National Institute for Health and Care Excellence

FINAL

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

[18] Evidence review: Modifiable risk factors for epilepsy related mortality

NICE guideline NG217

Evidence reviews underpinning recommendations 10.1.1 to 10.1.4 and research recommendations in the NICE guideline.

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FINAL

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1 Modifiable risk factors for epilepsy-related mortality, including SUDEP, and the magnitude of risk of those factors

1.1 Review question

What are the modifiable risk factors for epilepsy-related mortality, including SUDEP, and what is the magnitude of risk of the factors?

1.1.1. Introduction

Epilepsy is associated with a number of risks, including a risk of injury, including head injury, and mortality in the form of drowning and accidents. One significant cause of epilepsy-related mortality is Sudden Unexpected Death in Epilepsy (SUDEP). Overall, the rate of SUDEP is around 1 in 1000 people with epilepsy per year.

This review examines modifiable risk factors for epilepsy-related mortality, including SUDEP, to inform the approach to the management of seizures and the provision of information to people with epilepsy, their families and carers.

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 diagnosis of epilepsy. Exclusion: New-born babies with acute symptomatic seizures
Prognostic variable(s) under consideration	• Sleeping unsupervised/living alone • Prone sleeping position • Uncontrolled/frequent Generalised Tonic Clonic Seizures (GTCS) • Nocturnal GTCS • Substance abuse/alcohol dependence • ASM polytherapy • Other drug polytherapy • Insufficient ASM therapy/any changes in prescription of drugs that could increase seizure rate • Sleep deprivation/irregular sleep
Confounding factors	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 (the modifiable factors listed above plus other non-modifiable factors) by an appropriate method
Outcomes	• Death, related to epilepsy • SUDEP Follow up: any available but stratify according to: <1 yr., 1-5 yrs., >5 yrs.
Study design	A longitudinal design, such as prospective/retrospective cohort studies. Case-control studies will be allowed, provided they meet criteria.

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

1.1.4.1. Included studies

Four cohort[7, 10, 22, 30] studies and seven case-control[15, 23, 26, 35, 36, 39, 40] studies assessing the modifiable risk factors for epilepsy-related mortality (including SUDEP) were included within the review.

The following modifiable risk factors were investigated, but not limited to:

- Sleeping unsupervised / living alone
- Prone sleeping position
- Uncontrolled/frequent Generalised Tonic Clonic Seizures (GTCS)
- Nocturnal GTCS
- Substance abuse/alcohol dependence
- Anti-seizure medication (ASM) polytherapy
- Other drug polytherapy
- Insufficient ASM therapy/any changes in prescription of drugs that could increase seizure rate
- Sleep deprivation / irregular sleep

Within the eleven studies included within the review, the risk factors considered were: different seizure types; comorbidities; seizure frequency; anti-seizure medications; changes to medications; substance abuse/alcohol dependence and psychosocial factors (education, living conditions and supervision).

Of the studies included, one[39] study looked at adults followed up over one to five years; three[10, 26, 30] studies assessed adults who were followed up for longer than five years; one[22] study investigated children who were followed up for over five years; one[7] study which looked at a mixed population of children and adults followed up between one to five years and five[15, 22, 35, 36, 40] studies with a mixed population who followed up the participants for over five years.

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.

1.1.4.2. 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
Walczak 2001[39]	Cases = 20 Controls = 80 Participants were prospectively enrolled after evaluation at three upper mid-western epilepsy centres. A surveillance system was set up to identify deaths in this prevalence cohort.	Prospective case control study with multivariate analysis	Number of seizures (number per month) Number of tonic-clonic seizures (per year)	Number of seizures (number per month) Number of tonic-clonic seizures (per year)	Risk of SUDEP	

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

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Comments
Faught 2008[10]	N=33,658 The study population was selected based on ≥18 years of age; ≥ one neurologist visit with a diagnosis of epilepsy or nonfebrile convulsions; ≥ two pharmacy dispensing's for anti-seizure medications	Retrospective open cohort study design. Multivariate analysis with Cox regression models	Adherence Use of ASM polytherapy Epilepsy related comorbidity	Adherence status Gender Age Race Use of ASM polytherapy Epilepsy related co-morbidities	Mortality	

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Comments
Ryu 2015[26]	N=104 individuals who had died, had a diagnosis of epilepsy registered on the death certificate and were treated for epilepsy at the centre in the study period, and met the criteria for SUDEP	Case control study with multivariate regression analysis	Seizure frequency Number of ASM's	Age at onset Duration of disease Aura Family history of epilepsy Psychiatric conditions Epilepsy classification Seizure frequency Seizure related to lesion on MR imagine Number of ASMs Type of ASM	Risk of SUDEP	
Si 2018[30]	N = 456 The number of patients included in the study were those with epilepsy who died and deceased patients without epilepsy as comparison.	Prospective cohort study with logistic regression analysis	CNS infections Metastatic cancer Solid tumour without metastasis Depression Diabetes without complications Peripheral vascular disease Traumatic brain and head injuries	Age Gender CNS infections Metastatic cancer Renal disease Solid tumour without metastasis Anoxic brain injury Cardiac arrhythmias Encephalopathy Depression Paraplegia, hemiplegia Diabetes without complications Peripheral vascular disease Traumatic brain and head injuries	Mortality	

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

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Comments
Nickels 2012[22]	n= 467 All children ages 1 month through 17 years diagnosed with new-onset epilepsy while resident in Olmsted County from 1980 to 2009 and had follow-up beyond the initial epilepsy diagnosis were included	Cohort study with multivariate Cox regression models	Abnormal neurological examination Abnormal cognitive function Status epilepticus, ever Metabolic/ structural aetiology	Neurologic examination cognitive function previous status epilepticus mode of onset, aetiology usage of ≥ 2 ASM's seizure frequency intractable at last follow up	Mortality	

Table 5: Summary of studies included in the evidence review - mixed population of children <18 years and adults >18 years (follow up 1 - 5 years)

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Comments
Chen 2005[7]	n=263 Participants were prospectively recruited patients with epilepsy who were at least 17 years old and newly referred to the outpatient epilepsy clinics	Prospective cohort study with Cox proportional hazards regression model	Aetiology of seizure / epilepsy	Age of onset Frequency Imaging Type of seizure Aetiology Medication Age Gender	Mortality	

Table 6: Summary of studies included in the evidence review - mixed population of children <18 years and adults >18 years (follow up >5 years)

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Comments
Langan 2005[15]	Cases = 151 Controls = 534	Case control study with backward	History of generalized tonic clonic seizures	History of generalized tonic clonic seizures	Risk of SUDEP	Supervision at night was defined as the presence in the

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Comments
	People with epilepsy who died suddenly between the ages of 16 and 50 years were identified by coroners and neurologists and by interviews with bereaved families	stepwise conditional logistic regression	No of tonic clonic seizures in previous 3 months Total number of anti-seizure medications Carbamazepine usage Supervision Asthma	No of tonic clonic seizures in previous 3 months Total number of anti-seizure medications Carbamazepine usage Supervision Asthma		bedroom of an individual of normal intelligence and at least 10 years old or the use of special precautions. Special precautions involved regular checks throughout the night or the use of a listening device.
Nilsson 1999[23]	Cases = 57 Controls = 171 Cases were individuals who had died with a diagnosis of epilepsy registered on the death certificate and who after review of medical and necropsy records were found to meet SUDEP criteria.	Nested case control study with multivariate analysis	Seizure frequency during last year Epilepsy type Number of ASM Changes in dose of ASM per year Anxiolytic medication Antipsychotic medication	Seizure frequency during last year Epilepsy type Number of ASM Changes in dose of ASM per year	Risk of SUDEP	
Sveinsson 2020[36] *(Sveinsson a)*	Cases n = 255 Controls n=1148 All deaths with epilepsy written on the death certificate (n = 1,276), were eligible SUDEP cases.	Case control study with conditional logistic regression and individual modelling	ASM therapy Monotherapy Nonadherence	ASM therapy Medication Time since last dispensed ASM Nonadherence	Risk of SUDEP	Model 3 from analysis used within review: adjusted for the same variables as model 2 together with history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Comments
Sveinsson 2020[35] *(Sveinsson b)*	Cases n = 255 Controls n=1148 All deaths with epilepsy written on the death certificate (n = 1,276), were eligible SUDEP cases.	Case control study with conditional logistic regression and individual modelling	Type of Epilepsy Living conditions Highest education Alcohol dependence Substance abuse	Age Sex Generalized tonic-clonic seizures frequency and nocturnal generalized tonic-clonic seizures last year of observation Living conditions Antiepileptic drugs	Risk of SUDEP	Model 3 from analysis used within review: Adjusted for age, sex, generalized tonic-clonic seizure frequency and nocturnal generalized tonic-clonic seizures last year, living conditions and epileptic drugs.
Zhang 2016[40]	Probable SUDEP n = 35 Control n = 105 Patients with convulsive epilepsy	Case control study with multivariate logistic regression analysis	Seizure frequency Seizure free prior (prior to SUDEP)	Onset age Seizure frequency at baseline (n/year) Seizure free prior to probable SUDEP (1 month)	Risk of probable SUDEP	

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

Table 7: Clinical evidence summary: one to five seizures per month

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP - Male	No seizures as reference		
	20 (1 study) 1 - 5 years	⊕⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	OR 3.40 (0.5 to 23.12)
SUDEP - Female	No seizures as reference		
	20 (1 study) 1 - 5 years	⊕⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	OR 5.70 (0.6 to 54.15)

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 non-modifiable confounders
3 Downgraded by 1 increment if the confidence interval crossed the null line
4 Outcomes adjusted for number of seizures (per month) and number of tonic clonic seizures (per year)

Table 8: Clinical evidence summary: Over five seizures per month

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP - Male	No seizures as reference		
	20 (1 study) 1 - 5 years	⊕⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	OR 1.0 (0.1 to 10)
SUDEP – Female	No seizures as reference		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
	20 (1 study) 1 - 5 years	⨁⨁⊖⊖ LOW1,2,3,4 due to risk of bias, indirectness	OR 7.40 (1.3 to 42.12)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Downgraded by 1 increment if the confidence interval crossed the null line
4 Outcomes adjusted for number of seizures (per month) and number of tonic clonic seizures (per year)

Table 9: Clinical evidence summary: One to three tonic-clonic seizures per year

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP - Male	No tonic – clonic seizures as reference		
	20 (1 study) 1 - 5 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	OR 4.30 (0.5 to 36.98)
SUDEP - Female	No tonic – clonic seizures as reference		
	20 (1 study) 1 - 5 years	⨁⨁⊖⊖ LOW1,2,3 due to risk of bias, indirectness	OR 11.20 (1.6 to 78.39)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Downgraded by 1 increment if the confidence interval crossed the null line
4 Outcomes adjusted for number of seizures (per month) and number of tonic clonic seizures (per year)

Table 10: Clinical evidence summary: Over three tonic-clonic seizures per year

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP – Male	No tonic – clonic seizures as reference		
	20 (1 study) 1 - 5 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	OR 3.30 (0.5 to 21.78)
SUDEP - Female	No tonic – clonic seizures as reference		
	20 (1 study) 1 - 5 years	⨁⨁⊖⊖ LOW1,2,3 due to risk of bias, indirectness	OR 28.00 (3.8 to 206.31)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Downgraded by 1 increment if the confidence interval crossed the null line
4 Outcomes adjusted for number of seizures (per month) and number of tonic clonic seizures (per year)

1.1.7. Summary of the prognostic evidence – Adults >18 years (follow up > 5 years)

Table 11: Clinical evidence summary: Seizure frequency

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	One or less than one seizure compared to over one seizure per month		
	104 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	OR 2.50 (0.9 to 6.95)

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

4 Outcomes adjusted for Age at onset, Duration of disease, Aura, Family history of epilepsy, Psychiatric conditions, Epilepsy classification, Seizure frequency, Seizure related to lesion on MR imaging, Number of ASMs, Type of ASM

Table 12: Clinical evidence summary: Number of anti-seizure medications

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	Less ASM's compared to more ASM's		
	104 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2, 3 due to risk of bias, indirectness	OR 1.80 (1.1 to 2.95)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Outcomes adjusted for Age at onset, Duration of disease, Aura, Family history of epilepsy, Psychiatric conditions, Epilepsy classification, Seizure frequency, Seizure related to lesion on MR imaging, Number of ASMs, Type of ASM

Table 13: Clinical evidence summary: Adherence status: Nonadherence of medications

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	Adherence to medication as reference		
	33,658 (1 study) >5 years	⨁⨁⨁⊖ MODERATE1,2 due to risk of bias	HR 3.32 (3.11 to 3.54)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Outcomes adjusted for adherence status, gender, age, race, use of ASM polytherapy, epilepsy related comorbidities

Table 14: Clinical evidence summary: Adherence status: Untreated Epilepsy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	Adherence to medication as reference		
	33,658 (1 study) >5 years	⨁⨁⊖⊖ LOW1,2,3 due to risk of bias, imprecision	HR 0.92 (0.84 to 1.01)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed the null line
3 Outcomes adjusted for adherence status, gender, age, race, use of ASM polytherapy, epilepsy related comorbidities

Table 15: Clinical evidence summary: Polytherapy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	No ASM polytherapy compared to ASM polytherapy		
	33,658 (1 study) >5 years	⨁⨁⨁⊖ MODERATE1,2 due to risk of bias	HR 0.75 (0.69 to 0.82)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Outcomes adjusted for adherence status, gender, age, race, use of ASM polytherapy, epilepsy related comorbidities

Table 16: Clinical evidence summary: Alzheimer's Disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	No Neurological condition as reference		
	33,658 (1 study) >5 years	⨁⨁⨁⊖ MODERATE1,2 due to risk of bias	HR 1.7 (1.54 to 1.88)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Outcomes adjusted for adherence status, gender, age, race, use of ASM polytherapy, epilepsy related comorbidities

Table 17: Clinical evidence summary: Brain tumour

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	No Neurological condition as reference		
	33,658 (1 study) >5 years	⨁⨁⨁⊖ MODERATE1,2 due to risk of bias	HR 1.58 (1.39 to 1.8)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Outcomes adjusted for adherence status, gender, age, race, use of ASM polytherapy, epilepsy related comorbidities

Table 18: Clinical evidence summary: Meningitis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	No Neurological condition as reference		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
	33,658 (1 study) >5 years	⨁⨁⨁⨀ MODERATE1,2 due to risk of bias	HR 1.34 (1.08 to 1.66)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Outcomes adjusted for adherence status, gender, age, race, use of ASM polytherapy, epilepsy related comorbidities

Table 19: Clinical evidence summary: Stroke

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	No Neurological condition as reference		
	33,658 (1 study) >5 years	⨁⨁⨁⨀ MODERATE1,2 due to risk of bias	HR 1.3 (1.22 to 1.39)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Outcomes adjusted for adherence status, gender, age, race, use of ASM polytherapy, epilepsy related comorbidities

Table 20: Clinical evidence summary: Charlson Comorbidity Index

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	Lower CCI compared to higher CCI		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
	33,658 (1 study) >5 years	⨁⨁⨁⨀ MODERATE1,2 due to risk of bias	HR 1.19 (1.18 to 1.2)

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

2 Outcomes adjusted for adherence status, gender, age, race, use of ASM polytherapy, epilepsy related comorbidities

Table 21: Clinical evidence summary: CNS infections

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	No CNS infection as reference		
	456 (1 study) 1 - 5 years	⨁⨁⨀⨀ LOW1,2,3 due to risk of bias, indirectness	OR 6.10 (4.1 to 9.08)

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

2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders

3 Outcomes adjusted for age, gender, CNS infections, metastatic cancer, renal disease, solid tumours without metastasis, anoxic brain injury, cardiac arrhythmias, encephalopathy, depression, paraplegia, diabetes without complications, peripheral vascular disease, traumatic brain and head injuries

Table 22: Clinical evidence summary: Metastatic Cancer

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	No metastatic cancer as reference		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
	456 (1 study) 1 - 5 years	⨁⨁⨀⨀ LOW1,2,3 due to risk of bias, indirectness	OR 3.70 (2.2 to 6.22)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Outcomes adjusted for age, gender, CNS infections, metastatic cancer, renal disease, solid tumours without metastasis, anoxic brain injury, cardiac arrhythmias, encephalopathy, depression, paraplegia, diabetes without complications, peripheral vascular disease, traumatic brain and head injuries

Table 23: Clinical evidence summary: Solid Tumour (no metastasis)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	No solid tumour as reference		
	456 (1 study) 1 - 5 years	⨁⨁⨀⨀ LOW1,2,3 due to risk of bias, indirectness	OR 2.0 (1.1 to 3.64)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Outcomes adjusted for age, gender, CNS infections, metastatic cancer, renal disease, solid tumours without metastasis, anoxic brain injury, cardiac arrhythmias, encephalopathy, depression, paraplegia, diabetes without complications, peripheral vascular disease, traumatic brain and head injuries

Table 24: Clinical evidence summary: Depression

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	No depression as reference		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
	456 (1 study) 1 - 5 years	⨁⨁⨀⨀ LOW1,2,3 due to risk of bias, indirectness	OR 0.20 (0.1 to 0.4)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Outcomes adjusted for age, gender, CNS infections, metastatic cancer, renal disease, solid tumours without metastasis, anoxic brain injury, cardiac arrhythmias, encephalopathy, depression, paraplegia, diabetes without complications, peripheral vascular disease, traumatic brain and head injuries

