm J et al. Predictors of preoperative and early postoperative seizures in patients with intra-axial primary and metastatic brain tumors: A retrospective observational single center study. Annals of Neurology. 2015; 78(6):917-928
49. Skardelly M, Rother C, Noell S, Behling F, Wuttke TV, Schittenhelm J et al. Risk factors of preoperative and early postoperative seizures in patients with meningioma: A retrospective single-center cohort study. World Neurosurgery. 2017; 97:538-546
50. Stimmel GL, Dopheide JA. Psychotropic drug-induced reductions in seizure threshold. Incidence and consequences. CNS Drugs. 1996; 5(1):37-50
51. Tosun A, Koturoglu G, Serdaroglu G, Polat M, Kurugol Z, Gokben S et al. Ratios of nine risk factors in children with recurrent febrile seizures. Pediatric Neurology. 2010; 43(3):177-182
52. Turon M, Abraira L, Cazorla S, Fonseca E, Quintana M, Toledo M et al. Vascular risk factors as independent predictors of neurocognitive impairments in patients with late-onset epilepsy who have small-vessel disease. Epilepsy & Behavior. 2020; 104(Pt B):106443
53. Vaaramo K, Puljula J, Tetri S, Juvela S, Hillbom M. Predictors of new-onset seizures: a 10-year follow-up of head trauma subjects with and without traumatic brain injury. Journal of Neurology, Neurosurgery and Psychiatry. 2014; 85(6):598-602
54. Wolpert F, Lareida A, Terziev R, Grossenbacher B, Neidert MC, Roth P et al. Risk factors for the development of epilepsy in patients with brain metastases. Neuro-Oncology. 2020; 22(5):718-728
55. Wu CS, Liu HY, Tsai HJ, Liu SK. Seizure risk associated with antidepressant treatment among patients with depressive disorders: A population-based case-crossover study. Journal of Clinical Psychiatry. 2017; 78(9):e1226-e1232
56. Wu CS, Wang SC, Yeh IJ, Liu SK. Comparative risk of seizure with use of first- and second-generation antipsychotics in patients with schizophrenia and mood disorders. Journal of Clinical Psychiatry. 2016; 77(5):e573-579

57. Xue H, Sveinsson O, Bartek J, Jr., Forander P, Skyrman S, Kihlstrom L et al. Long-term control and predictors of seizures in intracranial meningioma surgery: a population-based study. Acta Neurochirurgica. 2018; 160(3):589-596

Appendices

Appendix A Review protocols

A.1 Review protocol for modifiable risk factors for second seizure

ID	Field	Content
0.	**PROSPERO registration number**	Not registered
1.	**Review title**	Modifiable risk factors for a further seizure after a first seizure, and the magnitude of risk of those factors.
2.	**Review question**	What are the modifiable risk factors for a further seizure after a first seizure, and what is the magnitude of risk of those factors?
3.	**Objective**	To identify the modifiable variables that have an independent association with repeat seizure incidence, in a population of people who have had a single seizure. To identify the strength of those independent associations.
4.	**Searches**	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language Other searches: • None The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	**Condition or domain being studied**	Epilepsies

6.	**Population**	Inclusion: People with a history of a single seizure (as determined by specialist). These people, by definition, are unlikely to have a fixed diagnosis of epilepsy. Exclusion: New-born babies with acute symptomatic seizures
7.	**Risk factors (although the ideal study will have included all these factors, for inclusion a study need only evaluate one risk factor)**	• Vascular disease (Y/N) • Blood pressure (continuous or binary threshold as set in papers) • Activity/exercise levels (binary threshold as set in papers) • Alcohol/ recreational drugs (binary threshold as set in papers) • Psychological factors / stress (binary threshold as set in papers) • Psychosocial factors (binary threshold as set in papers) • Sleep deprivation (binary threshold as set in papers) • AED use (binary threshold as set in papers) • Other drugs that reduce seizure threshold (binary threshold as set in papers) • Tumours (binary threshold as set in papers) • Drugs affecting sleep (binary threshold as set in papers) • Systemic illness (i.e., autoimmune disorders) (binary threshold as set in papers)
8.	**Key confounding factors (that have to be adjusted for)**	No key confounders that have to be adjusted for have been identified, but the analysis report must demonstrate that it has tried to avoid bias arising from plausible potential confounders by an appropriate method such as regression/ANCOVA, stratification, or propensity matching. If all plausible confounders are shown to be reasonably matched at baseline (if the study is a simple RF/no RF design) this will also be regarded as adequate. **However, we will downgrade for indirectness if at least 2 of the other modifiable confounders have not been adjusted for.**
9.	**Types of study to be included**	A longitudinal design, such as prospective/retrospective cohort studies. Case control studies will be allowed, provided they meet criteria in row 8.
10.	**Other exclusion criteria**	Cross-sectional studies Papers that have not attempted to adjust for key potential confounding variables Non-English language studies.
11.	**Context**	It is believed that second seizures may be preventable, partly by attention to altering modifiable risk factors. This review therefore sets out to identify the modifiable risk factors for second seizure.

12.	**Primary outcomes (critical outcomes)**	Second seizure (as determined by specialist) Follow up: use all available but stratify: <6 months, 6-12 months, 1-5 years, >5 years
13.	**Secondary outcomes (important outcomes)**	None
14.	**Data extraction (selection and coding)**	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of these potentially eligible studies will be retrieved and assessed in line with the criteria outlined above. A standardised form will be used to extract data from the included studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: papers were included /excluded appropriately a sample of the data extractions correct methods are used to synthesise data a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Adjusted measures of effect (i.e., adjusted HRs, ORs) will be extracted, with a note of the variables adjusted for.
15.	**Risk of bias (quality) assessment**	Risk of bias quality assessment will be assessed using QUIPS. 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.

16.	**Strategy for data synthesis**	Where possible suitably adjusted data will be meta-analysed where appropriate. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.
17.	**Analysis of sub-groups**	*Non-conditional stratification* Follow up: <6 months, 6-12 months, 1-5 years, >5 years Children (<18yrs) vs adult (18 years or over) *Conditional stratification* If heterogeneity is identified, where data is available, subgroup analysis will be carried out for the following subgroups: • Young stratum subgroups: <2, 2-11, 11-18; Adult stratum subgroups: 18-55, >55 • Learning disability vs, no learning disability • Head injury vs no head injury • Type of epilepsy • gender
18.	**Type and method of review**	☐ Intervention ☐ Diagnostic ☒ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	**Language**	English
20.	**Country**	England

21.	**Anticipated or actual start date**			
22.	**Anticipated completion date**			
23.	**Stage of review at time of this submission**	Review stage	Started	
		Preliminary searches	☐	
		Piloting of the study selection process	☐	
		Formal screening of search results against eligibility criteria	☐	
		Data extraction	☐	
		Risk of bias (quality) assessment	☐	
		Data analysis	☐	
24.	**Named contact**	Named contact • National Guideline Centre Named contact e-mail: • NGCEpilepsies@nice.org.uk		

		Organisational affiliation of the review • National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	**Review team members**	From the National Guideline Centre:
26.	**Funding sources/sponsor**	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	**Conflicts of interest**	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	**Collaborators**	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112.
29.	**Other registration details**	N/A
30.	**Reference/URL for published protocol**	
31.	**Dissemination plans**	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. [Add in any additional agree dissemination plans.]
32.	**Keywords**	Epilepsies, risk factors, seizure

33.	**Details of existing review of same topic by same authors**	N/A
34.	**Current review status**	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35.	**Additional information**	N/A
36.	**Details of final publication**	www.nice.org.uk

A.2 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2004 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[40] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with "Minor limitations" then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with "Very serious limitations" then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies.