Table 25: Clinical evidence summary: Diabetes (no complications)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	No diabetes as reference		
	456 (1 study) 1 - 5 years	⨁⨁⨀⨀ LOW1,2,3 due to risk of bias, indirectness	OR 1.40 (1 to 1.96)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Outcomes adjusted for age, gender, CNS infections, metastatic cancer, renal disease, solid tumours without metastasis, anoxic brain injury, cardiac arrhythmias, encephalopathy, depression, paraplegia, diabetes without complications, peripheral vascular disease, traumatic brain and head injuries

Table 26: Clinical evidence summary: Peripheral vascular disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	No peripheral vascular disease as reference		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
	456 (1 study) 1 - 5 years	⨁⨁⨀⨀ LOW1,2,3 due to risk of bias, indirectness	OR 0.50 (0.3 to 0.83)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Outcomes adjusted for age, gender, CNS infections, metastatic cancer, renal disease, solid tumours without metastasis, anoxic brain injury, cardiac arrhythmias, encephalopathy, depression, paraplegia, diabetes without complications, peripheral vascular disease, traumatic brain and head injuries

Table 27: Clinical evidence summary: Traumatic brain and head injury

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	No traumatic brain and head injury as reference		
	456 (1 study) 1 - 5 years	⨁⨁⨀⨀ LOW1,2,3 due to risk of bias, indirectness	OR 5.10 (2.8 to 9.29)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Outcomes adjusted for age, gender, CNS infections, metastatic cancer, renal disease, solid tumours without metastasis, anoxic brain injury, cardiac arrhythmias, encephalopathy, depression, paraplegia, diabetes without complications, peripheral vascular disease, traumatic brain and head injuries

1.1.8. Summary of the prognostic evidence – Children <18 years (follow up > 5 years)

Table 28: Clinical evidence summary: Abnormal neurological examination

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	Normal neurological examination as reference		
	467 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness	HR 12.80 (1.4 to 116.96)

1 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
2 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
3 Adjusted for neurologic examination, cognitive function, previous status epilepticus, mode of onset, aetiology, usage of ≥ 2 ASM's, seizure frequency, intractable at last follow up

Table 29: Clinical evidence summary: Abnormal cognitive function

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	Normal cognitive function as reference		
	467 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	HR 3.78 (0.42 to 34.02)

1 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
2 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
3 Adjusted for neurologic examination, cognitive function, previous status epilepticus, mode of onset, aetiology, usage of ≥ 2 ASM's, seizure frequency, intractable at last follow up
4 Unclear which factors were adjusted for in the multivariate analysis

Table 30: Clinical evidence summary: Status Epilepticus (ever)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	No status epilepticus as reference		
	467 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	HR 1.34 (0.48 to 3.74)

1 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
2 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
3 Downgraded by 1 increment if the confidence interval crossed the null line
4 Adjusted for neurologic examination, cognitive function, previous status epilepticus, mode of onset, aetiology, usage of ≥ 2 ASM's, seizure frequency, intractable at last follow up

Table 31: Clinical evidence summary: Metabolic / Structural Aetiology

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	No metabolic / structural aetiology as reference		
	467 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	HR 2.62 (0.69 to 9.95)

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 non-modifiable confounders
3 Downgraded by 1 increment if the confidence interval crossed the null line
4 Adjusted for neurologic examination, cognitive function, previous status epilepticus, mode of onset, aetiology, usage of ≥ 2 ASM's, seizure frequency, intractable at last follow up

1.1.9. Summary of the prognostic evidence – Mixed population of children <18 years and adults >18 years (follow up 1 – 5 years)

Table 32: Clinical evidence summary: Tumour aetiology

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	Cryptogenic aetiology as reference		
	263 (1 study) 1 - 5 years	⨁⨁⨁⊖ MODERATE1 due to risk of bias	HR 4.67 (1.76 to 12.39)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed the null line
3 Adjusted for age of onset, frequency, imaging, type of seizure, aetiology, medication, age, gender

Table 33: Clinical evidence summary: Vascular lesion aetiology

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	Cryptogenic aetiology as reference		
	263 (1 study) 1 - 5 years	⨁⨁⊖⊖ LOW1,2,3 due to risk of bias, imprecision	HR 1.37 (0.46 to 4.08)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed the null line
3 Adjusted for age of onset, frequency, imaging, type of seizure, aetiology, medication, age, gender

Table 34: Clinical evidence summary: Trauma aetiology

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	Cryptogenic aetiology as reference		
	263 (1 study) 1 - 5 years	⨁⨁⊖⊖ LOW1,2,3 due to risk of bias, imprecision	HR 0.81 (0.22 to 2.98)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed the null line
3 Adjusted for age of onset, frequency, imaging, type of seizure, aetiology, medication, age, gender

Table 35: Clinical evidence summary: Infection aetiology

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Mortality	Cryptogenic aetiology as reference		
	263 (1 study) 1 - 5 years	⨁⨁⊖⊖ LOW1,2,3 due to risk of bias, imprecision	HR 1.18 (0.15 to 9.28)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed the null line
3 Adjusted for age of onset, frequency, imaging, type of seizure, aetiology, medication, age, gender

1.1.10. Summary of the prognostic evidence – Mixed population of children <18 years and adults >18 years (follow up >5 years)

Table 36: Clinical evidence summary: Seizure frequency - >10 seizures per year (at baseline)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
probable SUDEP	≤Ten seizures per year as reference		
	35 (1 study) >5 years	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, imprecision	OR 5.90 (2.2 to 15.82)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Adjusted for age at onset, duration of epilepsy, type of epilepsy, causes of epilepsy, living conditions, highest education

Table 37: Clinical evidence summary: Seizures prior to SUDEP

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
probable SUDEP	Seizure free prior to SUDEP as reference		
	35 (1 study) >5 years	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness	OR 9.50 (3 to 30.08)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Adjusted for age at onset, duration of epilepsy, type of epilepsy, causes of epilepsy, living conditions, highest education

Table 38: Clinical evidence summary: Seizure frequency – (3 – 12 seizures past year)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	0 – 2 seizures as reference		
	57 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness	RR 4.47 (1.33 to 15.02)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year.

Table 39: Clinical evidence summary: six to ten tonic-clonic seizures (previous 3 months)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	0 – 5 seizures as reference		
	151 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	OR 0.70 (0.2 to 2.45)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Downgraded by 1 increment if the confidence interval crossed the null line
4 Adjusted for History of generalized tonic clonic seizures, No of tonic clonic seizures in previous 3 months, Total number of anti-seizure medications, Carbamazepine usage, Supervision, Asthma

Table 40: Clinical evidence summary: eleven to twenty tonic-clonic seizures (previous 3 months)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	0 – 5 seizures as reference		
	151 (1 study) >5 years	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness	OR 19.40 (1.7 to 221.4)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Adjusted for history of GTCS, number of TCS in the previous 3 months, number of ASMs, carbamazepine usage, supervision level, asthma

Table 41: Clinical evidence summary: Twenty-one to fifty tonic-clonic seizures (previous 3 months)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	0 – 5 seizures as reference		
	151 (1 study) >5 years	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness	OR 14.60 (1.3 to 163.96)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Adjusted for history of GTCS, number of TCS in the previous 3 months, number of ASMs, carbamazepine usage, supervision level, asthma

Table 42: Clinical evidence summary: Over fifty tonic-clonic seizures (previous 3 months)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	0 – 5 seizures as reference		
	151 (1 study) 5 years	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	OR 11.70 (0.3 to 456.31)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Downgraded by 1 increment if the confidence interval crossed the null line
4 Adjusted for history of GTCS, number of TCS in the previous 3 months, number of ASMs, carbamazepine usage, supervision level, asthma

Table 43: Clinical evidence summary: History of generalized tonic-clonic seizures

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No history of generalized tonic clonic seizures as reference		
	151 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness	OR 13.80 (6.6 to 28.85)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Adjusted for history of GTCS, number of TCS in the previous 3 months, number of ASMs, carbamazepine usage, supervision level, asthma

Table 44: Clinical evidence summary: Focal seizures

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	Generalized seizures as reference		
	255 (1 study) >5 years	⨁⨁⨁⊖ MODERATE1,2 due to imprecision	OR 1.34 (0.77 to 2.33)

1 Downgraded by 1 increment if the confidence interval crossed the null line

2 Adjusted for age, sex, generalized tonic-clonic seizures frequency and nocturnal generalized tonic-clonic seizures last year of observation, living conditions and antiepileptic drugs.

Table 45: Clinical evidence summary: Focal and generalized seizures

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	Generalized seizures as reference		
	255 (1 study) >5 years	⨁⨁⨁⊖ MODERATE1,2 due to imprecision	OR 1.42 (0.49 to 4.12)

1 Downgraded by 1 increment if the confidence interval crossed the null line

2 Adjusted for age, sex, generalized tonic-clonic seizures frequency and nocturnal generalized tonic-clonic seizures last year of observation, living conditions and antiepileptic drugs.

Table 46: Clinical evidence summary: Undetermined seizures

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	Generalized seizures as reference		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
	255 (1 study) >5 years	⨁⨁⨁⨁ HIGH1	OR 3.51 (1.44 to 8.56)

1 Adjusted for age, sex, generalized tonic-clonic seizures frequency and nocturnal generalized tonic-clonic seizures last year of observation, living conditions and antiepileptic drugs.

Table 47: Clinical evidence summary: Substance abuse

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	255 (1 study) >5 years	⨁⨁⨁⨁ HIGH1	OR 2.07 (1.04 to 4.01)

1 Adjusted for age, sex, generalized tonic-clonic seizures frequency and nocturnal generalized tonic-clonic seizures last year of observation, living conditions and antiepileptic drugs.

Table 48: Clinical evidence summary: Alcohol dependence

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	255 (1 study) >5 years	⨁⨁⨁⊖ MODERATE1,2	OR 2.30 (1.02 to 5.21)

1 Adjusted for age, sex, generalized tonic-clonic seizures frequency and nocturnal generalized tonic-clonic seizures last year of observation, living conditions and antiepileptic drugs.

2 Downgraded by 1 increment if the confidence interval crossed the null line

Table 49: Clinical evidence summary: Alcoholism

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	Generalized idiopathic seizures as reference		
	57 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	RR 1.42 (0.68 to 2.97)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Downgraded by 1 increment if the confidence interval crossed the null line
4 Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 50: Clinical evidence summary: Local symptomatic seizures

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	Generalized idiopathic seizures as reference		
	57 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	RR 1.15 (0.18 to 7.35)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Downgraded by 1 increment if the confidence interval crossed the null line
4 Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 51: Clinical evidence summary: Local cryptogenic seizures

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	Generalized idiopathic seizures as reference		
	57 (1 study) >5 years	⊕⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	RR 1.94 (0.27 to 13.94)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Downgraded by 1 increment if the confidence interval crossed the null line
4 Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 52: Clinical evidence summary: Undetermined seizures

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	Generalized idiopathic seizures as reference		
	57 (1 study) >5 years	⊕⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	RR 1.17 (0.14 to 9.78)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Downgraded by 1 increment if the confidence interval crossed the null line
4 Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 53: Clinical evidence summary: Anti-seizure medication therapy - monotherapy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No ASM as reference		
	255 (1 study) >5 years	⨁⨁⨁⊖ MODERATE1,2 due to imprecision	OR 0.79 (0.44 to 1.42)

1 Downgraded by 1 increment if the confidence interval crossed the null line

2 Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 54: Clinical evidence summary: Anti-seizure medication therapy – Polytherapy (≥2 medications)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No ASM as reference		
	255 (1 study) >5 years	⨁⨁⨁⨁ HIGH1	OR 0.48 (0.26 to 0.89)

1 Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 55: Clinical evidence summary: Anti-seizure medication therapy – Two anti-seizure medications

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No ASM as reference		
	255 (1 study) >5 years	⨁⨁⨁⊖ MODERATE1,2 due to imprecision	OR 0.59 (0.31 to 1.12)

1 Downgraded by 1 increment if the confidence interval crossed the null line

2 Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 56: Clinical evidence summary: Two antiseizure medications

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	One ASM as reference		
	57 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	RR 1.95 (0.65 to 5.58)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Downgraded by 1 increment if the confidence interval crossed the null line
4 Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 57: Clinical evidence summary: Three antiseizure medications

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	One ASM as reference		
	57 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness	RR 10.23 (1.86 to 56.27)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 58: Clinical evidence summary: Anti-seizure medication therapy – Polytherapy (> 3 anti-seizure medications)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No ASM as reference		
	255 (1 study) >5 years	⨁⨁⨁⨁ HIGH1	OR 0.31 (0.14 to 0.69)

1 Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 59: Clinical evidence summary: three to four anti-seizure medications

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	One to two ASM as reference		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
	151 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	OR 1.30 (0.6 to 2.82)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Downgraded by 1 increment if the confidence interval crossed the null line
4 Adjusted for history of GTCS, number of TCS in previous 3 months, total number of ASM, carbamazepine usage, supervision, asthma

Table 60: Clinical evidence summary: Over four anti-seizure medications

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	One to two ASM as reference		
	151 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness	OR 3.10 (1.4 to 6.86)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Adjusted for history of GTCS, number of TCS in previous 3 months, total number of ASM, carbamazepine usage, supervision, asthma

Table 61: Clinical evidence summary: No anti-seizure medications

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	One to two ASM as reference		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
	151 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness	OR 21.70 (4.4 to 107.03)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Adjusted for history of GTCS, number of TCS in previous 3 months, total number of ASM, carbamazepine usage, supervision, asthma

Table 62: Clinical evidence summary: Monotherapy – Carbamazepine

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No ASM as reference		
	255 (1 study) >5 years	⨁⨁⨁⊖ MODERATE1,2 due to imprecision	OR 1 (0.48 to 2.08)

1 Downgraded by 1 increment if the confidence interval crossed the null line
2 Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 63: Clinical evidence summary: Monotherapy – Carbamazepine

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No carbamazepine use as reference		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
	151 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness	OR 2.00 (1.1 to 3.64)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Adjusted for history of GTCS, number of TCS in previous 3 months, total number of ASM, carbamazepine usage, supervision, asthma

Table 64: Clinical evidence summary: Monotherapy – Lamotrigine

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No ASM as reference		
	255 (1 study) >5 years	⨁⨁⨁⊖ MODERATE1,2 due to imprecision	OR 0.93 (0.41 to 2.11)

1 Downgraded by 1 increment if the confidence interval crossed the null line
2 Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 65: Clinical evidence summary: Monotherapy – Valproic Acid

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No ASM as reference		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
	255 (1 study) >5 years	⨁⨁⨁⨀ MODERATE1,2 due to imprecision	OR 0.52 (0.2 to 1.35)

1 Downgraded by 1 increment if the confidence interval crossed the null line

2 Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 66: Clinical evidence summary: Monotherapy – Phenytoin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No ASM as reference		
	255 (1 study) >5 years	⨁⨁⨁⨀ MODERATE1,2 due to imprecision	OR 0.56 (0.17 to 1.84)

1 Downgraded by 1 increment if the confidence interval crossed the null line

2 Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 67: Clinical evidence summary: Monotherapy – Levetiracetam

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No ASM as reference		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
	255 (1 study) >5 years	⨁⨁⨁⨁ HIGH1	OR 0.1 (0.02 to 0.5)

1 Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 68: Clinical evidence summary: Monotherapy – Oxcarbazepine

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No ASM as reference		
	255 (1 study) >5 years	⨁⨁⨁⨀ MODERATE1,2 due to imprecision	OR 0.58 (0.09 to 3.74)

1 Downgraded by 1 increment if the confidence interval crossed the null line

2 Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 69: Clinical evidence summary: Monotherapy – Topiramate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No ASM as reference		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
	255 (1 study) >5 years	⨁⨁⨁⨀ MODERATE1,2 due to imprecision	OR 2.02 (0.29 to 14.07)

1 Downgraded by 1 increment if the confidence interval crossed the null line

2 Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 70: Clinical evidence summary: Monotherapy – Other anti-seizure medication

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No ASM as reference		
	255 (1 study) >5 years	⨁⨁⨁⨀ MODERATE1,2 due to imprecision	OR 1.32 (0.39 to 4.47)

1 Downgraded by 1 increment if the confidence interval crossed the null line

2 Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 71: Clinical evidence summary: Nonadherence

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	Adherence as reference		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
	255 (1 study) >5 years	⨁⨁⨁⨁ HIGH1	OR 2.75 (1.58 to 4.79)

1 Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 72: Clinical evidence summary: One to two changes in dose of antiseizure medication (per year)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No changes as reference		
	57 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	RR 0.69 (0.26 to 1.83)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Downgraded by 1 increment if the confidence interval crossed the null line
4 Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 73: Clinical evidence summary: Three to five changes in dose of antiseizure medication (per year)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No changes as reference		
	57 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness	RR 9.32 (1.95 to 44.54)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 74: Clinical evidence summary: Antipsychotic medication

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No antipsychotic medication as reference		
	57 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	RR 2.14 (0.90 to 5.09)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Downgraded by 1 increment if the confidence interval crossed the null line
4 Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 75: Clinical evidence summary: Anxiolytic medication

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No anxiolytic medication as reference		
	57 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness	RR 3.00 (1.16 to 7.76)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 76: Clinical evidence summary: Asthma

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No asthma as reference		
	151 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness	OR 0.20 (0.1 to 0.4)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Adjusted for history of TCS, number of TCS in previous 3 months, total number of anti-seizure medications, carbamazepine usage, supervision, asthma

Table 77: Clinical evidence summary: Sharing household but not sharing a bedroom

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	Sharing household and bedroom as reference		
	255 (1 study) >5 years	⨁⨁⨁⨁ HIGH1	OR 2.28 (1.14 to 4.56)

1 Adjusted for age at onset, duration of epilepsy, type of epilepsy, causes of epilepsy, living conditions, highest education

Table 78: Clinical evidence summary: Living alone

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	Sharing household and bedroom as reference		
	255 (1 study) >5 years	⨁⨁⨁⨁ HIGH1	OR 5.01 (2.93 to 8.57)

1 Adjusted for age at onset, duration of epilepsy, type of epilepsy, causes of epilepsy, living conditions, highest education

Table 79: Clinical evidence summary: Secondary education

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	Post-secondary education as reference		
	255 (1 study) >5 years	⨁⨁⨁⊖ MODERATE1,2 due to imprecision	OR 1.59 (0.78 to 3.24)

1 Downgraded by 1 increment if the confidence interval crossed the null line

2 Adjusted for age at onset, duration of epilepsy, type of epilepsy, causes of epilepsy, living conditions, highest education

Table 80: Clinical evidence summary: Primary education

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	Post-secondary education as reference		
	255 (1 study) >5 years	⨁⨁⨁⊖ MODERATE1,2 due to imprecision	OR 1.21 (0.58 to 2.52)

1 Downgraded by 1 increment if the confidence interval crossed the null line

2 Adjusted for age at onset, duration of epilepsy, type of epilepsy, causes of epilepsy, living conditions, highest education

Table 81: Clinical evidence summary: Same room supervision at night

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No supervision at night as reference		
	151 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness	OR 0.10 (0.03 to 0.3)

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

3 Adjusted for history of TCS, number of TCS in previous 3 months, total number of anti-seizure medications, carbamazepine usage, supervision, asthma

Table 82: Clinical evidence summary: Special supervision at night (regular checks throughout the night or the use of a listening device)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
SUDEP	No special precautions for supervision at night as reference		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
	151 (1 study) >5 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness	OR 0.40 (0.2 to 0.8)

1 Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
2 Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
3 Adjusted for history of TCS, number of TCS in previous 3 months, total number of anti-seizure medications, carbamazepine usage, supervision, asthma

See Appendix F for full GRADE tables.