	Setting: • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 (including any such studies included in the previous guideline(s)) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

This literature search strategy was used for the following reviews:

- What are the modifiable risk factors for a further seizure after a first seizure, and what is the magnitude of risk of those factors?
- What are the modifiable risk factors for epilepsy-related mortality, including SUDEP, and what is the magnitude of risk of the factors?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[40]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using the following approach:

- Population AND risk factor terms

Table 20: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 30 October 2020	Exclusions
Embase (OVID)	1974 – 30 October 2020	Exclusions

Medline (Ovid) search terms

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.

24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	exp risk/
28.	Risk factors/
29.	Prevalence/
30.	Incidence/
31.	(risk* or prevalence* or incidence* or predict* or associat*).ti.
32.	risk factors.ab.
33.	or/27-32
34.	26 and 33

Embase (Ovid) search terms

1.	exp epilepsy/
2.	seizure/
3.	epileptic state/
4.	febrile convulsion/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	risk/
26.	Risk factors/
27.	Prevalence/
28.	Incidence/
29.	(risk* or prevalence* or incidence* or predict* or associat*).ti.
30.	risk factors.ab.
31.	or/25-30
32.	24 and 31

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to an Epilepsies population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and quality of life studies.

Table 21: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	Health Economics 1 January 2014 – 13 May 2021 Quality of Life 1946 – 13 May 2021	Health economics studies Quality of life studies Exclusions
Embase	Health Economics 1 January 2014 – 13 May 2021 Quality of Life 1974 – 13 May 2021	Health economics studies Quality of life studies Exclusions
Centre for Research and Dissemination (CRD)	HTA - Inception – 13 May 2021 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/

22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	quality-adjusted life years/
45.	sickness impact profile/
46.	(quality adj2 (wellbeing or well being)).ti,ab.
47.	sickness impact profile.ti,ab.
48.	disability adjusted life.ti,ab.
49.	(qal* or qtime* or qwb* or daly*).ti,ab.
50.	(euroqol* or eq5d* or eq 5*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/44-61
63.	26 and (43 or 62)

Embase (Ovid) search terms

1.	exp *epilepsy/
2.	*landau kleffner syndrome/

3.	exp *seizure/
4.	"seizure, epilepsy and convulsion"/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	quality adjusted life year/
40.	sickness impact profile/
41.	(quality adj2 (wellbeing or well being)).ti,ab.
42.	sickness impact profile.ti,ab.
43.	disability adjusted life.ti,ab.
44.	(qal* or qtime* or qwb* or daly*).ti,ab.
45.	(euroqol* or eq5d* or eq 5*).ti,ab.
46.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.

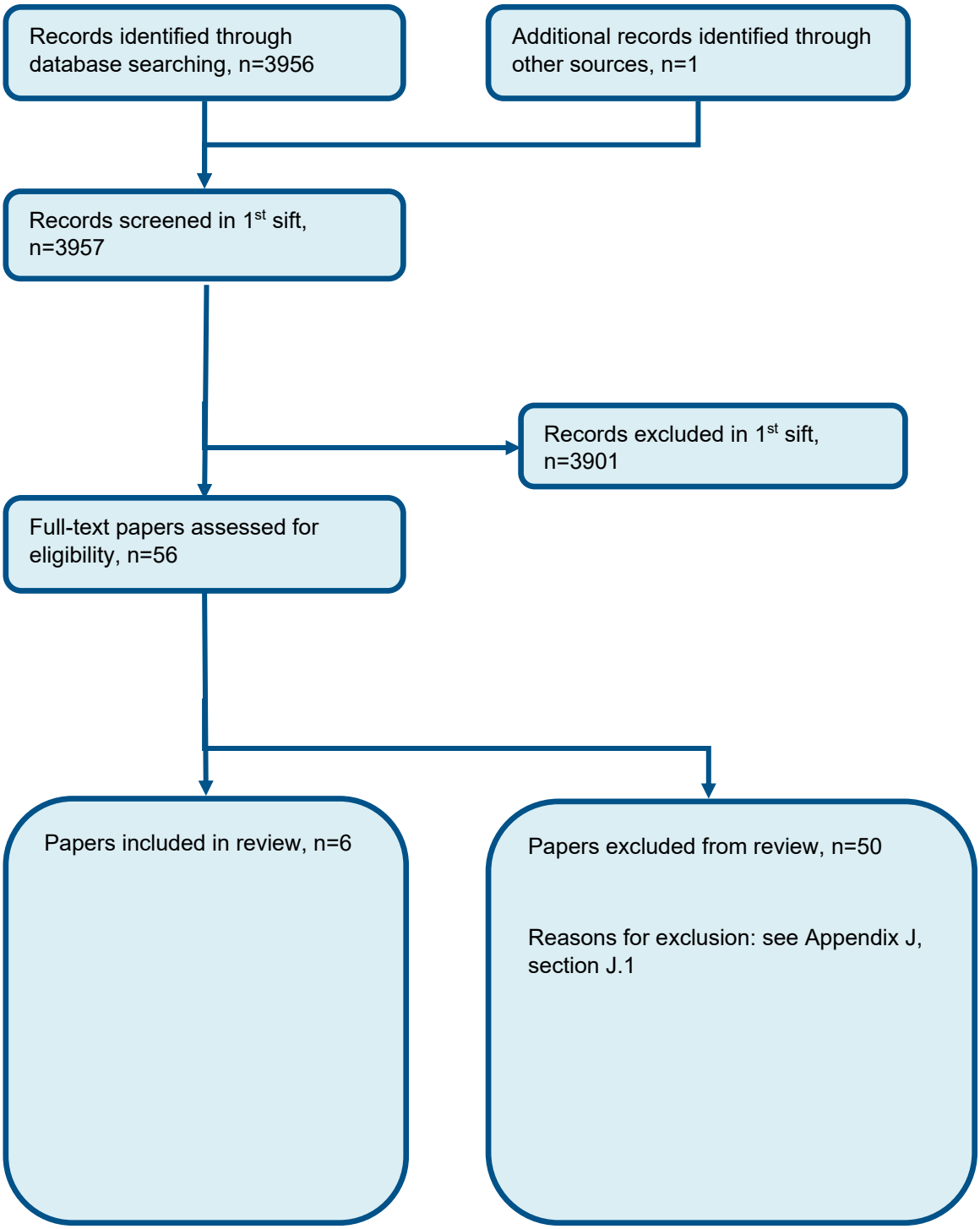
47.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
48.	(hui or hui1 or hui2 or hui3).ti,ab.
49.	(health* year* equivalent* or hye or hyes).ti,ab.
50.	discrete choice*.ti,ab.
51.	rosser.ti,ab.
52.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
53.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
54.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
55.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
56.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
57.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
58.	or/39-57
59.	24 and (38 or 58)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Epilepsy EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Seizures EXPLODE ALL TREES
#3.	MeSH DESCRIPTOR Status Epilepticus EXPLODE ALL TREES
#4.	MeSH DESCRIPTOR Seizures, Febrile EXPLODE ALL TREES
#5.	((dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome))
#6.	#1 OR #2 OR #3 OR #4 OR #5

Appendix C Prognostic evidence study selection

Figure 1: Flow chart of clinical study selection for the review of modifiable risk factors for second seizure



Appendix D Prognostic evidence

Reference	**Assis 2019[2]**
Study type and analysis	Prospective, cohort, single-centre study with multivariate analysis of the risk factors for early seizure recurrence
Number of participants and characteristics	N = 109 Patients aged ≥60 years who were consecutively admitted to Hospital São Rafael, a general tertiary teaching hospital with 356 beds in Salvador, Brazil, between November 2015 and April 2018. Inclusion criteria: Elderly inpatients with seizures that either led to their hospital admission or occurred during a period of care in the emergency room or during hospitalization. All patients were under the care of a neurological team. Exclusion criteria: The exclusion criteria consisted of (1) elderly inpatients who had been admitted with a diagnosis of seizure that had not been confirmed Or who were later diagnosed with other paroxysmal neurological disorders such as syncope, delirium, or transient ischemic attack; (2) patients who had seizures in the setting of an acute traumatic brain injury (TBI) and were followed up by the neurosurgery service; and (3) patients who were lost to follow-up. Late-onset seizures/epilepsy were conventionally defined as seizures first occurring in subjects older than 60 years. New-onset seizures were defined as a first-ever seizure, including acute symptomatic seizures or unprovoked seizures, occurring at the time of the study. Unprovoked seizure was defined as a seizure occurring in the absence of precipitating factors and that may have been caused by a static or progressive injury. First unprovoked seizure might be considered epilepsy in special situations or in cases of relapse. The index seizure was the seizure that led the patient to be included in the study.

Reference	**Assis 2019[2]**		
	Early recurrent seizure was defined as a second seizure event, unprovoked, and separated from the first seizure by more than 24 h up to the 30th day after the index seizure. Early recurrent seizure assessment (up to 30 days) was prospectively performed through scrutiny of the inpatient medical records or via telephone interview for patients who had been discharged from the hospital.		
	Mean age: 75.9±9.6 years M/F ratio: 61/48		
Prognostic variable	Sepsis, psychiatric disorders		
Confounders	Univariate analysis	Multivariate analysis	
	Comorbidities	Cardiac Arrhythmias	
	Neurological disorders	Sepsis	
	Clinical disorders	Psychiatric Disorders	
		Other factors which were significant in univariate analysis were also included but have not been specified.	
Outcomes and effect sizes	Multivariate analysis of the risk factors for Second seizure (adjusted odds ratio and final p values according to the Wald statistic)		
		Odd ratio (95% CI)	p value
	Sepsis	4.52 (1.42–14.36)	0.011
	Psychiatric disorders	2.88 (1.09–7.60)	0.032
Comments	Risk of bias – High (assessed with the QUIPS checklist)		

Reference	Assis 2019[2]
	The paper states that it included any factors that were significant from univariate analysis within the multivariate analysis. Independent variables were considered for multivariate analysis if the variable was recognised as being plausible according to the main study hypothesis and when bivariate test showed a p value of 0.25 or less. The risk factor of cardiac arrhythmias was not included as it was not a relevant modifiable risk factor. 22 out of the 103 patients over the age of 60 had a previous diagnosis of epilepsy at the time of hospital admission.

Reference	Baldin 2017[4]
Study type and analysis	Retrospective cohort study with multivariable Cox regression
Number of participants and characteristics	N=52, USA Inclusion: An unprovoked seizure was defined as a seizure or multiple seizures within a 24hr period without an identified proximate precipitant. Newly diagnosed subjects were followed for 2 years to assess seizure recurrence. Patients were found through emergency department records from Columbia Presbyterian Medical Centre and its community hospital (The Allen Pavilion), St. Luke's-Roosevelt Hospital Centre, and Mount Sinai Medical Centre. This covered residents of Northern Manhattan and Harlem (New York City). Exclusion: People with incident acute symptomatic seizures and incident or recurrent febrile seizures. Subjects residing in zip codes outside the community and children younger than 18 years of age were also excluded. Screening for potential incident subjects was done weekly by two research assistants. After a review of medical records for potential incident subjects, those judged eligible received a letter signed by the ED director or their attending physician. After 2 weeks, if the potential subjects had not called to refuse, they were telephoned by a research assistant to confirm eligibility, using a semi structured seizure screen, and to invite eligible individuals to participate. Patients were followed up over a 2-year period, subjects were interviewed over the phone every 4 months about any new seizures and their medical care for seizures. A recurrent seizure was defined as the first unprovoked seizure occurring >24h after the first unprovoked seizure or epilepsy diagnosis.

Reference	Baldin 2017[4]	
	Age at index date; median (IQR): 55.3 (28.2 – 75.8) M / F ratio: 28 / 24	
	Seizure recurrence	
	Yes	20
	no	32
	Time to recurrence (months)	
	Median (IQR)	12.2 (3.7 – 12.2)
	Annual household income	
	<$15,000	17
	$15,000-49,999	31
	≥50,000	4
	Obesity	
	Yes	13
	No	35
	Hypertension	
	Yes	20
	No	29
	Lifetime major depressive episode	
	Yes	11

Reference	**Baldin 2017[4]**		
	No	41	
	Lifetime generalized anxiety disorder		
	Yes	6	
	No	46	
	Lifetime mood disorders		
	Yes	17	
	No	35	
Prognostic variable(s)	Lifetime generalized anxiety disorder Lifetime mood disorder		
Confounders OR Stratification strategy	Multivariate analysis		
	Lifetime generalized anxiety disorder	All outcomes were adjusted for age at diagnosis and gender	
	Lifetime mood disorder		
Outcomes and effect sizes	Multivariable Cox regression for second seizure with mood disorders and generalized anxiety disorders.		
	Lifetime generalized anxiety disorder (Adjusted HR (95% CI))		
	Yes	2.4 (0.8 – 7.7)	p value 0.1
	No	1.0 (reference)	
	Lifetime mood disorder (Adjusted HR (95% CI))		
	Yes	1.9 (0.8 – 4.7)	p value 0.2
	No	1.0 (reference)	

Reference	**Baldin 2017[4]**
Comments	Risk of bias – Moderate (assessed with the QUIPS checklist)