1.1.11. Economic evidence

1.1.11.1. Included studies

No health economic studies were included.

1.1.11.2. 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.

1.1.12. Economic model

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

1.1.13. Evidence statements

1.1.13.1. Effectiveness

- None.

1.1.13.2. Economic

- No relevant economic evaluations were identified.

1.1.14. The committee's discussion and interpretation of the evidence

1.1.14.1. The outcomes that matter most

The two outcomes for this evidence review were death related to epilepsy or sudden unexpected death in Epilepsy (SUDEP). This was to ensure that the modifiable risk factors being assessed were in the context of the impact they would have on mortality and SUDEP. This was important as modifiable risk factors could be assessed in people who have been diagnosed with epilepsy, and the recommendations would potentially have the greatest impact for the person with epilepsy, their families, or carers, as well as the clinicians managing their epilepsy.

1.1.14.2. The quality of the evidence

The majority of results were of low or very low-quality evidence for all the stratifications for the outcomes of epilepsy-related mortality or SUDEP. The main reasons for this were: the risk of bias, indirectness for not adjusting for modifiable confounders and crossing of the null line. There were cohort studies and case-control studies included within this review. As all the studies were observational studies, they had to show adjustment was made for potential confounders. The evidence was downgraded if the study did not adjust for at least two of the four non-modifiable risk factors specified (age, gender, developmental/intellectual disability, and duration of epilepsy). Evidence of adjusting shows that the results are what they would be if all other variables were set to be the same across the risk factor and no risk factor group. In turn, this increases our confidence that the results are not confounded. Where the confidence interval of the odds, hazard or risk crossed one, or the null line, this signified that the result is consistent with no effect from the risk factor. This allowed the results to be divided into significant factors and non-significant factors. The committee took note of all

these different elements in the quality assessment of the evidence to decide on recommendations.

There were several outcomes within some of the stratifications that were of moderate or high-quality evidence. Within the adults (follow up over 5 years) adherence, polytherapy, neurological conditions and Charlson Comorbidity Index; mixed population (follow up 1 - 5 years) tumour aetiology; and mixed population (follow up over 5 years) undetermined seizures, substance abuse, alcohol, dependence, polytherapy (2 or more anti-seizure medications or more than 3 anti-seizure medications, use of levetiracetam, non-adherence and living conditions were all of moderate to high quality and significant outcomes. The committee discussed all of the factors in relation to their quality and significance and decided those that were modifiable were important to consider for recommendations.

1.1.14.3. Benefits and harms

People with epilepsy are at increased risk (approximately 7 – 12% cumulative lifetime risk) of premature mortality and SUDEP so the identification of risk factors, particularly modifiable risk factors is of benefit to people with epilepsy and their families and carers. This can provide important information of their own risk but also what steps can be taken to manage the risk.

In adults who were followed up from one to five years there did not appear to be a significant difference in risk of death or SUDEP resulting from 1 – 5 seizures a month, >5 seizures a month, 1 – 3 tonic clonic seizures per year or > 3 tonic clonic seizures per year. However, for adults followed up over five years, being on more ASM's led to an almost doubling of the odds of SUDEP compared to less ASMs; non-adherence of ASM's led to an almost 3.5 times greater odds of death compared to being adherent to medications, and people with polytherapy (2 or more anti-seizure medications) had three-quarters the hazard of mortality as people not on polytherapy.

Comorbidities such as brain tumours, meningitis and stroke had almost two times the hazard of mortality compared to no neurological comorbidities. Although not modifiable risk factors, these conditions are important in a cumulative risk calculation.

Unexpectedly, the evidence showed that depression led to one-fifth of the risk of premature mortality compared to no depression, and having peripheral vascular disease led to approximately half the odds of mortality compared to the odds experienced without peripheral vascular disease. This is contrary to the understanding in current clinical practice that depression and peripheral vascular disease are modifiable risk factors that increase the risk of premature mortality. However, a higher score on the Charlson co-morbidity index, which is a measure of co-morbidities including cardiovascular disorders such as heart failure, stroke and peripheral heart disease as well as other chronic conditions, is associated with an increase in mortality. In children followed up for more than five years, having an abnormal neurological exam confers a hazard of mortality that is 12 times greater than the hazard experienced without an abnormal neurological exam and having abnormal cognitive function confers a hazard of mortality that is almost 4 times greater than the hazard experienced without abnormal cognitive function. Knowledge of the magnitude of these risk factors can contribute to the approach to epilepsy management.

Within a mixed population of children and adults who were followed up for one to five years, the evidence showed having a tumour has a hazard of mortality that is 4.5 times greater than the hazard experienced without having a tumour.

In studies of a mixed population followed up for over five years, there were several significant risk factors that had an impact on the risk of premature mortality. For example, having over ten seizures per year has almost six times greater odds of SUDEP than the odds experienced with less than ten seizures per year, and having a history of generalized tonic

clonic seizures has almost fourteen times greater odds of SUDEP than the odds experienced without a history of generalized tonic clonic seizures. In relation to medication and treatment of epilepsy, some results showed that three to five changes in dose of ASM per year has a risk of SUDEP that is nearly ten times greater than the risk experienced with no changes in ASM over a year and people on three ASM has an odds of SUDEP ten times greater than the odds experienced with monotherapy.

The committee agreed that these modifiable risk factors shown to have an impact on premature mortality or SUDEP could be grouped into a recommendation focused on treating seizures adequately with medication and adherence to medication. The committee agreed that focal to bilateral tonic-clonic seizures should be listed along with generalised tonic-clonic seizures as these more often cause convulsive seizures and are increasingly associated with drug-resistant epilepsy. In addition to this, social and lifestyle factors also showed an impact on premature mortality. For example, special supervision at night had about half of the odds of SUDEP compared to people with no supervision overnight and living alone has an odds of SUDEP that is five times greater than the odds when sharing a household and bedroom. The committee recognised the importance of these findings and included them as part of the recommendations to discuss whether night-time supervision might be helpful for some people who have seizures during sleep and are at higher risk of mortality. The committee discussed the challenges surrounding such an intervention and how it would not be feasible or appropriate in many circumstances but acknowledged parents or carers reported gaining some reassurance from the use of a night monitor in a child's room.

The committee noted the importance of ongoing dialogue between the person with epilepsy, their families or carers, and their clinicians about the general management of their epilepsy, medications and seizures, which can help in tailoring treatment and enhance adherence to medications. A person's risk of premature mortality or SUDEP can change at different stages in their life, which can be affected by how well their epilepsy is managed but also different environmental factors which indirectly affect their risks, such as stress and lifestyle choices. So, conversations around the risks of premature mortality need to be adapted according to risk factors which are relevant at the time of follow up.

The committee acknowledged it is important to note that the modifiable risk factors identified in the evidence are not the only risk factors that may have an impact on the risk of premature mortality and SUDEP. The committee agreed that the evidence base was limited with respect to many of the biologically plausible risk factors that had been included in the review protocol and were aware that absence of evidence did not equate to 'evidence of absence'. They, therefore, suggested that discussions about modifiable risk factors between clinician and patient should not be limited to those mentioned in the recommendations and may include other risk factors such as sleep deprivation or sleeping position, and drug polytherapy.

1.1.15. Cost effectiveness and resource use

No health economic evidence was identified for this review question.

The committee discussed the clinical evidence presented and noted that people with epilepsy should be supported to understand their individual risk of mortality, including SUDEP, from the time of their epilepsy diagnosis and throughout the duration of their care. The committee acknowledged that the prospect of SUDEP could be extremely worrying for people with epilepsy causing increased anxiety and depression, worsening people's quality of life. Therefore, support from health care professionals for people with epilepsy to understand their individualised risk is instrumental in improving patient's quality of life. In addition, for those patients who are at greater risk of premature mortality, the committee discussed that healthcare workers should work with patients to reduce this risk. The committee noted that these recommendations are reflective of current practice and so are not expected to result in a substantial resource impact.

The committee also discussed the modifiable risk factors and co-morbidities associated with the risk of epilepsy-related mortality. It was noted that modifiable risk factors and co-morbidities should be discussed with people upon an initial diagnosis of a person's epilepsy as well as throughout the duration of treatment. The committee acknowledged that in current practice, the degree to which modifiable risk factors are discussed with people varies. However, because the information provided on the modifiable risk factors of SUDEP is discussed at existing appointments people attend, this recommendation is not expected to result in a substantial resource impact.

Night-time supervision for people with epilepsy was also discussed. The committee noted that night-time supervision could be especially beneficial for people who have seizures during their sleep and have been assessed to be at high risk of epilepsy-related mortality as intercepting a person's nocturnal seizure can be lifesaving. There are, however, significant implications associated with night-time monitoring. Night-time monitoring of people living in residential care should already be provided; however, the committee noted that, if possible, the level of supervision should be increased. This is because onset of a seizure when sleeping can start suddenly and unexpectedly, therefore without regular monitoring, there may be little benefit of monitoring at all. Overall, increasing the levels of monitoring of people residing in residential care should not result in a significant resource impact as there should already be night-time staff on shift able to conduct monitoring. The committee did, however, note that for places that do not currently provide regular monitoring, an additional member of staff may be required if the workload of night-staff is already high.

The committee acknowledged that night-time supervision for people with epilepsy not residing in care could be extremely challenging. Monitoring can be achieved through the use of baby monitors or other technologies which provide an alert to a parent, guardian, or partner when a person with epilepsy is experiencing a seizure. The purpose of the recommendation made by the committee is to inform people of the risks of night-time seizures and to make sure the correct approach to monitoring is adopted if appropriate. Advice on a person's individualised risks of night-time seizures and the best way to monitor these can be provided by health care professionals. In general, the cost of monitoring devices is incurred by careers, guardians, or patients. Therefore, this recommendation is not expected to lead to a significant resource impact.

The committee also discussed that monitoring may not be possible for adults living alone or in other settings such as living in a house with friends. The committee noted that in these circumstances, the risks and the benefits should be assessed with the help of a healthcare professional for the appropriate course of action to be taken.

1.1.16. Other factors the committee took into account

The committee acknowledged the importance of the 2020 MBRRACE-UK report, which focuses on improving the lives of pregnant women and mothers. The report highlighted that 13% of women died from epilepsy and stroke during or up to six weeks after their pregnancy. In relation to the recommendations made as part of this review, the report urges for the risk related to night-time seizures, uncontrolled seizures, and ineffective treatment to be discussed with pregnant women to reduce the risk of premature mortality and SUDEP.

1.1.17. Recommendations supported by this evidence review

This evidence review supports recommendations 10.1.1 – 10.1.4 in the NICE guideline.

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1.1.17.1. 1.1.14.2 Economic evidence – included studies

[List references of studies included in the economic evidence review]

Appendices

Appendix A Review protocols

A.1 Review protocol for [add key area, for example, unplanned hospital admission]

ID	Field	Content
1.	Review title	Modifiable risk factors for epilepsy-related mortality, including SUDEP, and the magnitude of risk of those factors.
2.	Review question	What are the modifiable risk factors for epilepsy-related mortality, including SUDEP, and what is the magnitude of risk of the factors?
3.	Objective	To identify the modifiable variables that have an independent association with death, in a population of people who have a diagnosis of epilepsy. 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 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 diagnosis of epilepsy. Exclusion: New-born babies with acute symptomatic seizures
7.	Risk factors (Although the ideal study would probably look at all these factors together, for inclusion a study need only look at one risk factor, though please note comments in row 8)	the following modifiable factors: • Sleeping unsupervised / living alone • Prone sleeping position • Uncontrolled/frequent Generalised Tonic Clonic Seizures (GTCS) • Nocturnal GTCS • Substance abuse / alcohol dependence • ASM polytherapy

		• Other drug polytherapy • Insufficient ASM therapy / any changes in prescription of drugs that could increase seizure rate • Sleep deprivation / irregular sleep
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 (the modifiable factors listed above plus other non-modifiable factors) 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. Some important confounders that we would ideally like to see accounted for are the modifiable factors listed above and the following 4 non-modifiable factors: age, gender, developmental intellectual disability, duration of epilepsy. If at least 2 of the modifiable factors [other than the index factor], and 2 of these 4 non-modifiable factors are not included in the analysis we will still include the study, but we will downgrade for indirectness.
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 epilepsy-related death (including SUDEP) may be preventable, partly by attention to altering modifiable risk factors. This review therefore sets out to identify the modifiable risk factors for epilepsy related death (including SUDEP).
12.	Primary outcomes (critical outcomes)	• Death, related to epilepsy • SUDEP Follow up: any available but stratify according to: <1 yr., 1-5 yrs., >5 yrs.
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 CASP. 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: <1 yr., 1-5 yrs., >5 yrs. Children (<18yrs) vs adult (18 yrs. or over) *Conditional stratification* Young stratum: <2, 2-11, 11-18; older stratum: 18-55, >55 Learning disability vs none Head injury vs none Types of seizure 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	**5a. Named contact** National Guideline Centre **5b Named contact e-mail** **5e 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/documents
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.
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).[20] **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.[20]

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 83: 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 84: 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.