Reference	**Kim 2016[31]**			
Study type and analysis	Retrospective cohort study with multivariate logistic regression analysis			
Number of participants and characteristics	n= 124 Among a total of 3792 consecutive patients admitted to Ewha Womans University Hospital between 2001 and 2012 due to cerebral infarction, 124 post-stroke seizure after ischemic stroke patients (PSSi) were included in this study. Data were obtained from medical records of their routine care for stroke and seizure at admission and outpatient department visits. The study endpoint of each individual was the last outpatient visit or seizure recurrence. Mean follow-up duration was 44.4 months from relevant ischemic stroke insult and 29.9 months from PSSi onset. Seizure was diagnosed clinically, and distinguished as being partial or generalized, according to the 2010 International League Against Epilepsy (ILAE) criteria. Consequently, non-convulsive electroencephalographic (EEG) seizure was ruled out. Simple loss of consciousness or short-lasting episodes of mental confusion was not considered as sufficient for epileptic seizure diagnosis. Status epilepticus was defined as one continuous and unremitting seizure lasting for more than 5 min or recurrent seizures without restoration of consciousness for greater than 5 min. The recurred second seizure event was unprovoked and separated from the first one by more than 24 h according to the epilepsy definition			
		Total (n=124)	Early onset (n=48)	Late onset (n=76)
	Age (years), median (IQR)	68.0 (57.0 – 75.0)	68.0 (55.5 – 75.8)	69.0 (59.0 – 74.5)
	M/F ratio	69/55	9/19	40/36
	Diabetes Mellitus	44	20	24

Reference	**Kim 2016[31]**				
	Hypertension		89	33	56
	Atrial Fibrillation		36	8	28
	Lesion size	Small	10	7	3
		Moderate	31	17	14
		Large	83	24	59
	Functional Disability	Mild	28	16	12
		Moderate	35	6	29
		Severity	61	26	35
	Status Epilepticus		33	13	20
	EEG findings	Normal	20	9	11
		Generalized slow	17	9	8
		Regional slow	59	19	40
		Epileptiform discharge	20	8	12
	Clinical seizure type	Generalized	68	23	45
		Partial	56	24	31
	Seizure recurrence		54	17	37
Prognostic variable(s)	Post- ischemic stroke seizures				
Confounders OR Stratification strategy	Age				

Reference	**Kim 2016[31]**				
	Male gender				
	Diabetes Mellitus				
	Hypertension				
	Atrial Fibrillation				
	Lesion size				
	Cortical involvement				
	Haemorrhagic transformation				
	Functional disability				
	Status Epilepticus				
	Relevant EEG findings				
	Partial Seizure type				
Outcomes and effect sizes	Multivariable analysis for clinical characteristics related to seizure recurrence after late onset of post ischemic stroke seizure				
			Seizure recurrence	OR (95% CI)	p value
	Diabetes Mellitus		4	0.346 (0.038 – 3.167)	0.347
	Hypertension		10	0.353 (0.039–3.206)	0.355
	Atrial Fibrillation		5	10.451 (0.609–179.306)	0.106
	Functional disability	Mild	4	Not reported	0.402
		Moderate	2	0.386 (0.015–9.788)	0.564

Reference	**Kim 2016[31]**				
		Severe	11	3.517 (0.349–32.620)	0.293
	Status epilepticus		5	1.077 (0.151–7.673)	0.941
	Partial seizure type		11	4.619 (0.546–38.873)	0.159
Comments	Risk of bias – Low (assessed with the QUIPS checklist) For functional disability, no functional disability was assumed as the reference				

Reference	**Berg 1998[5]**		
Study type and analysis	Prospective cohort study with Cox regression model		
Number of participants and characteristics	n= 428 Inclusion and exclusion criteria Only children with a first febrile seizure, a temperature of ≥101F, no evidence of intracranial infection, and no history of unprovoked seizures were eligible. Parents were interviewed by telephone, and information about department visits was obtained through review of medical records. Parents were then telephoned every 3 months to ascertain the occurrence of any subsequent seizures and provocations for those seizures. Children with first febrile seizures were prospectively identified through the emergency departments of Bronx Municipal, Montefiore Hospital, and North Central Bronx Hospital in Bronx, New York from June 1989 through June 1991 and from Yale New Haven Hospital in New Haven, Connecticut from June 1989 through January 1992. Exclusion criteria not specified		
	Variable		N
	Age first febrile seizure (months)	<18	218
		18 – 23	81

Reference	**Berg 1998[5]**		
		24 – 29	49
		30 – 35	25
		36 – 41	18
		42 – 47	11
		≥48	26
	Family history of febrile seizures (1st degree relatives)	No	315
		Yes	106
	Temperature at hospital at time of first febrile seizure, F (C)	101 (38.3)	34
		102 (38.9)	87
		103 (39.4)	113
		104 (40.0)	127
		105 (40.6)	54
	Unprovoked seizure as second seizure ever	No	416
		Yes	12
Prognostic variable(s)	Temperature Unprovoked seizures		
Confounders OR Stratification strategy	Age Family history Duration of fever		

Reference	**Berg 1998[5]**	
	Temperature Unprovoked seizure	
Outcomes and effect sizes	Multivariate analysis of predictors of a second seizure with fever, Risk Ratio (95% CI)	
	Temperature per F	0.79 (0.68 – 0.91)
	Unprovoked Seizure	3.47 (1.61 – 7.49)
Comments	Risk of bias – High (assessed with the QUIPS checklist) Indirectness	

Reference	**Cheung 2015[12]**	
Study type and analysis	Retrospective cohort analysis with binomial logistic regression	
Number of participants and characteristics	N=650 Inclusion and exclusion criteria The study period was from 1st January 2008 to 31st December 2012. All children aged below 6 years presented with seizure attended A&E who required admissions to paediatric ward were included. All children presented with at least one episode of seizure before arriving A&E. Patients' records were traced through the hospital electronic database of a district hospital in Hong Kong. Exclusion criteria not specified	
	Patient characteristics	Total (n=650)
	Age on presentation (months in median [IQR])	28 [18-41.3]
	Temperature in A&E (°C in median [IQR])	38.7 [37.7-39.4]
	Age of first seizure (months in median [IQR])	19 [13-28]

Reference	**Cheung 2015[12]**		
	Male / female ratio		386 / 264
	Fever in A&E (≥38°C)		464
	Duration of pre-hospital seizure	<5 minutes	541
		5-15 minutes	92
		>15 minutes	17
	Duration of pre-hospital fever	None	109
		<1 day	44
		≥1 day	101
	History of brain insult		32
	History of febrile seizure		241
	History of epilepsy		81
	Family history of epilepsy		37
	More than one seizure before A&E arrival		15
Prognostic variable(s)	Fever in A&E (≥38°C)		
Confounders OR Stratification strategy	Pre-hospital seizure duration between 5-15 minutes Pre-hospital seizure duration more than 15 minutes History of prematurity History of epilepsy Fever in A&E (≥38°C)		

Reference	**Cheung 2015[12]**	
	Paracetamol taken within 4 hours on A&E arrival History of brain insult	
Outcomes and effect sizes	Logistic regression of seizure recurrence (second seizure after first seizure pre-hospital admission)	
	Predictor	Odds ratio (95% CI)
	Fever in A&E (≥38°C)	2.072 (1.071-4.013)
Comments	Risk of bias – Moderate (assessed with the QUIPS checklist) Indirectness	