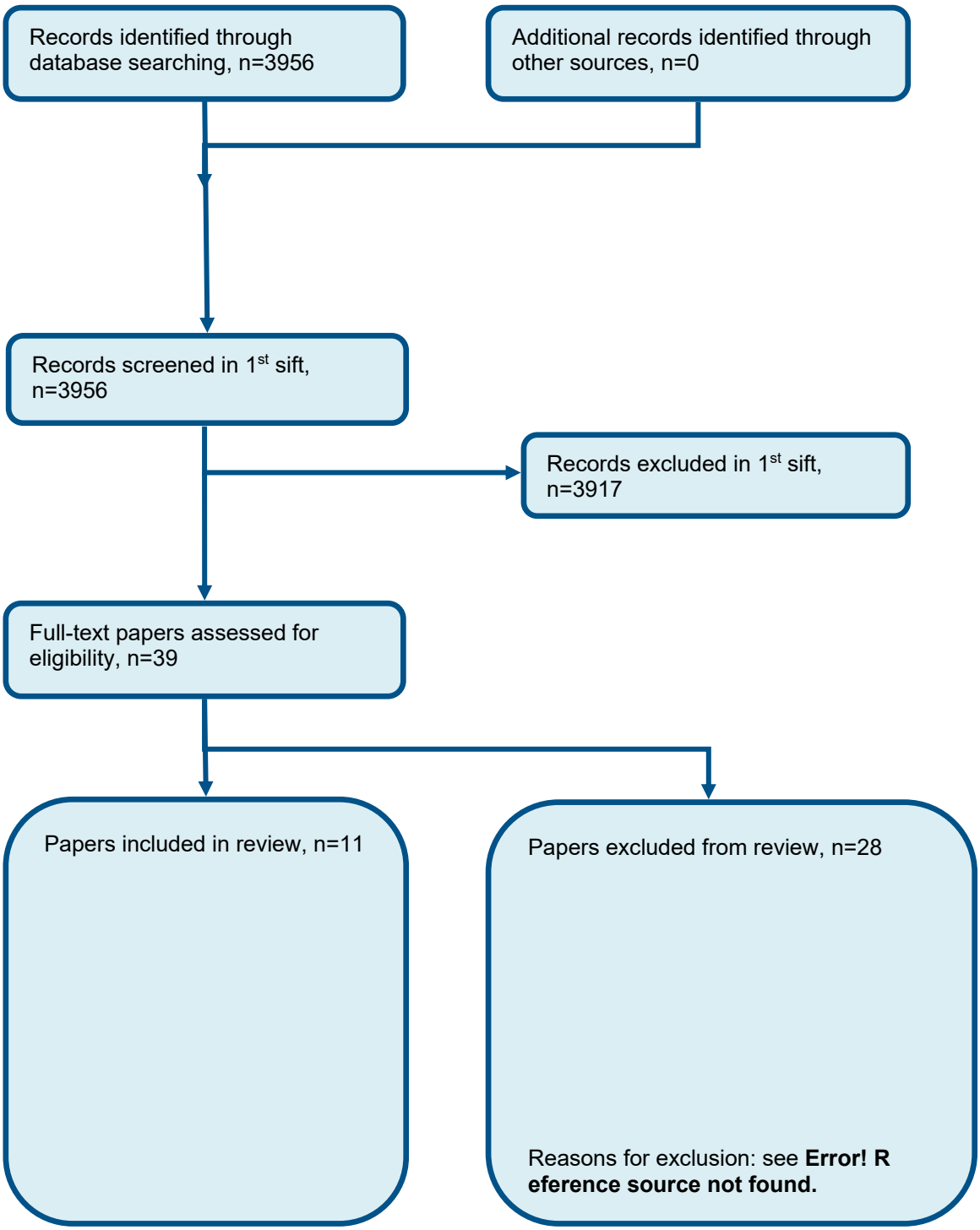
47.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
48.	(hui or hui1 or hui2 or hui3).ti,ab.
49.	(health* year* equivalent* or hye or hyes).ti,ab.
50.	discrete choice*.ti,ab.
51.	rosser.ti,ab.
52.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
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 epilepsy related mortality



Appendix D Prognostic evidence

Reference	**Walczak 2001[39]**	
Study type and analysis	Prospective case control study with multivariate analysis	
Number of participants and characteristics	Cases = 20 Controls = 80 Participants were prospectively enrolled after evaluation at three upper mid-western epilepsy centres. A surveillance system was set up to identify deaths in this prevalence cohort. All deaths were investigated to distinguish between SUDEP and other causes of death. Definite SUDEP required the following 1) a history of epilepsy (more than one epileptic seizure during a period of less than 5 years; 2) that the death occur suddenly; 3) that the death was unexpected; and 4) that the death remained unexplained after all investigative efforts, including autopsy. Probable SUDEP was considered with criteria 1 – 3. All deaths between June 1 1991 and December 31 1996 were analysed. Unclear how the controls were selected	
	Age	Cases
	20 – 29	6
	30 – 39	7
	40 – 49	4
	50 – 59	3

Reference	**Walczak 2001[39]**		
Prognostic variable(s)	Number of seizures (number per month) Number of tonic-clonic seizures (per year)		
Confounders OR Stratification strategy	Number of seizures (number per month) Number of tonic-clonic seizures (per year)		
Outcomes and effect sizes	Risk of SUDEP;		
	Risk Factor	OR (95% CI)	
		Males	Females
	Any Seizures, n / month	**<1**	**1.0 (reference)**	**1.0 (reference)**
		1 – 5	3.4 (0.5 – 22)	5.7 (0.6 – 43.9)
		>5	1.0 (0.1 – 7.9)	7.4 (1.3 – 43.0)
	No. of tonic-clonic seizures	**0**	**1.0 (reference)**	**1.0 (reference)**
		1 – 3	4.3 (0.5- 37.3)	11.2 (1.6 – 78.4)
		>3	3.3 (0.5 – 22.1)	28.0 (3.8 – 205.8)
Comments	Risk of bias – Moderate (assessed with the QUIPS checklist)		

Reference	**Faught 2008[10]**
Study type and analysis	Retrospective open cohort study design. Multivariate analysis with Cox regression models
Number of participants and characteristics	N=33,658

Reference	**Faught 2008[10]**		
	The study population was selected based on the following inclusion criteria: ≥18 years of age; ≥ one neurologist visit with a diagnosis of epilepsy or nonfebrile convulsions; ≥ two pharmacy dispensing's for ASMs (carbamazepine, ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate, valproic acid, or zonisamide) following epilepsy/seizure diagnosis; and ≥6 months of continuous Medicaid enrolment before the first post epilepsy/seizure ASM dispensing (index date) to allow for a baseline period for assessing certain covariates. Patients from the three Medicaid databases who fulfilled all the above criteria with no subsequent gaps in enrolment were pooled together to form the study population. Health insurance claims data made available to the authors from the Florida (FL), New Jersey (NJ), and Iowa (IA) Medicaid programs were used for this analysis. The choice of states was driven solely by data availability. The datasets contain complete medical and pharmacy dispensing claims for eligible people during the covered years, including Medicare/Medicaid crossovers. Combined, the datasets spanned a period from January 1997 through June 2006, including 9 million covered lives. Adherence status was evaluated separately for each treated quarter using a variation of the medication possession ratio (MPR), a common means for assessing adherence in claims data. MPR = number of days in quarter with supplies for 1 ASM / number of days in quarter. A threshold of 0.80 was used to determine adherence.		
			Total Patients
	All patients		33,658
	Age	18 – 39	15,325
		40 – 64	14,412
		≥65	3,912
	M/F ratio		14,566/19,092
	Race / Ethnicity	White	17,181
		African American	7,319

Reference	**Faught 2008[10]**		
		Other	6,400
		Unknown	2,758
	Mortality		5,405
Prognostic variable(s)	Epileptic patients on anti-seizure medication		
Confounders OR Stratification strategy	Adherence status Gender Age Race Use of ASM polytherapy Epilepsy related co-morbidities		
Outcomes and effect sizes	Multivariate mortality analysis: Results from Cox regression model		
	Risk factor		HR 95% CI
	Adherence status	**Adherent**	**Reference**
		Non adherent	3.32 (3.11 – 3.54) p value <0.001
		Untreated	0.92 (0.84 – 1.01) p value 0.067
	Use of ASM polytherapy (compared to no ASM polytherapy)		0.75 ((0.69 – 0.81) p value <0.001
	Epilepsy related comorbidity	Alzheimer's disease	1.70 (1.54 – 1.87) p value <0.001
		Brain tumour	1.58 (1.39 – 1.79) p value <0.001
		Meningitis	1.34 (1.08 – 1.65) p value 0.007

Reference	**Faught 2008[10]**		
		Stroke	1.30 (1.21 – 1.39) p value <0.001
	Charlson comorbidity index (higher index score compared to lower index score)		1.19 (1.18 – 1.20) p value <0.001
Comments	Risk of bias – Moderate (assessed with the QUIPS checklist)		

Reference	**Ryu 2015[26]**
Study type and analysis	Retrospective case control study with multivariate regression analysis
Number of participants and characteristics	N=104 Inclusion criteria: Cases were individuals who had died, had a diagnosis of epilepsy registered on the death certificate and were treated for epilepsy at the centre in the study period, and met the criteria for SUDEP. SUDEP was defined according to the following criteria: 1) Patient has the disease of epilepsy, 2) unexpected death occurred while the patient was in a reasonable state of health, 3) death was sudden, 4) death occurred during normal activities and benign circumstances, 5) there was no evidence of an obvious medical cause of death, and 6) death did not occur as a result of direct insult of status epilepticus or seizure. SUDEP is typically classified as definite if an autopsy has been performed and probable if no autopsy has been performed. In Asian countries such as Korea, cultural customs and habits mean that is not common to perform an autopsy, so all SUDEP patients in the present study were classed as probable SUDEP. All included subjects were receiving ASM stationary at least more than 1 yr. Control subjects were living epilepsy patients matched for age, sex, and initial date of enrolment at our medical centre. Tree control participants were included for each case. Exclusion criteria: People were excluded if they were followed for less than 5 year and cases aged < 5 year or > 70 year, because unexpected death in these age groups may have many differential causes

Reference	**Ryu 2015[26]**			
	The subjects in this study were patients who were registered and treated for epilepsy at Asan Medical Centre, University of Ulsan College of Medicine, Korea, the tertiary hospital in Korea, between 1993 and 2011. A total of 35,638 patients with epilepsy were enrolled. Epilepsy was defined as a history of two or more unprovoked seizures or a single seizure with evidence of epileptiform activity recorded by electroencephalogram or structural lesions documented by brain imaging. Medical records of patients were reviewed in detail and information on the cause of death was collected from the National Statistics Office database, which is matched to the hospital records using the unique national identification number of each patient.			
			SUDEP (n=26)	Controls (n=78)
	Age, mean (SD) years		41.5 ± 11.3	41.2 ± 11.4
	Age on seizure onset, mean (SD) years		19.6 ± 15	22.7 ± 13
	Disease duration, mean (SD) years		22.7 ± 11.5	22.3 ± 8.7
	M/F ratio		17/9	51/27
	Psychiatric condition (depression, anxiety)		1	6
	Seizure frequency	0 – 12 / year (<1/month)	11	53
		≥ 13 / year (>1/month)	15	25
	Epilepsy classification	Generalized idiopathic	5	12
		Symptomatic partial	11	26
		Cryptogenic partial	5	10
		Undetermined	5	30
	Number of ASM		2.0 ± 1.1	1.4 ± 0.7

Reference	**Ryu 2015[26]**		
	Family history of epilepsy	1	6
Prognostic variable(s)	Seizure frequency Number of ASM's		
Confounders OR Stratification strategy	Age at onset Duration of disease Aura Family history of epilepsy Psychiatric conditions Epilepsy classification Seizure frequency Seizure related to lesion on MR imaging Number of ASMs Type of ASM		
Outcomes and effect sizes	Multivariate regression analysis for risk of SUDEP		
	Risk factor	OR (95% CI)	
	Seizure frequency (one or less than one seizure compared to over one seizure per month)	2.5 (0.9 – 7.0)	P value 0.07
	Number of ASM's (less ASM's compared to more ASM's)	1.8 (1.1 – 3.1)	P value 0.026
Comments	Risk of bias – High (assessed with the QUIPS checklist)		

Reference	**Si 2018[30]**		
Study type and analysis	Prospective cohort study with logistic regression analysis		
Number of participants and characteristics	n=456 Inclusion and exclusion criteria The study population was formed by inpatients who were admitted to Sichuan Provincial People's Hospital, which is one of the largest tertiary hospitals in Chengdu China from January 1 2007 to July 31 2017. The patients were from different medical departments except outpatient clinic divisions. All inpatients from different age groups who were confirmed with epilepsy were recruited. The number of patients included in the analysis were those with epilepsy who died and deceased patients without epilepsy as comparison. Patients discharged to another institution or discharged against medical advice were excluded. Characteristics relevant to topic of interest		
	Factor	Deceased with epilepsy	Deceased without epilepsy
	Age (mean ± SD)	66.9 ± 20.2	66.8 ± 22.5
	Hospital stay (IQR days)	5 – 23	5 – 21
	Alcohol abuse	2	0
	Aspiration pneumonia	4	5
	Brain tumour	11	2

Reference	Si 2018[30]		
	CNS infections	35	5
	Cerebrovascular disease	163	21
	Dementia	34	2
	Depression	3	0
	Diabetes with complications	16	3
	Diabetes with no complications	69	12
	Drug abuse	1	0
	Hypertension	157	41
	Metastatic cancer	52	27
	Solid tumour without metastasis	38	6
	Psychoses	2	0
	Traumatic brain and head injuries	13	4
Prognostic variable(s)	CNS infections Metastatic cancer Solid tumour without metastasis Depression Diabetes without complications Peripheral vascular disease Traumatic brain and head injuries		

Reference	**Si 2018[30]**	
Confounders OR Stratification strategy	Age Gender CNS infections Metastatic cancer Renal disease Solid tumour without metastasis Anoxic brain injury Cardiac arrhythmias Encephalopathy Depression Paraplegia, hemiplegia Diabetes without complications Peripheral vascular disease Traumatic brain and head injuries Unclear which factors suggested in the paper are used directly within the Logistic regression model	
Outcomes and effect sizes	In hospital death in patients with epilepsy	
	Risk factors	OR (95% CI)
	CNS infections	6.1 (4.1 – 9.1)

Reference	**Si 2018[30]**	
	Metastatic cancer	3.7 (2.2 – 6.3)
	Solid tumour without metastasis	2.0 (1.1 – 3.7)
	Depression	0.2 (0.1 – 0.8)
	Diabetes without complications	1.4 (1.0 – 1.9)
	Peripheral vascular disease	0.5 (0.3 – 0.7)
	Traumatic brain and head injuries	5.1 (2.8 – 9.5)
Comments	Risk of bias – Moderate (assessed with the QUIPS checklist) MVA analysis confounders and factors within model unclear	

Reference	**Nickels 2012[22]**
Study type and analysis	Retrospective cohort study with multivariate Cox regression models
Number of participants and characteristics	n= 467 Inclusion criteria: The Medical Diagnostic Index of the Rochester Epidemiology Project was searched for all codes related to seizure and convulsion in children between the ages birth through 17 years who were residents of Olmsted County from 1980 to 2009. All identified charts were reviewed by a paediatric epileptologist. All children ages 1 month through 17 years diagnosed with new-onset epilepsy while resident in Olmsted County from 1980 to 2009 and had follow-up beyond the initial epilepsy diagnosis were included. Children with neonatal seizures that resolved during the neonatal period were included only if there was seizure recurrence

Reference	Nickels 2012[22]		
	after age 1 month. The date of epilepsy diagnosis was defined as the date the patient was first given the diagnosis of epilepsy by a physician and is used as the baseline visit for analyses in this report. The historical records of all patients were reviewed to abstract potential risk factors including seizure mode of onset, epilepsy aetiology, history of status epilepticus, the presence and severity of neurologic impairment, and epilepsy outcome. Exclusion criteria: Those children treated after a single unprovoked seizure, but without any of the preceding abnormalities, and those with only febrile convulsions were excluded. In addition, those with only acute symptomatic seizures, defined as ‘‘seizure at the time of a systemic insult or in close association with an acute neurologic insult’’ were excluded		
	Male / female ratio		246/221
	Neurologic examination	Normal	348
		Abnormal	119
	Cognitive development	Normal	275
		Mild/moderate delay	109
		Severe delay	83
	Status epilepticus (ever)	No	373
		Yes	94
	Mode of onset	Generalized	113
		Focal	317
		Unknown	19
		Spasm	14
		Generalized and focal	4

Reference	**Nickels 2012[22]**		
	ASMs used at last visit	No ASM	190
		1	199
		2	58
		3	15
		≥4	5
	ASMs discontinued due to lack of efficacy	No failed ASM	322
		1	71
		2	31
		≥3	43
	Seizure control at last follow-up	Seizure free >12 months	312
		Seizure 6–12 months	48
		Seizure 3–6 months	28
		Seizure >3 every month	79
Prognostic variable(s)	Abnormal neurological examination Abnormal cognitive function Status epilepticus, ever		
Confounders OR Stratification strategy	Neurologic examination cognitive function previous status epilepticus		

Reference	**Nickels 2012[22]**			
	mode of onset, aetiology usage of ≥ 2 ASM's seizure frequency intractable at last follow up			
Outcomes and effect sizes	Multivariate analysis for risk of death in children with Epilepsy			
	Risk factor	HR	95% CI	P value
	Abnormal neurological examination	12.80	1.40 – 116.96	0.02
	Abnormal cognitive function	3.78	0.42 – 33.80	0.23
	Status epilepticus, ever	1.34	0.48 – 3.77	0.58
	Metabolic/ structural aetiology	2.62	0.69 – 9.90	0.16
Comments	Risk of bias – High (assessed with the QUIPS checklist) Reference or comparison values assumed to be without the risk factor (e.g., abnormal neurological examination compared to no abnormal neurological examination)			

Reference	**Chen 2005[7]**
Study type and analysis	Prospective cohort study with Cox proportional hazards regression model
Number of participants	n=263

and characteristics	Epilepsy is defined as recurrent seizures without an acute cause. Participants were prospectively recruited patients with epilepsy who were at least 17 years old and newly referred to the outpatient epilepsy clinics at the National Taiwan University Hospital (NTUH) between 1st January 1991 and 31 December 1991. The NTUH is the largest university teaching hospital and one of the major tertiary referral centres in Taiwan. All the patients underwent thorough clinical assessment to ensure that they had active epilepsy, this definition being restricted to patients with epilepsy who had experienced recurrent seizures within the past 5 years or who had been taking anticonvulsants within the last 5 years. Patients with seizures provoked by acute symptomatic causes were excluded. A total of 263 patients with active epilepsy formed the dataset for analysis. This cohort was followed until 31 December 2000. The authors recorded 32 deaths out 263 patients. The cause of death was assessed in the light of documentary evidence, including medical charts, autopsy findings, and pathological reports. Sudden unexpected death (SUD) was defined as, non-traumatic death in a patient with epilepsy who had been previously healthy or had suffered from a disease which would not normally be expected to result in immediate or sudden death, and those deaths not directly related to seizure or status epilepticus.		
	Age at onset (years)	0 – 19	125
		20 – 39	95
		40 – 59	28
		60+	15
	Male / female ratio	144 / 119	
	Seizure type	Generalized	53
		Partial seizure	210
	Frequency	>1/day	21
		1/day - >1/week	58
		1/week - >1/month	63
		≤1/month	121

	Medication	Monotherapy	157
		Polytherapy	106
Prognostic variable(s)	Aetiology of seizure / epilepsy		
Confounders OR Stratification strategy	Age of onset Frequency Imaging Type of seizure Aetiology Medication Age Gender		
Outcomes and effect sizes	Multivariate analysis of clinical variable association with death in epilepsy		
	Risk factor	Hazard Ratio (95% CI)	
	Aetiology	**Cryptogenic (reference)**	**1.00**
		Tumour	4.67 (1.76 – 12.37)
		Vascular lesions	1.37 (0.46 – 4.13)
		Trauma	0.81 (0.22 – 2.95)
		Infection	1.18 (0.15 – 9.27)
Comments	Risk of bias – Moderate (assessed with the QUIPS checklist)		

Reference	**Langan 2005[15]**			
Study type and analysis	Case control study with backward stepwise conditional logistic regression			
Number of participants and characteristics	Cases = 151 Controls = 534 Inclusion and exclusion criteria People with epilepsy who died suddenly between the ages of 16 and 50 years were identified by coroners and neurologists and by interviews with bereaved families. Deaths occurred between 1989 and 1998. Cases were also identified through interviews with self- referred parents and partners of the deceased through Epilepsy Bereaved?, a UK support charity. Interviews involved a semi-structured questionnaire that examined aspects of the patients' epilepsy, medical and social background, and the circumstances of death. Written informed consent was obtained before the interview. Subjects were individuals with a history of active epilepsy (at least one seizure in the past 5 years or taking an ASM if in remission) whose death fulfilled the following definition: sudden, unexpected, witnessed, or unwitnessed, nontraumatic, and non-drowning death in an individual with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus in which the post-mortem examination does not reveal a cause for death. Each case had four controls matched for age (±5 years) and geographic location. Practices in the appropriate geographic areas were identified from the MRC General Practice Research Framework, a network of approximately 900 groups of family practitioners (general practitioners) throughout the United Kingdom and includes practices in urban and rural areas. Individuals with epilepsy suitable to act as controls were identified using a diagnostic index or prescription database. Controls were randomly chosen from this eligible population, and, once a diagnosis of epilepsy was confirmed, data were extracted from the patients' medical records.			
	Mean age	32 years		
	M / F ratio	97/57		
			Cases	Controls
	History of GCTC seizures	No	31	426

Reference	**Langan 2005[15]**			
		Yes	120	108
	No. of tonic clonic seizures in previous 3 months	0 - 5	87	496
		6 - 10	17	13
		11 - 20	13	2
		21 - 50	7	3
		>50	7	3
	Total no. of ASMs ever	1 – 2	42	400
		3 – 4	30	128
		>4	47	50
		0	14	12
		Not known	21	26
	Carbamazepine (current use)	No	72	381
		Yes	74	235
	Supervision	None	109	169
		Same room	34	156
		Special precautions	11	42
	Asthma	No	142	522
		Yes	6	67
Prognostic variable(s)	History of generalized tonic clonic seizures			

Reference	**Langan 2005[15]**		
	No of tonic clonic seizures in previous 3 months		
	Total number of anti-seizure medications		
	Carbamazepine usage		
	Supervision		
	Asthma		
Confounders OR Stratification strategy	History of generalized tonic clonic seizures		
	No of tonic clonic seizures in previous 3 months		
	Total number of anti-seizure medications		
	Carbamazepine usage		
	Supervision		
	Asthma		
Outcomes and effect sizes	Risk of SUDEP;		
	Risk factor		OR (95% CI)
	History of generalized tonic clonic seizures	**No (reference)**	**1**
		Yes	13.8 (6.6 – 29.1)
	No of tonic clonic seizures in previous 3 months	**0 – 5 (reference)**	**1**
		6 – 10	0.7 (0.2 – 2.5)
		11 – 20	19.4 (1.7 – 226)
		21 – 50	14.6 (1.3 – 165)

Reference	**Langan 2005[15]**		
		>50	11.7 (0.3 – 419)
	Total number of anti-seizure medications	**1 – 2 (reference)**	**1**
		3 – 4	1.3 (0.6 – 2.8)
		>4	3.1 (1.4 – 7.0)
		0	21.7 (4.4 – 106)
		Not known	8 (2.7 – 25.6)
	Carbamazepine	**No (reference)**	**1**
		Yes	2 (1.1 – 3.8)
	Supervision	**None (reference)**	**1**
		Same room	0.4 (0.2 – 0.8)
		Special precautions	0.1 (0.0 – 0.3)
	Asthma	**No (reference)**	**1**
		Yes	0.2 (0.1 – 0.9)
Comments	Risk of bias – High (assessed with the QUIPS checklist) Supervision at night was defined as the presence in the bedroom of an individual of normal intelligence and at least 10 years old or the use of special precautions. Special precautions involved regular checks throughout the night or the use of a listening device.		

Reference	**Nilsson 1999[23]**			
Study type and analysis	Nested case control study with multivariate analysis			
Number of participants and characteristics	Cases = 57 Controls = 171 The study is based on a cohort of people aged between 15 – 70 who during 1980 – 1989 had been admitted to and discharged with a diagnosis of epilepsy from any hospital in the county of Stockholm. The study population was followed up through the National Cause of Death Register until December 31 1991. Cases were individuals who had died with a diagnosis of epilepsy registered on the death certificate and who after review of medical and necropsy records were found to meet SUDEP criteria. Three control participants, who were living epilepsy patients matched for age and sex were selected from the same cohort for each case. All medical records were examined.			
			Cases	Controls
	M/F ratio		34/23	69/102
	Epilepsy type	Localisation related symptomatic	26	90
		Localisation related cryptogenic	17	45
		Generalized idiopathic	7	12

Reference	Nilsson 1999[23]			
		Undetermined	7	24
	Mean duration of epilepsy in years (SD)		19.9 (13.0)	13.5 (12.3)
	CNS abnormality	No	49	152
		Yes	8	19
	Febrile seizures	No	54	168
		Yes	3	3
	CNS trauma	No	40	133
		Yes	17	38
	Cerebrovascular disease	Yes	53	139
		No	4	32
	Heart Disease	No	56	157
		Yes	1	14
	CNS infection	No	50	156
		Yes	7	15
	Neoplasms	No	54	150
		Yes	3	19
	Psychiatric Disorder	No	51	159
		Yes	6	12

Reference	**Nilsson 1999[23]**			
	Alcoholism	No	37	121
		Yes	20	50
	Dementia	No	51	168
		Yes	6	3
Prognostic variable(s)	Seizure frequency during last year Epilepsy type Number of ASM Changes in dose of ASM per year			
Confounders OR Stratification strategy	Seizure frequency during last year Age in years at epilepsy onset Epilepsy type Number of ASM Changes in dose of ASM per year			
Outcomes and effect sizes	Risk of SUDEP			
	Risk factor			RR 95% CI
	Seizure frequency during the last year	0 – 2 (reference)		1.00
		3 - 12		4.47 (1.33 – 15.03)
		>12		4.64 (1.22 – 17.63)
	Epilepsy type	Generalized Idiopathic (reference)		1.00

Reference	**Nilsson 1999[23]**		
		Localisation related symptomatic	1.15 (0.18 – 7.17)
		Localisation related cryptogenic	1.94 (0.27- 13.71)
		Undetermined	1.17 (0.14 – 9.78)
	Number of ASMs	1 (reference)	1.00
		2	1.95 (0.65 – 5.81)
		3	10.23 (1.86 – 56.45)
	Changes in dose of ASM per year	0 (reference)	1.00
		1 – 2	0.69 (0.26 – 1.82)
		3 – 5	9.32 (1.95 – 44.50)
	Antipsychotic Medication	No (reference)	1.00
		Yes	2.14 (0.90 – 5.10)
	Anxiolytic Medication	No (reference)	1.00
		Yes	3.0 (1.16 – 7.76)
	Alcoholism	No (reference)	1.00
		Yes	RR 1.42 (0.68 – 2.97)
Comments	Risk of bias – High (assessed with the QUIPS checklist)		

Reference	**Sveinsson 2020[36] *(Sveinsson a)***
Study type and analysis	Case control study with conditional logistic regression and individual modelling
Number of participants and characteristics	Cases n = 255 Controls n=1148 Cases: Using linkage to the National Cause of Death Registry (ICD-10 classified since 1994),18 9,605 deaths were identified from the study population during the follow-up time from July 1, 2006, to December 31, 2011. All deaths with epilepsy written on the death certificate (n = 1,276), together will all individuals who died during 2008 (n = 1,890), were eligible SUDEP cases. One neurologist reviewed all death certificates. Excluded from further analysis of case records were obvious non-SUDEP deaths such as malignancy, terminal illness, stroke, myocardial infarct, and post-mortem confirmed pneumonia (figure 1). For the remaining cases (n = 1,373), where SUDEP could potentially be the cause of death, patient records from family physicians, hospital records, nursing homes or other institutions, police records, and autopsy records were reviewed. Controls: From the study population, 5 epilepsy controls (n = 1,275) for each SUDEP case, of the same sex, who were alive at the case's time of death were randomly selected by the National Board of Health and Welfare. The case's time of death served as an index date for the controls, who thus were matched with the cases for sex and calendar time. We acquired medical records for 1,232 (97%) controls, of which 84 (6.8%) were adjudicated not to have epilepsy after case review. The remaining 1,148 individuals served as controls in the current study

Reference	**Sveinsson 2020[36] *(Sveinsson a)***						
	Together with each individual's personal identification number, the Swedish National Patient Register (SNPR) contains ICD codes for all patients hospitalized (starting in 1968, with total national coverage from 1987) or managed in hospital-based ambulatory care since 2001.17 Our study population was composed of all individuals who were registered at any time during 1998–2005 in the SNPR with an ICD-10 code for epilepsy (G 40) (n = 78,424) who were alive on June 30, 2006 (n = 60,952)						
		Cases (n=255)			Controls (n=1148)		
		No ASMs	Monotherapy	Polytherapy	No ASMs	Monotherapy	Polytherapy
	Total	46	113	96	265	483	400
	Age at diagnosis	21 (12 – 15)	17 (4 – 46)	5 (1 – 24)	9 (4 – 22)	16 (7 – 41)	9 (3 – 21)
	Duration, years	12 (7 – 27)	17 (9 – 31)	30 (14 – 46)	10 (8 – 16)	14 (8 – 25)	21 (12 – 36)
	M/F ratio	33/13	65/48	56/40	170/95	274/109	236/164
	Sharing bedroom	6	17	9	77	179	135
	Generalized Epilepsy	8	17	12	68	131	68
	Focal epilepsy	27	88	71	175	311	308
	Generalized and focal	1	2	7	4	10	17
	Intellectual disability	7	36	54	44	107	172
	Substance Abuse	11	17	6	18	16	19
	Alcohol dependence	8	13	5	13	13	8
	Primary school education	23	59	61	152	223	246

Reference	**Sveinsson 2020[36] *(Sveinsson a)***						
	History of GTCS	44	111	96	195	401	347
	GTCS last year	34	94	89	32	95	153
	Nocturnal GTCS last year	13	51	46	13	24	62
	Carbamazepine	-	45	40	-	130	149
	Lamotrigine	-	27	38	-	104	177
	Valproic Acid	-	17	30	-	126	153
	Levetiracetam	-	2	27	-	26	142
	Phenytoin	-	10	19	-	44	55
	Topiramate	-	2	20	-	11	54
	Oxcarbazepine	-	3	4	-	17	28
Prognostic variable(s)	ASM therapy Monotherapy Nonadherence mentioned in medical record						
Confounders OR Stratification strategy	ASM therapy Medication Time since last dispensed ASM Nonadherence						
Outcomes and effect sizes	Risk of SUDEP						
	Risk factor	Cases	Controls	Model 3 OR (95% CI)			

Reference	**Sveinsson 2020[36] *(Sveinsson a)***				
	ASM therapy	**No ASM (reference)**	**46**	**265**	**1**
		Monotherapy	113	483	0.79 (0.44 – 1.41)
		Polytherapy (≥2ASMs)	96	400	0.48 (0.26 – 0.90)
		2 ASMs	65	272	0.59 (0.31 – 1.12)
		Polytherapy (>3 ASMs)	31	128	0.31 (0.14 – 0.67)
	Monotherapy	**No ASM (reference)**	**46**	**265**	**1**
		Carbamazepine	45	130	1.0 (0.48 – 2.11)
		Lamotrigine	27	104	0.93 (0.41 – 2.12)
		Valproic Acid	17	126	0.52 (0.20 – 1.30)
		Phenytoin	10	44	0.56 (0.17 – 1.88)
		Levetiracetam	2	26	0.10 (0.02 – 0.61)
		Oxcarbazepine	3	17	0.58 (0.09 – 3.69)
		Topiramate	2	11	2.02 (0.29 – 14.26)
		Other	7	25	1.32 (0.39 – 4.53)
	Nonadherence mentioned in medical record	**No (reference)**	**173**	**886**	**1**
		Yes	62	118	2.75 (1.58 – 4.78)
Comments	Risk of bias – Low (assessed with the QUIPS checklist)				

Reference	**Sveinsson 2020[36] *(Sveinsson a)***
	Model 3 – adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year Model 3 was used within the analysis as it adjusted for the most potential confounders

Reference	**Sveinsson 2020[35] *(Sveinsson b)***
Study type and analysis	Case control study with conditional logistic regression and individual modelling
Number of participants and characteristics	Cases n = 255 Controls n=1148 Cases: Using linkage to the National Cause of Death Registry (ICD-10 classified since 1994),18 9,605 deaths were identified from the study population during the follow-up time from July 1, 2006, to December 31, 2011. All deaths with epilepsy written on the death certificate (n = 1,276), together will all individuals who died during 2008 (n = 1,890), were eligible SUDEP cases. One neurologist (O.S.) reviewed all death certificates. Excluded from further analysis of case records were obvious non-SUDEP deaths such as malignancy, terminal illness, stroke, myocardial infarct, and post-mortem confirmed pneumonia (figure 1). For the remaining cases (n = 1,373), where SUDEP could potentially be the cause of death, patient records from family physicians, hospital records, nursing homes or other institutions, police records, and autopsy records were reviewed. Controls:

Reference	**Sveinsson 2020[35] *(Sveinsson b)***		
	From the study population, 5 epilepsy controls (n = 1,275) for each SUDEP case, of the same sex, who were alive at the case's time of death were randomly selected by the National Board of Health and Welfare. The case's time of death served as an index date for the controls, who thus were matched with the cases for sex and calendar time. We acquired medical records for 1,232 (97%) controls, of which 84 (6.8%) were adjudicated not to have epilepsy after case review. The remaining 1,148 individuals served as controls in the current study Together with each individual's personal identification number, the Swedish National Patient Register (SNPR) contains ICD codes for all patients hospitalized (starting in 1968, with total national coverage from 1987) or managed in hospital-based ambulatory care since 2001.17 Our study population was composed of all individuals who were registered at any time during 1998–2005 in the SNPR with an ICD-10 code for epilepsy (G 40) (n = 78,424) who were alive on June 30, 2006 (n = 60,952)		
		Cases	Controls
	Total number	255	1148
	M/F ratio	154/101	680/468
	Age at death, y/index, mean (range)	47 (4–92)	39 (3–94)
	Age at epilepsy diagnosis, y, mean (range)	22.4 (0–86)	20.0 (0–86)
	Duration of epilepsy, y, mean under (range)	24 (1–81)	20 (1–78)

Reference	Sveinsson 2020[35] *(Sveinsson b)*			
	Type of epilepsy, n (%)	Generalized	37 (14.5)	267 (23.3)
		Focal	186 (73.0)	794 (69.3)
		Focal and generalized	10 (4.0)	31 (2.7)
		Unknown	22 (8.6)	56 (4.9)
	Causes of epilepsy, n (%)	Genetic	48 (18.8)	303 (26.4)
		Structural	129 (50.6)	444 (38.7)
		Infectious	12 (4.7)	42 (3.7)
		Metabolic	2 (0.8)	9 (0.8)
		Autoimmune	2 (0.8)	10 (0.9)
		Unknown	66 (25.9)	359 (31.3)
	Living conditions, n (%)	Sharing household and bedroom	32 (12.5)	391 (34.1)
		Sharing household but not bedroom	49 (19.2)	398 (34.7)
		Not sharing household	174 (68.2)	304 (26.5)
		Unknown	0	55 (4.8)
	Highest education, n (%)	Postsecondary education	26 (10.2)	168 (14.6)

Reference	**Sveinsson 2020[35] *(Sveinsson b)***			
		High school/secondary education	86 (33.7)	359 (31.3)
		Primary education	86 (33.7)	297 (25.8)
		Missing education	57 (22.4)	324 (28.2)
Prognostic variable(s)	Type of epilepsy Living conditions Highest education			
Confounders OR Stratification strategy	Age Sex Generalized tonic-clonic seizures frequency and nocturnal generalized tonic-clonic seizures last year of observation Living conditions Antiepileptic drugs			
Outcomes and effect sizes	Risk of SUDEP			
	Risk factors	Cases	Controls	Model 3 (OR 95% CI)
	Type of epilepsy	**Generalized (reference)**	**37**	**267**	**1**
		Focal	186	794	1.34 (0.77–2.33)
		Focal and generalized	10	31	1.42 (0.49–4.15)
		Unknown	22	56	3.51 (1.44–8.55)

Reference	**Sveinsson 2020[35] *(Sveinsson b)***				
	Living conditions	**Sharing household and bedroom (reference)**	**32**	**391**	**1**
		Sharing household but not bedroom	49	398	2.28 (1.14–4.58)
		Not sharing household	174	359	5.01 (2.93–8.57)
	Highest education	**Postsecondary education (reference)**	**26**	**168**	**1**
		High school education/secondary education	86	359	1.59 (0.78–3.27)
		Primary education	86	297	1.21 (0.58–2.56)
	Comorbidity	Substance abuse	34	53	2.07 (1.07-4.01)
	Comorbidity	Alcohol dependence	26	34	2.30 (1.02-5.21)
Comments	Risk of bias – Moderate (assessed with the QUIPS checklist) Model 3 – Adjusted for age, sex, generalized tonic-clonic seizure frequency and nocturnal generalized tonic-clonic seizures last year, living conditions and epileptic drugs. Model 3 was used within the analysis as it adjusted for the most potential confounders				