Reference	**Kumar 2019[33]**	
Study type and analysis	Prospective cohort study with multiple logistic regression	
Number of participants and characteristics	N=528 Study participants included children between 6 months and 5 years, presenting with seizure accompanied by fever, that is, a core body temperature (rectal temperature) of 100.4°F or 38°C, without central nervous system infection whose parents had given written informed consent. All children attending the department from February 2015 to January 2016 presenting with first febrile seizures were included in the study and followed up for recurrence. Children with previous febrile seizures, unprovoked seizures, and children with intracranial infections were excluded from the study. Furthermore, those children whose parents did not give consent were excluded. Written informed consent was obtained from the parents of children who were included in the study. They were interviewed using a predesigned and pretested questionnaire. The questionnaire was administered by a single interviewer, who was a postgraduate student in the department of paediatrics, to all the participants included in the study. The questionnaire was translated into Hindi (local language), validated by professors of Hindi and English language and pretested before being administered.	
	Risk Factor	N
	Male / female ratio	201 / 327

Reference	**Kumar 2019[33]**		
	Age at first seizure (months)	<18	271
		≥18	257
	Duration of fever (hours)	<1	110
		≥1	478
	Temperature (°F)	101	40
		102	107
		103	139
		104	155
		≥105	87
	Family history of febrile seizures	Present	134
		Absent	394
	Type of seizure	Simple	340
		Complex	76
	Neurodevelopmental disorders	Present	17
		Absent	504
	Family history of epilepsy	Present	14
		Absent	514
Prognostic variable(s)	Temperature (during seizure) per ° Fahrenheit – compared to those without recurrent febrile seizures		
Confounders OR Stratification strategy	Gender		

Reference	**Kumar 2019[33]**	
	Age at first seizure	
	Temperature	
	Duration of fever	
	Family history of febrile seizures	
	Family history of epilepsy	
Outcomes and effect sizes	Multivariate logistic regression analysis for risk factors for recurrence of febrile seizure (second seizure)	
	Factor	OR (95% CI)
	Temperature (per ^{o}F)	0.34 (0.15 – 0.76)
Comments	Risk of bias – Moderate (assessed with the QUIPS checklist) Indirectness	

Appendix E Forest plots

E.1 Adults >18 years (follow up 1 – 5 years)

Figure 2: Lifetime generalized anxiety disorder

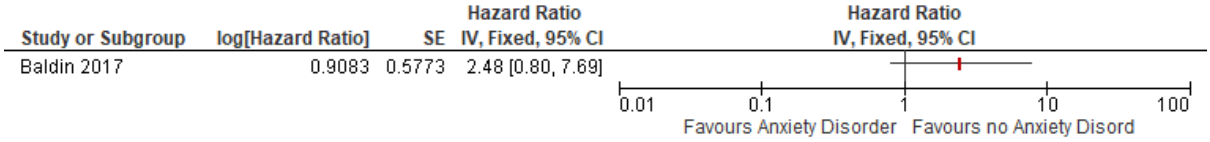


Figure 3: Lifetime mood disorder

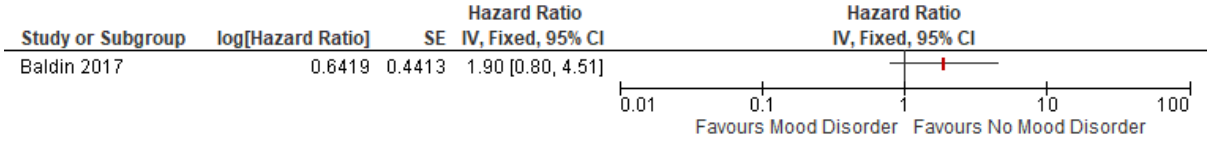


Figure 4: Psychiatric Disorders

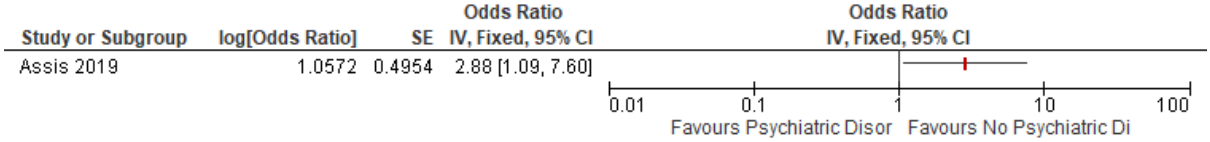
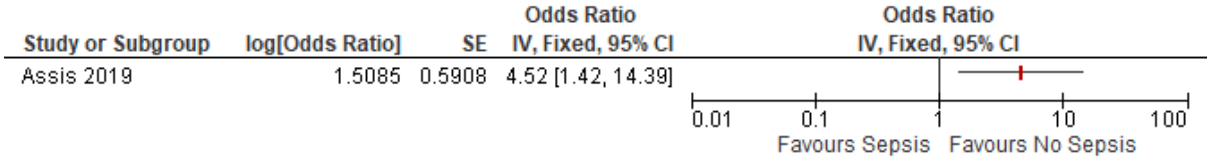


Figure 5: Sepsis



E.2 Adults >18 years (follow up >5 years)

Figure 6: Partial seizure type

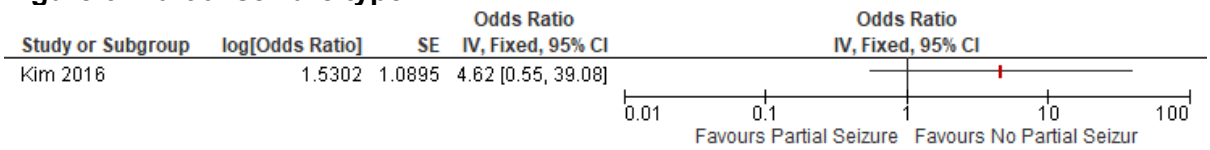


Figure 7: Status Epilepticus

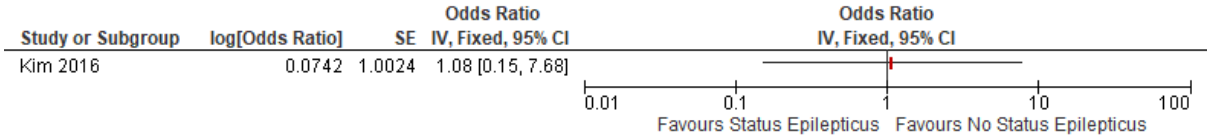


Figure 8: Diabetes Mellitus

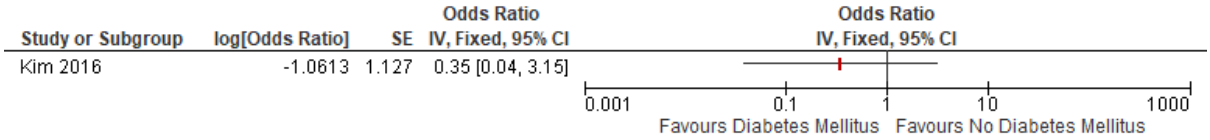


Figure 9: Hypertension

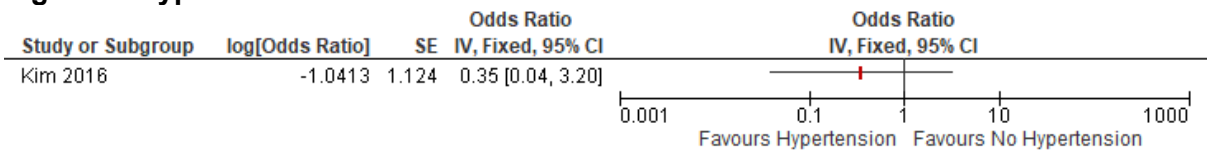


Figure 10: Atrial Fibrillation

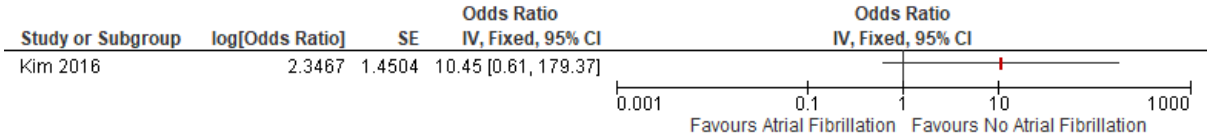


Figure 11: Functional Disability – Severe

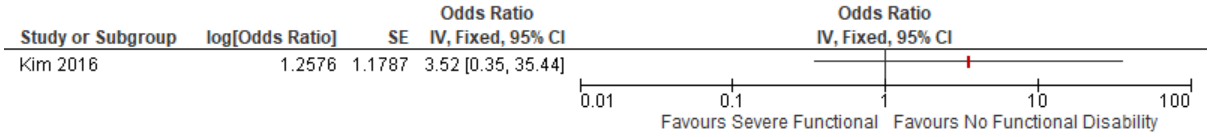
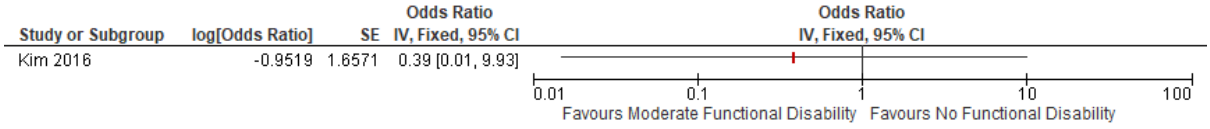


Figure 12: Functional Disability – Moderate



E.3 Children <18 years (follow up 1 – 5 years)

Figure 13: Unprovoked Seizures

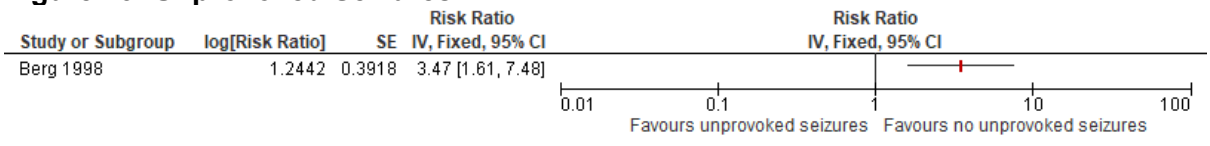


Figure 14: Temperature ≥38 degrees

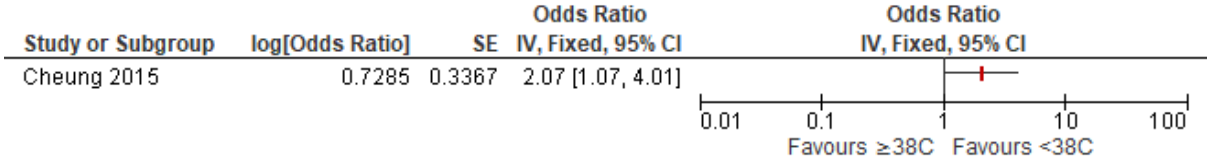


Figure 15: Temperature (per F increase)

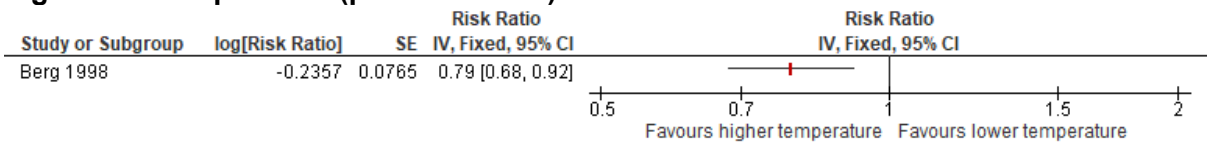
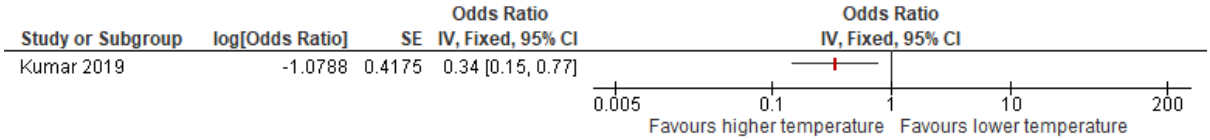


Figure 16: Temperature (per F increase)



Appendix F GRADE tables

F.1 Adults >18 years (follow up 1 – 5 years)

Table 22: Clinical evidence profile: Lifetime generalized anxiety disorder

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adult (f/u 1 - 5 years)	Control	Relative (95% CI)	Absolute		
Lifetime generalized anxiety disorder (follow-up 1-5 years)												
1	Observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	HR 2.48 (0.8 to 7.69)	-	⊕OOO VERY LOW[4]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Adjusted for age, gender, lifetime generalized anxiety disorder and lifetime mood disorder

Table 23: Clinical evidence profile: Lifetime mood disorder

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adult (f/u 1 - 5 years)	Control	Relative (95% CI)	Absolute		
Lifetime mood disorder (follow-up 1-5 years)												
1	Observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	HR 1.90 (0.8 to 4.51)	-	⊕OOO VERY LOW[4]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
[3] Downgraded by 1 increment if the confidence interval crossed the null line

[4] Adjusted for age, gender, lifetime generalized anxiety disorder and lifetime mood disorder

Table 24: Clinical evidence profile: Psychiatric Disorders

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adult (f/u 1 - 5 years)	Control	Relative (95% CI)	Absolute		
Psychiatric Disorders (follow-up 1-5 years)												
1	Observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	Adjusted OR 2.88 (1.09 to 7.60)	-	⊕⊕OO LOW[2]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Adjusted for multiple comorbidities, neurological disorders and clinical disorders

Table 25: Clinical evidence profile: Sepsis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adult (f/u 1 - 5 years)	Control	Relative (95% CI)	Absolute		
Sepsis (follow-up 1-5 years)												
1	Observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	Adjusted OR 4.52 (1.42 to 14.39)	-	⊕⊕OO LOW[2]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Adjusted for multiple comorbidities, neurological disorders and clinical disorders

F.2 Adults >18 years (follow up >5 years)

Table 26: Clinical evidence profile: Partial Seizure type

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adult (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Partial Seizure type (follow-up >5 years years)												
1	Observational studies	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	-	-	OR 4.62 (0.55 to 39.08)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
[2] Downgraded by 1 increment if the confidence interval crossed the null line
[3] Adjusted for age, male gender, diabetes mellitus, hypertension, atrial fibrillation, lesion size, cortical involvement, haemorrhagic transformation, functional disability, status epilepticus, relevant EEG findings, partial seizure type