Reference	**Zhang 2016[40]**
Study type and analysis	Case control study with multivariate logistic regression analysis

Reference	**Zhang 2016[40]**		
Number of participants and characteristics	Probable SUDEP n = 35 Control n = 105 Inclusion: In this study, patients with convulsive epilepsy were defined as (age, >2 years) those satisfying following diagnosis criteria: major criteria: (1) Loss of consciousness; (2) Rigidity; (3) Generalized convulsive movements; minor criteria: (1) Bitten tongue or injury sustained in falling; (2) Urinary incontinence; (3) Post-seizure fatigue; (4) Drowsiness; (5) Headache or muscle aches (positive diagnosis requires at least two major criteria and at least two minor criteria). Exclusion criteria: The exclusion criteria were as follows: (1) provoked seizures only; (2) age under two years at the time of recruitment; (3) presence of a learning disability or an active psychiatric condition; (4) presence of a progressive neurological condition; (5) presence of cardiac, hepatic, or renal disorders, or severe hypertension; (6) status epilepticus alone; (7) current medication possibly affecting PB usage. Three healthy controls per case were chosen as a control group. As part of an epilepsy management program, 16 target counties covering a population of 10.5 million individuals in rural West China were selected to undergo a convulsive epilepsy screening followed by pragmatic phenobarbital (PB) monotherapy at the primary care level from May 2005 to December 2013. In accordance with the rural management program, patients with convulsive epilepsy in each target county were identified at the first year and received PB intervention during follow-up.		
		Probable SUDEP	Control

Reference	**Zhang 2016[40]**			
	Age (mean, range)	40.2 (8 – 69)	40.2 (8 – 69)	
	M/F ratio:	18/17	54/51	
	History of regular ASM's	Pre study no treatment	15	54
		Pre study no regular ASMs	20	51
	Onset age (years)	≤10	12	13
		11-30	15	60
		>30	8	32
	Disease duration (years)	≤3	3	9
		4-10	10	34
		>10	25	24
	Seizure frequency at baseline (n/year)	≤3	2	28
		4-10	8	53
		>10	25	24
	Seizure frequency prior to SUDEP (n/month)	Seizure free	15	93
		1-2	12	10
		≥3	8	2
	Phenobarbital compliance	Bad	5	14
		Good	30	91
Prognostic variable(s)	Seizure frequency at baseline (n/year)			

Reference	**Zhang 2016[40]**					
	Seizure free prior to probable SUDEP (1 month)					
Confounders OR Stratification strategy	Onset age Seizure frequency at baseline (n/year) Seizure free prior to probable SUDEP (1 month)					
Outcomes and effect sizes	Risk of probable SUDEP					
			Probable SUDEP	Control	OR (95% CI)	P value
	Seizure frequency at baseline (n/year)	**≤10 (reference)**	**13**	**43**	**1**	**0.001**
		>10	22	62	5.9 (2.2 – 16.6)	
	Seizure free prior to probable SUDEP (1 month)	**Yes (reference)**	**15**	**93**	**1**	**<0.001**
		No	20	12	9.5 (3.0 – 30.1)	
Comments	Risk of bias – High (assessed with the QUIPS checklist)					

Appendix E Forest plots

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

Figure 2: One to five seizures per month

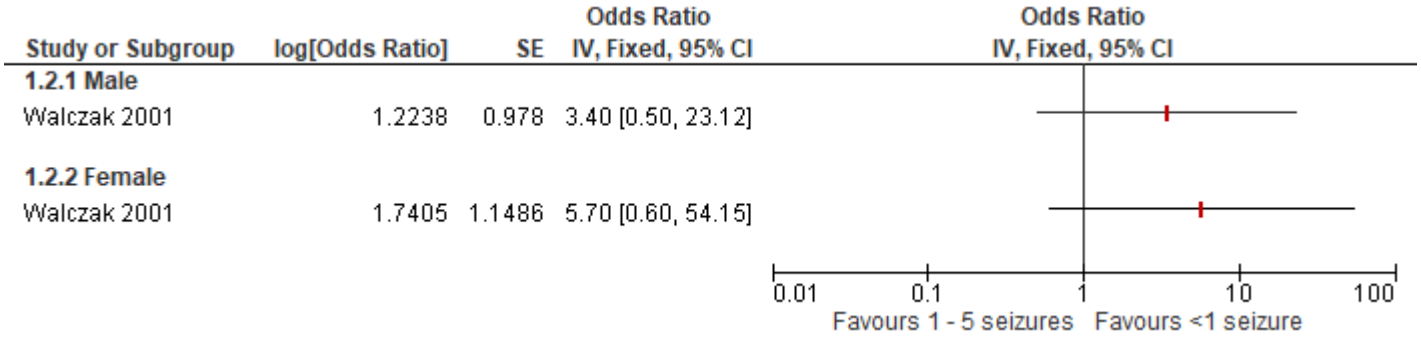


Figure 3: Over five seizures per month

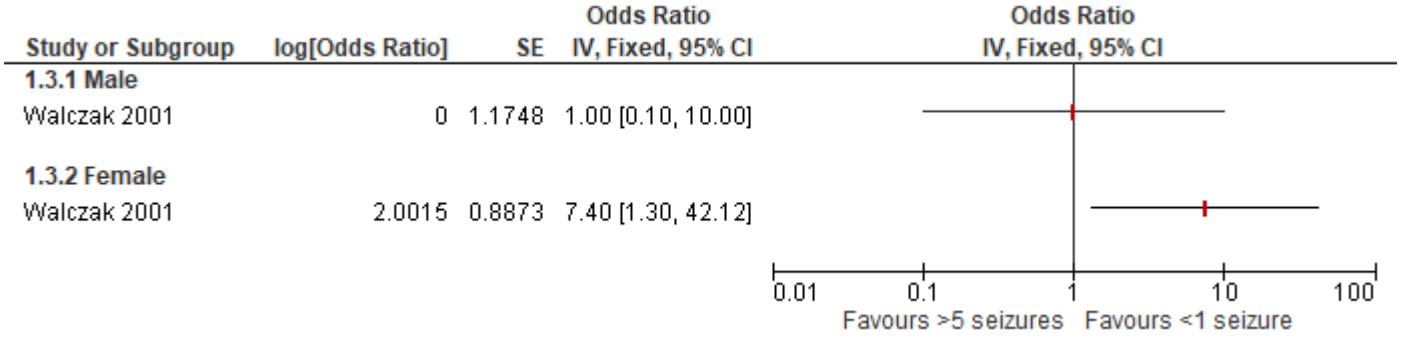


Figure 4: One to three tonic-clonic seizures per year

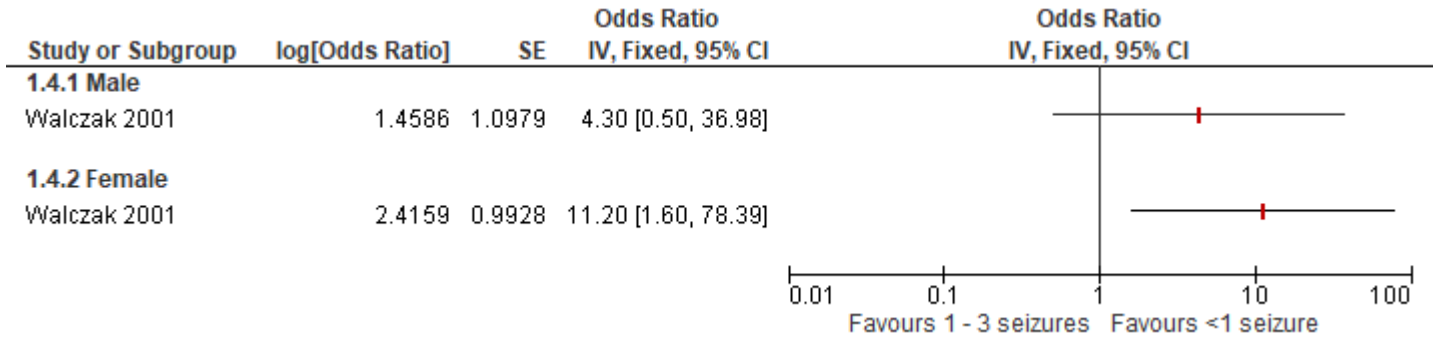
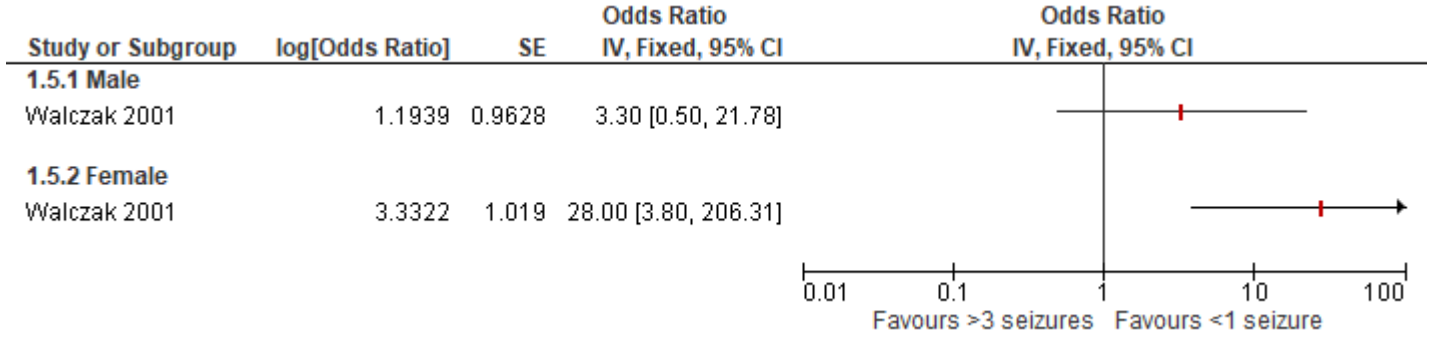