Table 27: Clinical evidence profile: Status Epilepticus

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adult (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Status Epilepticus (follow-up >5 years)												
1	Observational studies	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	-	-	OR 1.08 (0.15 to 7.68)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
[2] Downgraded by 1 increment if the confidence interval crossed the null line
[3] Adjusted for age, male gender, diabetes mellitus, hypertension, atrial fibrillation, lesion size, cortical involvement, haemorrhagic transformation, functional disability, status epilepticus, relevant EEG findings, partial seizure type

Table 28: Clinical evidence profile: Diabetes Mellitus

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adult (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Diabetes Mellitus (follow-up >5 years)												
1	Observational studies	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	-	-	OR 0.35 (0.04 to 3.15)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
[2] Downgraded by 1 increment if the confidence interval crossed the null line
[3] Adjusted for age, male gender, diabetes mellitus, hypertension, atrial fibrillation, lesion size, cortical involvement, haemorrhagic transformation, functional disability, status epilepticus, relevant EEG findings, partial seizure type

Table 29: Clinical evidence profile: Hypertension

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adult (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Hypertension (follow-up >5 years)												
1	Observational studies	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	-	-	OR 0.35 (0.04 to 3.2)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
[2] Downgraded by 1 increment if the confidence interval crossed the null line
[3] Adjusted for age, male gender, diabetes mellitus, hypertension, atrial fibrillation, lesion size, cortical involvement, haemorrhagic transformation, functional disability, status epilepticus, relevant EEG findings, partial seizure type

Table 30: Clinical evidence profile: Atrial Fibrillation

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adult (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Atrial Fibrillation (follow-up >5 years)												
1	Observational studies	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	-	-	OR 10.45 (0.61 to 179.37)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
[2] Downgraded by 1 increment if the confidence interval crossed the null line
[3] Adjusted for age, male gender, diabetes mellitus, hypertension, atrial fibrillation, lesion size, cortical involvement, haemorrhagic transformation, functional disability, status epilepticus, relevant EEG findings, partial seizure type

Table 31: Clinical evidence profile: Functional Disability - severe

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Adult (f/u >5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
Functional Disability - Severe (follow-up >5 years)												
1	Observational studies	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	-	-	OR 3.52 (0.35 to 35.44)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
[2] Downgraded by 1 increment if the confidence interval crossed the null line
[3] Adjusted for age, male gender, diabetes mellitus, hypertension, atrial fibrillation, lesion size, cortical involvement, haemorrhagic transformation, functional disability, status epilepticus, relevant EEG findings, partial seizure type

Table 32: Clinical evidence profile: Functional Disability - moderate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Adult (f/u >5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
Functional Disability - Moderate (follow-up >5 years)												

1	Observational studies	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	-	-	OR 0.39 (0.01 to 9.93)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
[2] Downgraded by 1 increment if the confidence interval crossed the null line
[3] Adjusted for age, male gender, diabetes mellitus, hypertension, atrial fibrillation, lesion size, cortical involvement, haemorrhagic transformation, functional disability, status epilepticus, relevant EEG findings, partial seizure type

F.3 Children <18 years (follow up 1 – 5 years)

Table 33: Clinical evidence profile: Unprovoked Seizures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Children (f/u 1 - 5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
Unprovoked Seizures (follow-up 1 - 5 years)												
1	Observational studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	RR 3.47 (1.61 to 7.48)	-	⊕OOO VERY LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
[3] Adjusted for age, family history of epilepsy, duration of fever, temperature, unprovoked seizure

Table 34: Clinical evidence profile: Temperature ≥ 38^{O}C

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Children (f/u 1 - 5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
Temperature ≥38 (follow-up 1 - 5 years)												

1	Observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 2.07 (1.07 to 4.01)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
[3] Adjusted for pre-hospital seizure duration between 5 – 15 minutes and more than 15 minutes, history of prematurity, history of epilepsy, fever in A&E(≥38oC), paracetamol taken within 4 hours on A&E arrival, history of brain insult

Table 35: Clinical evidence profile: Temperature (per F increase)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Children (f/u 1 - 5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
Temperature (per F increase) (follow-up 1 - 5 years)												
1	Observational studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	RR 0.79 (0.68 to 0.92)	-	⊕OOO VERY LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders
[3] Adjusted for age, family history of epilepsy, duration of fever, temperature, unprovoked seizure

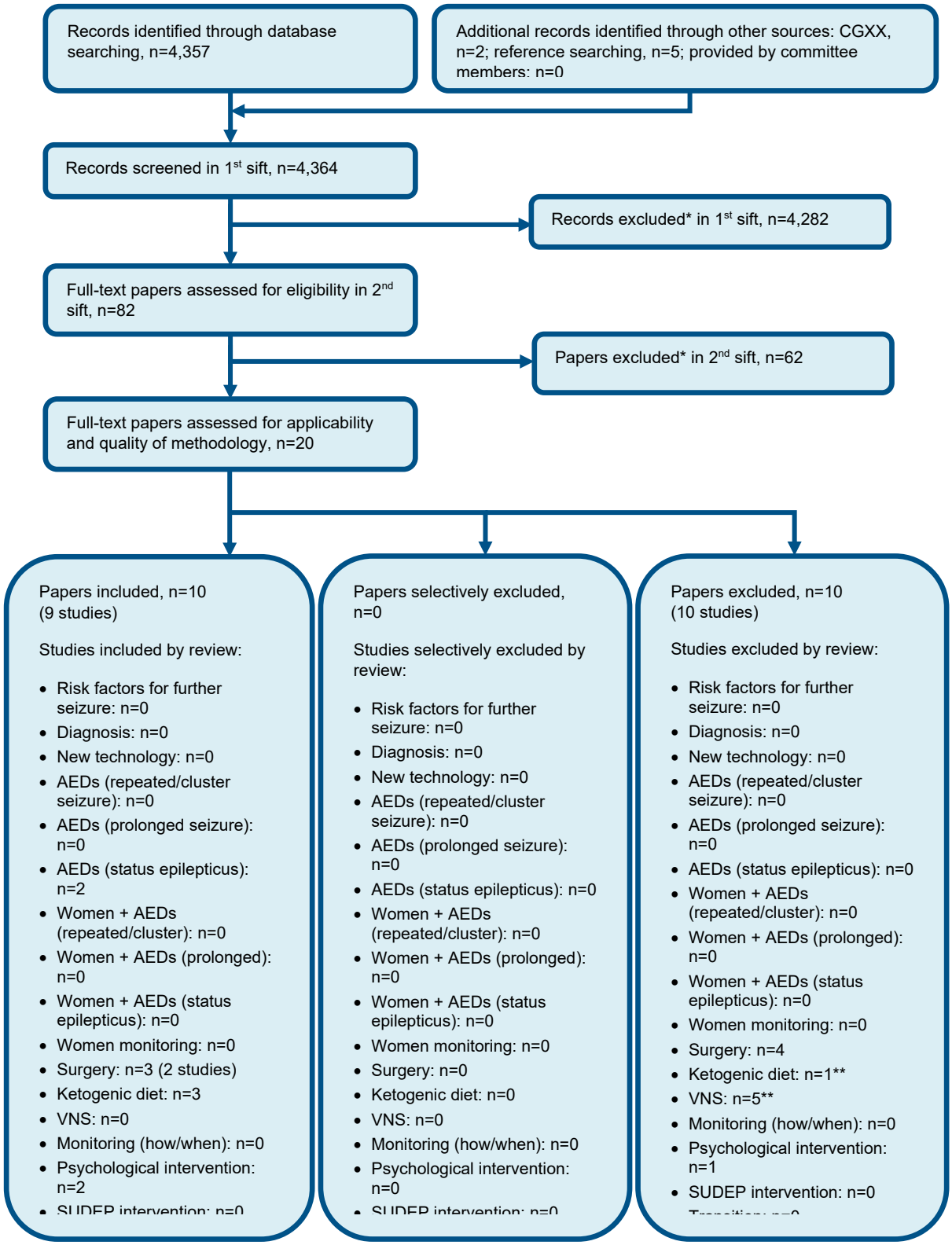
Table 36: Clinical evidence profile: Temperature (per F increase)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Children (f/u 1 - 5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
Temperature (per F increase) (follow-up 1 - 5 years)												
1	Observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 0.34 (0.15 to 0.77)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the modifiable confounders