Figure 5: Over three tonic-clonic seizures per year



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

Figure 6: Seizure frequency

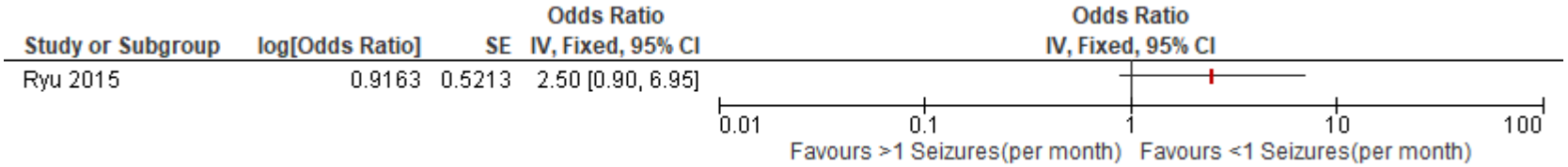


Figure 7: Number of ASM's

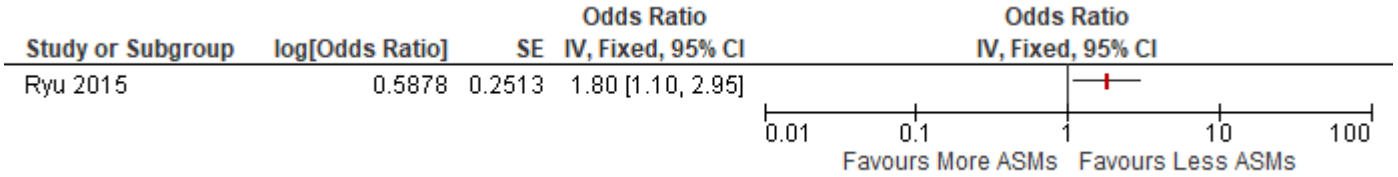


Figure 8: Nonadherence of medications

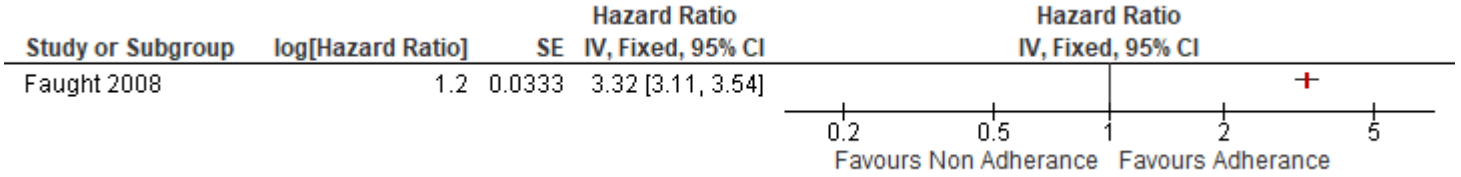


Figure 9: Untreated Epilepsy

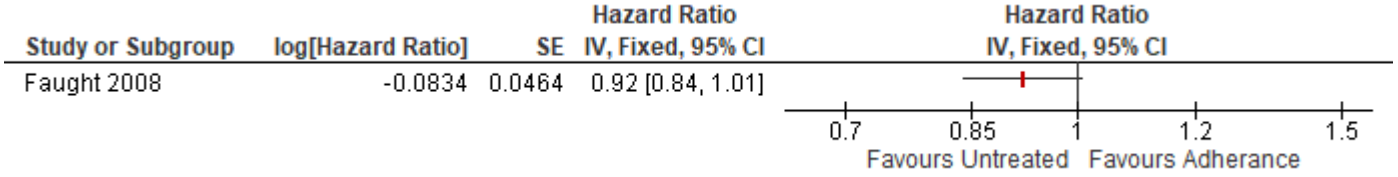


Figure 10: Polytherapy

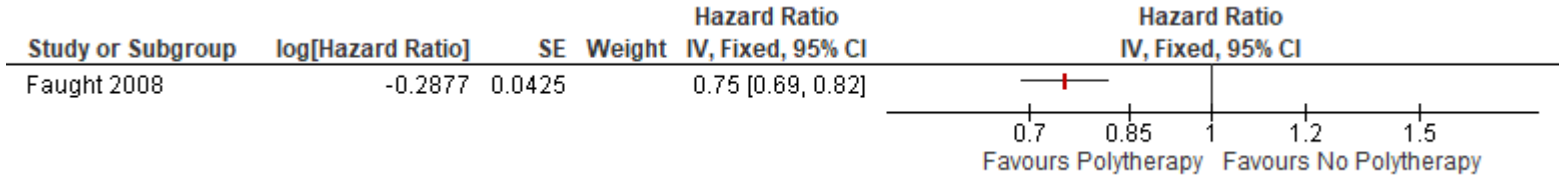


Figure 11: Neurological condition

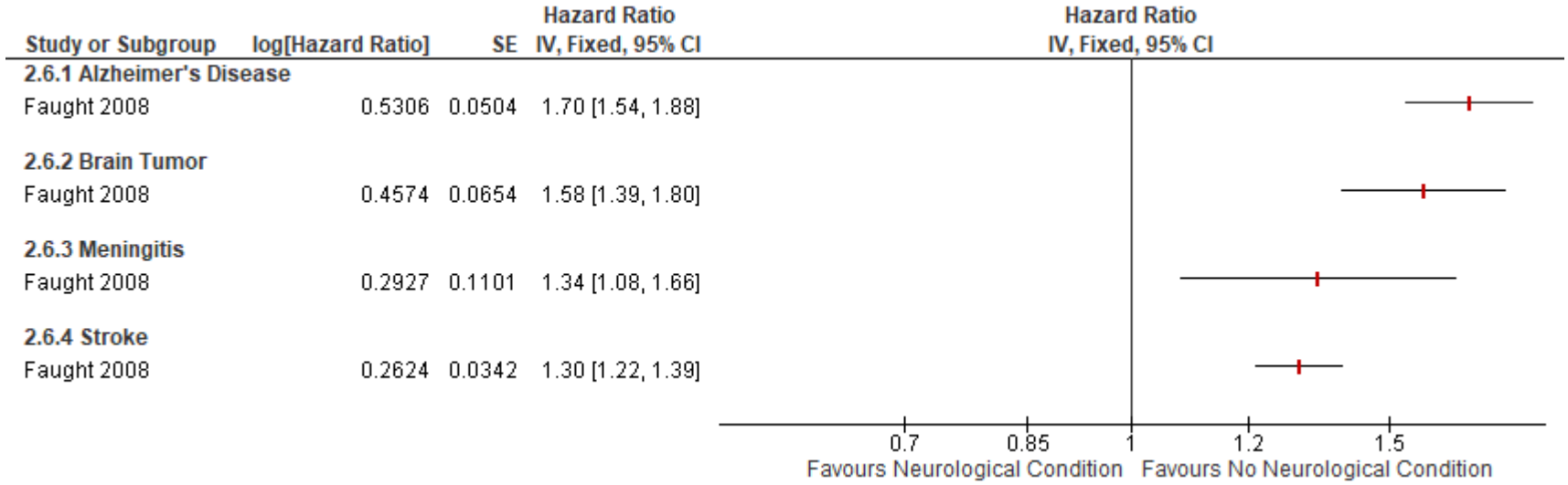


Figure 12: Charlson comorbidity Index

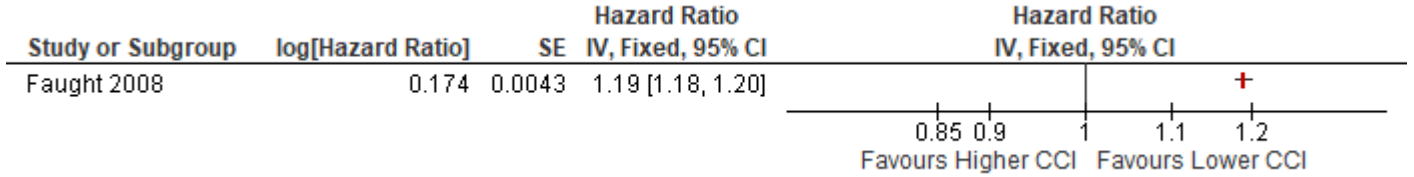


Figure 13: CNS infections

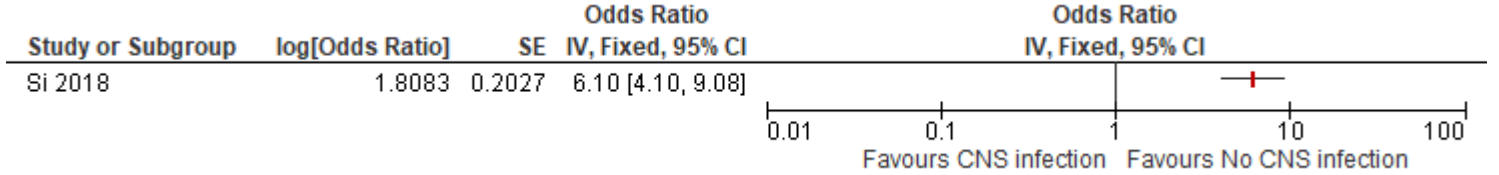


Figure 14: Metastatic Cancer

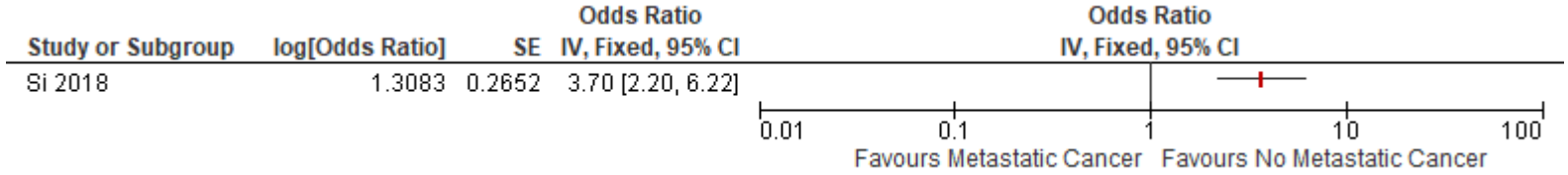


Figure 15: Solid tumour (no metastasis)

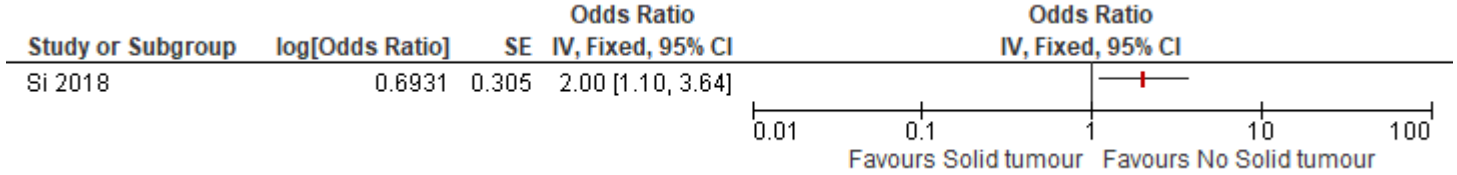


Figure 16: Depression

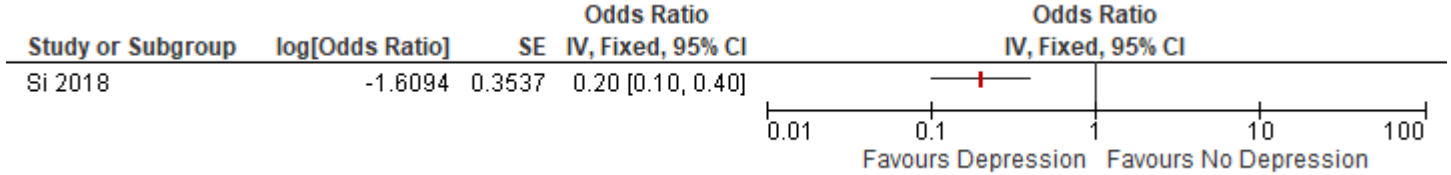


Figure 17: Diabetes (no complications)

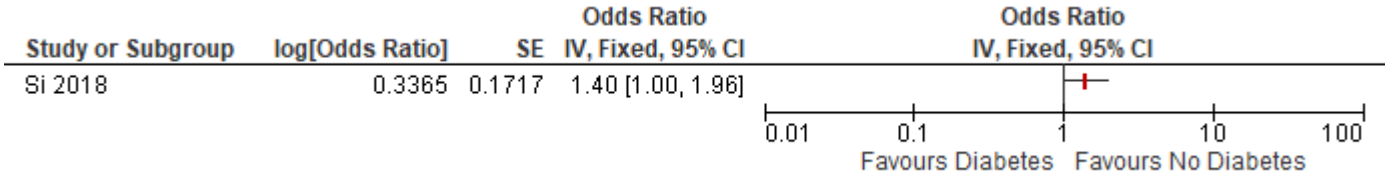


Figure 18: Peripheral vascular disease

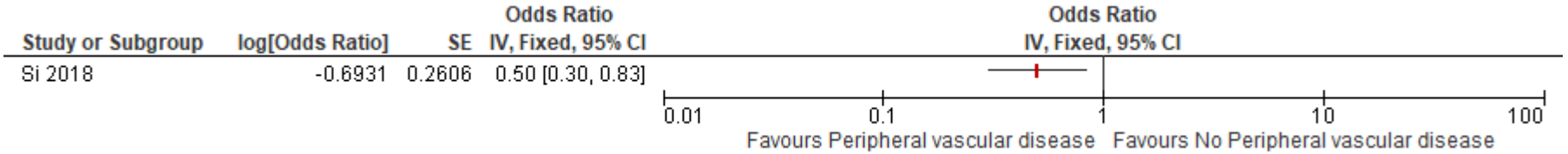
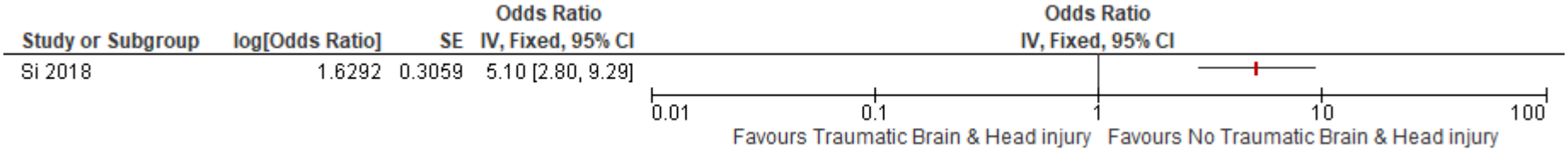


Figure 19: Traumatic brain and head injury



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

Figure 20: Abnormal neurological examination

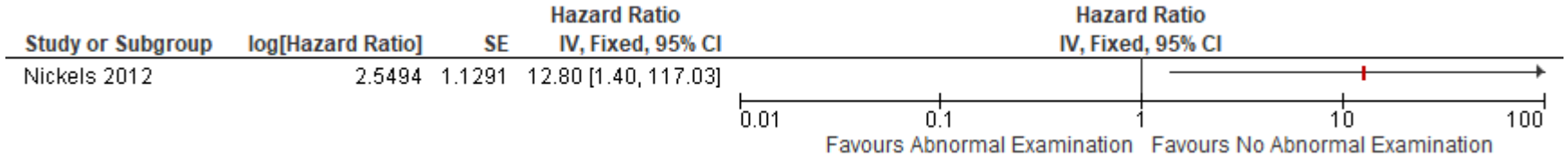


Figure 21: Abnormal cognitive function

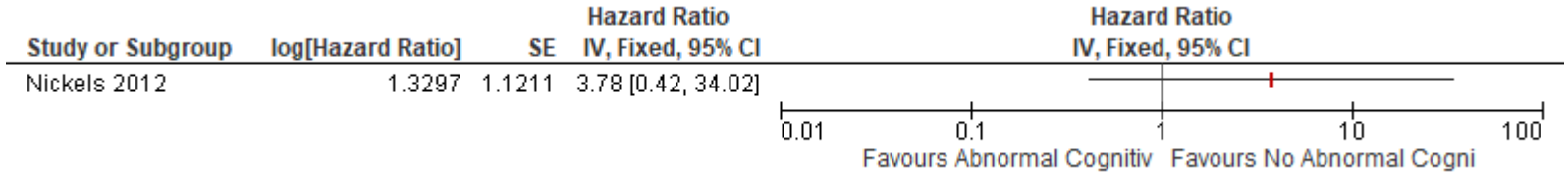


Figure 22: Status Epilepticus (ever)

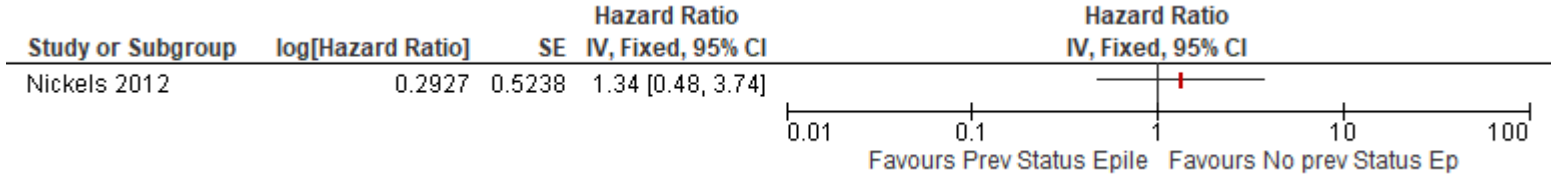
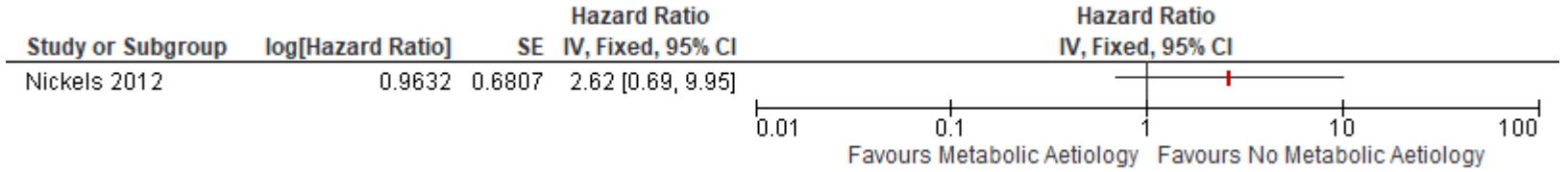


Figure 23:Metabolic / Structural Aetiology



E.4 Mixed population of children <18 years and adults >18 years (follow up 1 - 5 years)

Figure 24: Tumour Aetiology

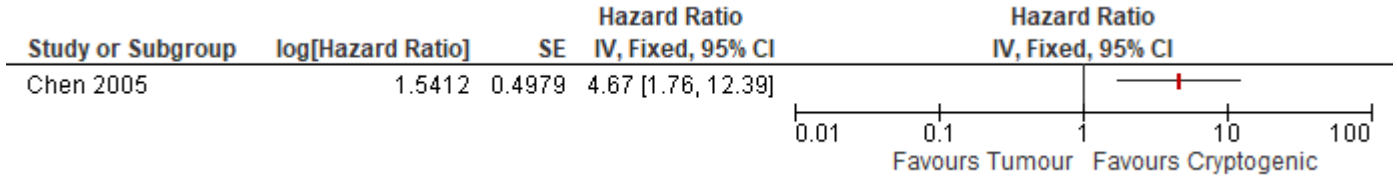


Figure 25: Vascular lesion Aetiology

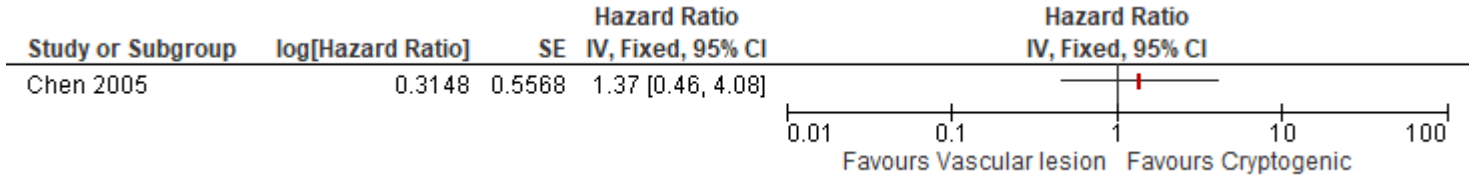


Figure 26: Trauma Aetiology

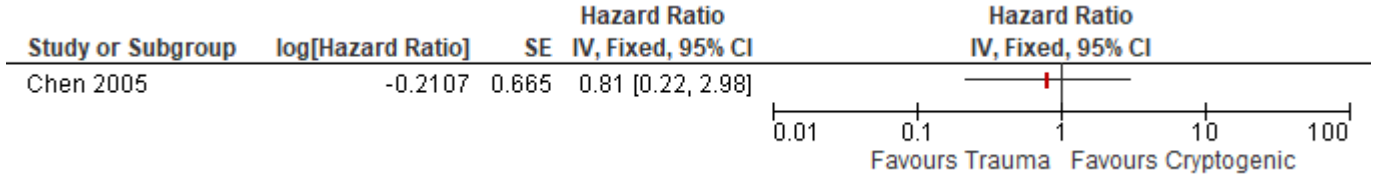
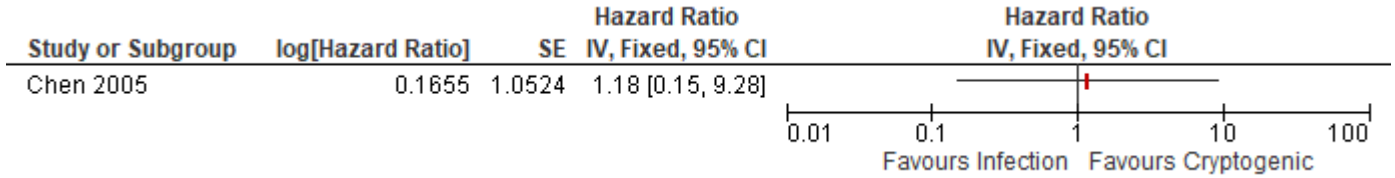


Figure 27: Infection Aetiology



E.5 Mixed population of children <18 years and adults >18 years (follow up > 5 years)

Figure 28: Seizure frequency at baseline

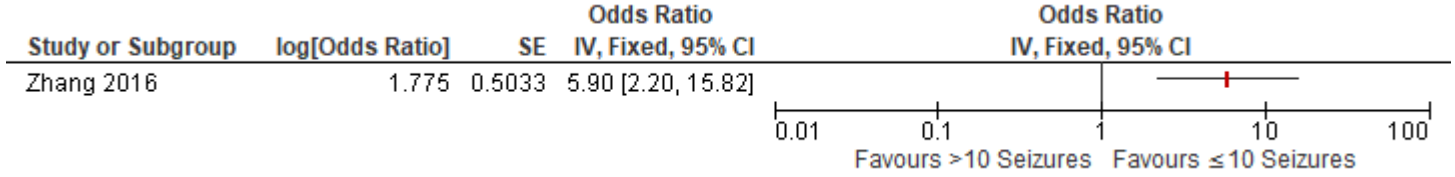


Figure 29: Seizure free (prior to SUDEP)

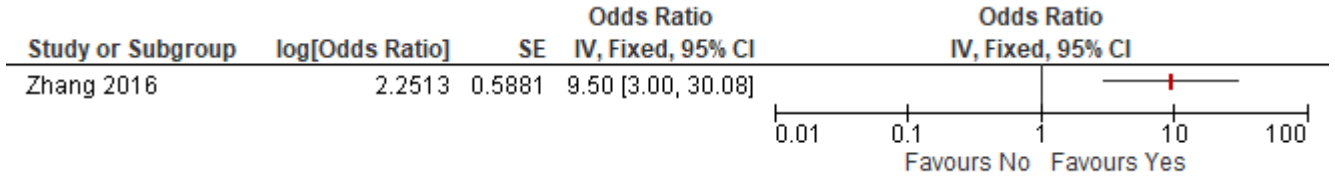


Figure 30: Seizure frequency – (3 – 12 seizures past year)

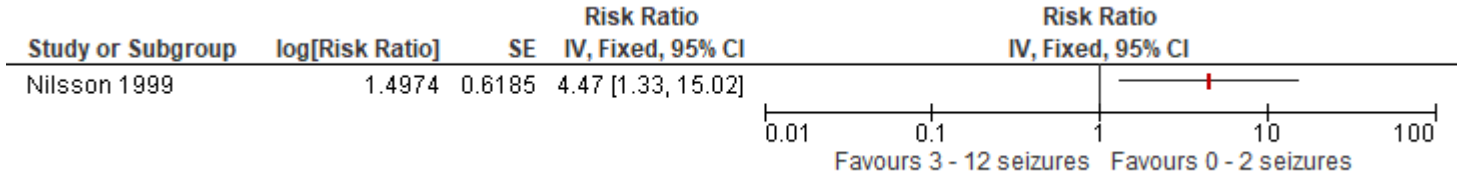


Figure 31: Six to ten tonic-clonic seizures (previous 3 months)