[3] Adjusted for age at first seizure, gender, temperature, duration of fever, family history of febrile seizures, family history of epilepsy

Appendix G Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language
**Please note that 1 article related to two questions. For this reason, the numbers listed for each review may not total the number of full text articles assessed for applicability and quality of methodology.

Appendix H Economic evidence tables

None.

Appendix I Health economic model

No original economic modelling was undertaken for this review question.

Appendix J Excluded studies

J.1 Clinical studies

Table 37: Studies excluded from the clinical review

Reference	Reason for exclusion
Arboix 1997[1]	Inappropriate comparison – Multivariate analysis not for modifiable risk factors or second seizure
Assis 2015[3]	Inappropriate comparison and population – Multivariate analysis for factors associated with death in hospital after seizures for 60 years and above
Berg 1995 [6]	Inappropriate comparison and population – Multivariate analysis for risk factors for febrile seizures
Bethune 1993[7]	Inappropriate comparison and population – Multivariate analysis for first seizure
Bhatia 2020[8]	Inappropriate study design – Abstract
Bleich 2000[9]	Inappropriate comparison – factors associated with alcohol withdrawal seizures, not second seizure
Chang 2016[10]	Inappropriate comparison – Multivariate analysis for risk of seizures associated with cocaine use and surgery for aneurysmal subarachnoid haemorrhage
Chen 2017[11]	Inappropriate comparison – preoperative seizures associated with tumours, not second seizure
Chopra 2019[13]	Inappropriate comparison – seizures associated with Varenicline use
Chou 2019[14]	Inappropriate study design – investigating the association between Multiple Sclerosis and Epilepsy
Christensen 2019[15]	Inappropriate comparison – risk of seizures after traumatic brain injury
Dayan 2015[16]	Inappropriate comparison – Multivariate analysis not for modifiable risk factors or second seizure
De Herdt 2011[17]	Inappropriate comparison – factors associated with onset seizures in people with intracranial haemorrhage
Delpisheh 2014[18]	Systematic Review – references checked
Dhakar 2015[19]	Inappropriate comparison – Multivariate analysis not for second seizure
Duncan 2008[20]	Inappropriate population – mixed population with people diagnosed with epilepsy
Dworetzky 2010[21]	Inappropriate comparison – Multivariate analysis not for second seizure
Eyer 2011[22]	Inappropriate comparison – Multivariate analysis for seizures in relation to alcohol withdrawal syndrome
Hamerle 2018[23]	Inappropriate comparison and population – Multivariate analysis for seizures in consumption in people with epilepsy
Huang 1999[24]	Inappropriate comparison – Univariate analysis for first seizure
Hundozi 2016[25]	Inappropriate comparison – assessing seizure risk post stroke intervention
Hwang 2019[26]	Inappropriate comparison – assessing seizure risk post meningioma intervention
Hwang 2004[27]	Inappropriate comparison – assessing seizure risk on presentation with astrocytoma tumours

Reference	Reason for exclusion
Jeon 2021[28]	Inappropriate comparison – risk of new onset seizures with anti-psychotic commencement
Johnson 2018[29]	Inappropriate comparison – multivariate analysis of risk factors for late onset epilepsy (not for second seizure)
Kantamalee 2017[30]	Inappropriate comparison – multivariate analysis of non-modifiable risk factors for recurrent febrile seizures
Kotsopoulos 2005[32]	Inappropriate comparison – multivariate analysis of risk factors for epileptic and non-epileptic seizures
Kumari 2012 [34]	Inappropriate comparison – assessing correlation between iron deficiency anaemia and first seizure
Labovitz 2001[35]	Inappropriate comparison – risk factors of stroke which may cause early seizures
Li 1997[36]	Inappropriate comparison – multivariate analysis of risk factors for lifetime epilepsy
Mehta 2018[37]	Inappropriate comparison – multivariate analysis of risk factors for first seizure after intracerebral haemorrhage
Morais 2013[38]	Inappropriate comparison – multivariate analysis of risk factors for early or late first seizure after stroke
Murray 2019[39]	Inappropriate comparison – development of first seizure after tramadol usage
Parmontree 2019[41]	Inappropriate comparison – multivariate analysis of risk factors posttraumatic seizures after traumatic brain injury
Phabphal 2013[42]	Inappropriate comparison – multivariate analysis of non-modifiable risk factors for recurrent seizures
Pugh 2009[43]	Inappropriate comparison – multivariate analysis of new onset seizures in older population; not clear for second seizure
Rantala 1994[44]	Inappropriate comparison – analysis unclear for seizure recurrence
Reith 1997[45]	Inappropriate comparison – analysis of new onset or recurrent seizures after stroke
Shinnar 1996[46]	Inappropriate comparison – multivariate analysis of non-modifiable risk factors for first or recurrent seizures after febrile seizures
Sittichanbuncha 2015 [47]	Inappropriate population – people with known epilepsy; first or recurrent seizures
Skardelly 2015 [48]	Inappropriate comparison – risk factors for pre or post op seizures in patients with glioma
Skardelly 2017 [49]	Inappropriate comparison – risk factors for pre or post op seizures in patients with meningioma
Stimmel 1996[50]	Inappropriate study design – narrative review of psychotropic drugs which may reduce seizure threshold
Tosun 2010[51]	Inappropriate comparison – Multivariate analysis for risk factors for febrile seizures; unclear if for first or recurrent seizures
Turon 2020[52]	Inappropriate comparison – Risk factors which contribute to neurocognitive impairments after late onset epilepsy
Vaaramo 2014[53]	Inappropriate comparison and population – Multivariate analysis for risk factors for seizures after head injury; unclear if for first or recurrent seizures
Wolpert 2020[54]	Inappropriate comparison and population – Multivariate analysis for risk factors for seizures with brain metastases; unclear if for first or recurrent seizures
Wu 2017[55]	Inappropriate comparison and population – Multivariate analysis for risk factors for seizure while using antidepressant medication

Reference	Reason for exclusion
Wu 2016[56]	Inappropriate comparison and population – Multivariate analysis for risk factors for seizure while using antipsychotic medication
Xue 2018[57]	Inappropriate comparison and population – Multivariate analysis for risk factors for seizures with intracranial meningioma; unclear if for first or recurrent seizures

J.2 Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 38: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	