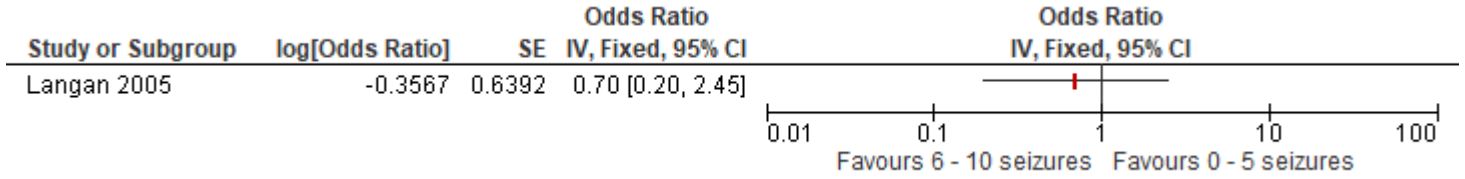


Figure 32: Eleven to twenty tonic-clonic seizures (previous 3 months)

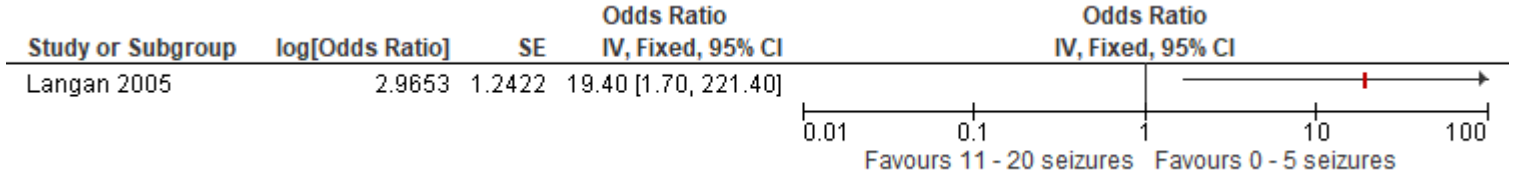


Figure 33: Twenty-one to fifty tonic-clonic seizures (previous 3 months)

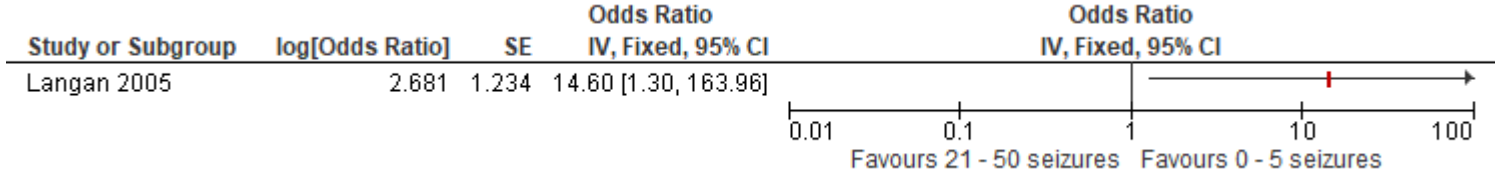


Figure 34: Over fifty tonic-clonic seizures (previous 3 months)

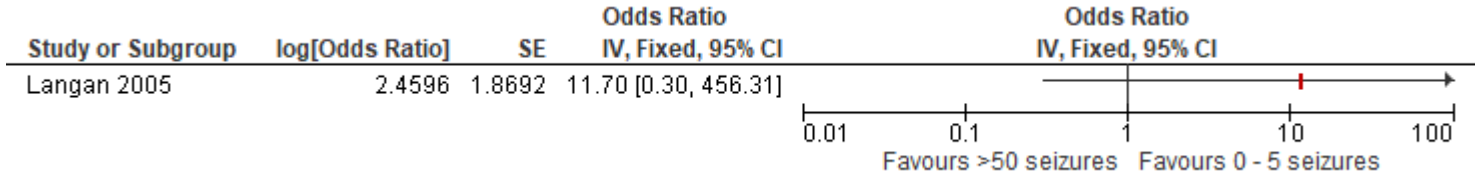


Figure 35: History of generalized tonic-clonic seizures

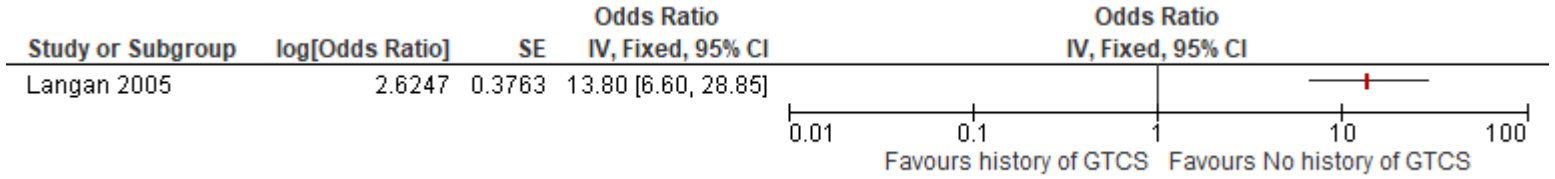


Figure 36: Focal seizures

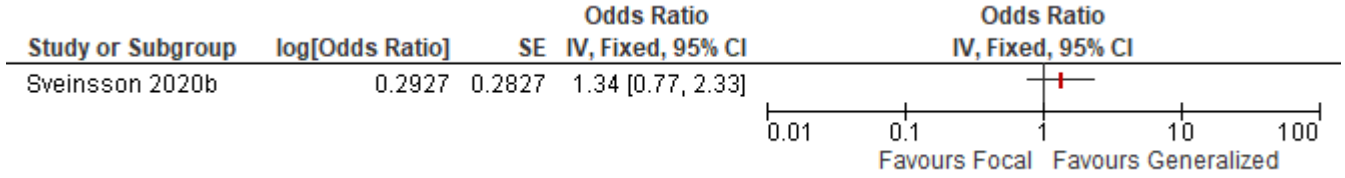


Figure 37: Focal and generalized seizures

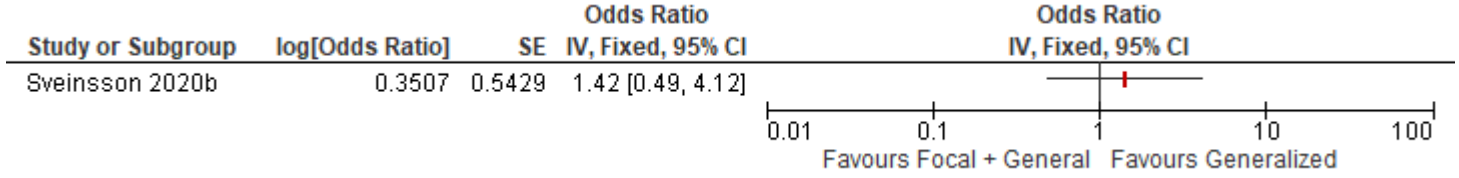


Figure 38: Undetermined seizures

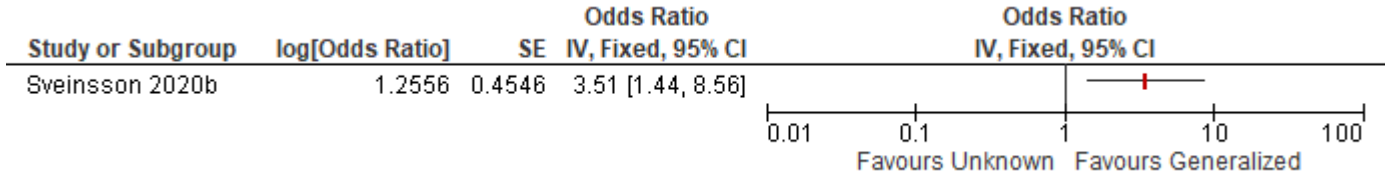


Figure 39: Substance abuse

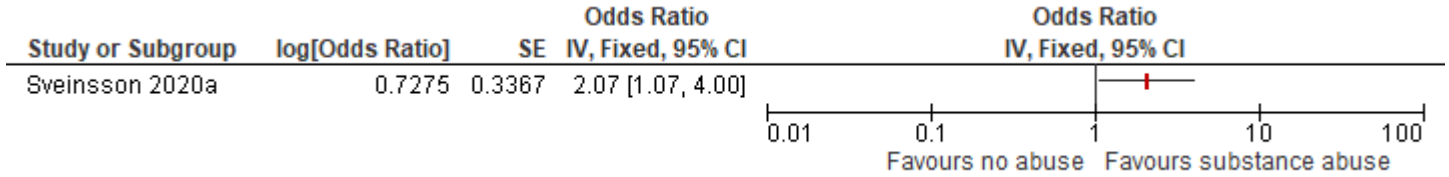


Figure 40: Alcohol dependence

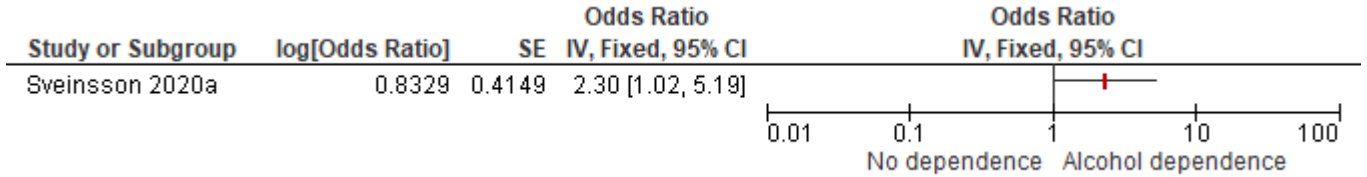


Figure 41: Alcoholism

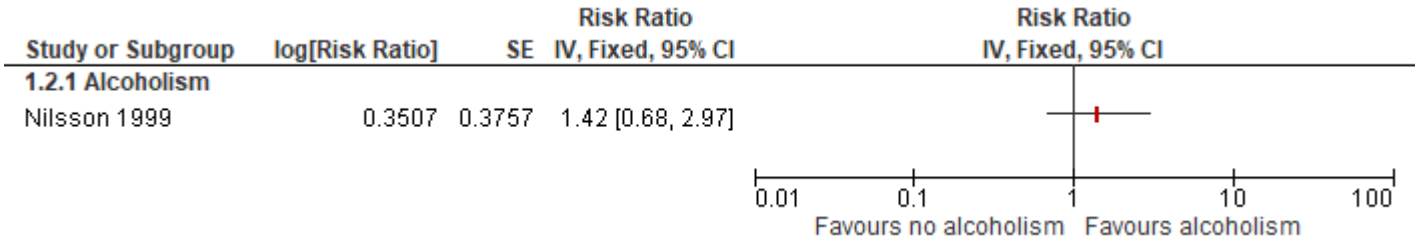


Figure 42: Local symptomatic seizures

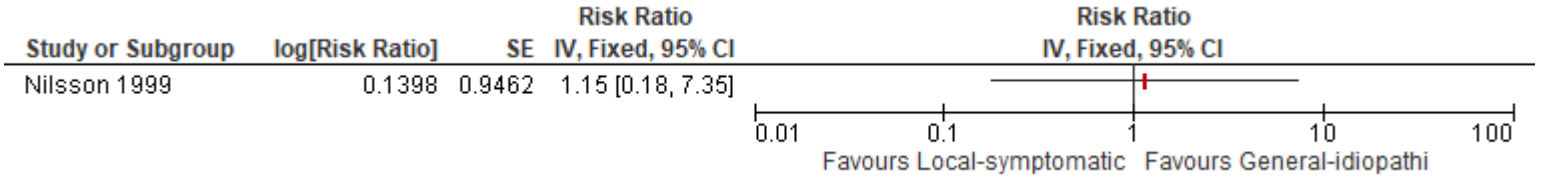


Figure 43: Local cryptogenic seizures

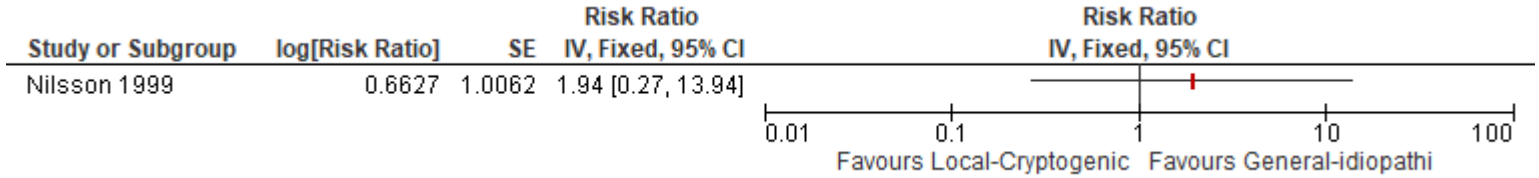


Figure 44: Undetermined seizures

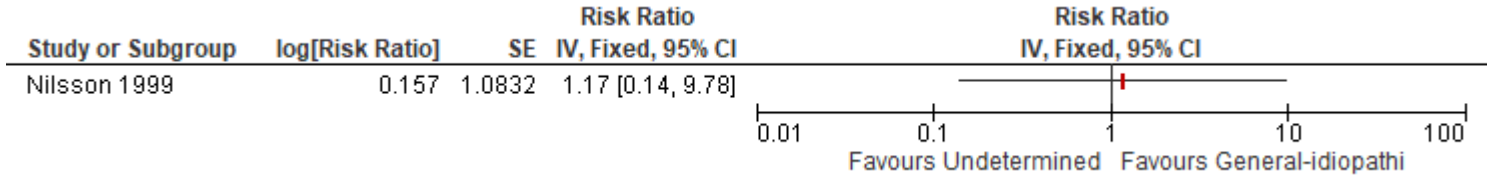


Figure 45: Anti-seizure medication therapy - monotherapy

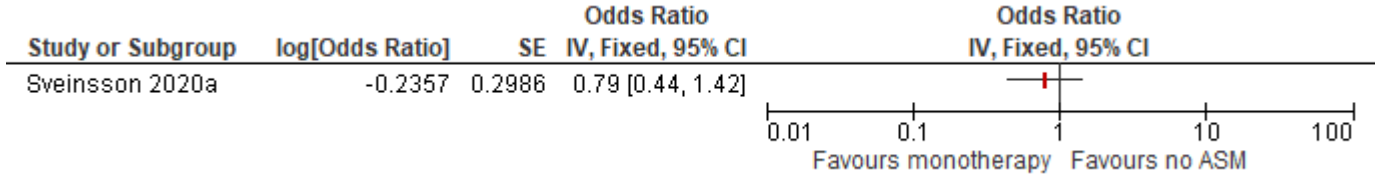


Figure 46: Anti-seizure medication therapy – Polytherapy (≥2 medications)

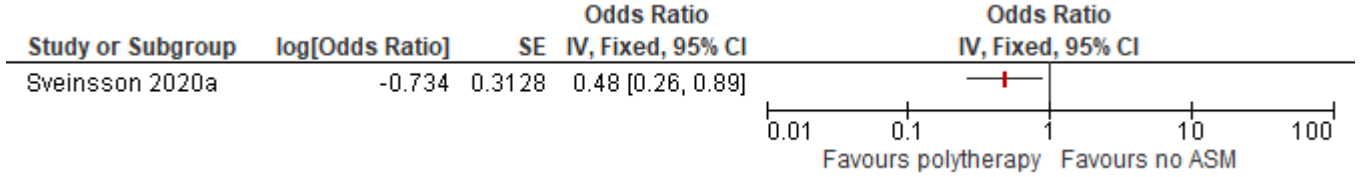


Figure 47: Anti-seizure medication therapy – Two anti-seizure medications

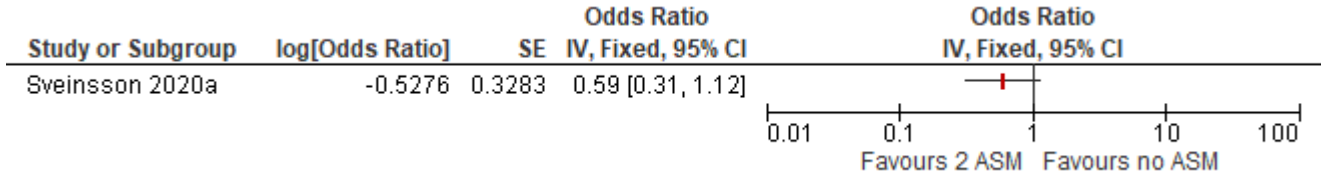


Figure 48: Two anti-seizure medications

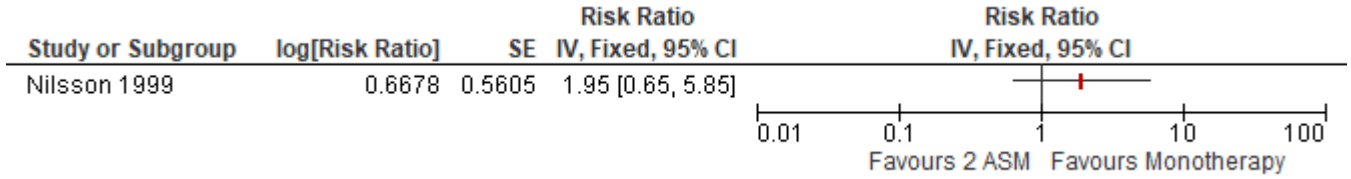


Figure 49: Three anti-seizure medications

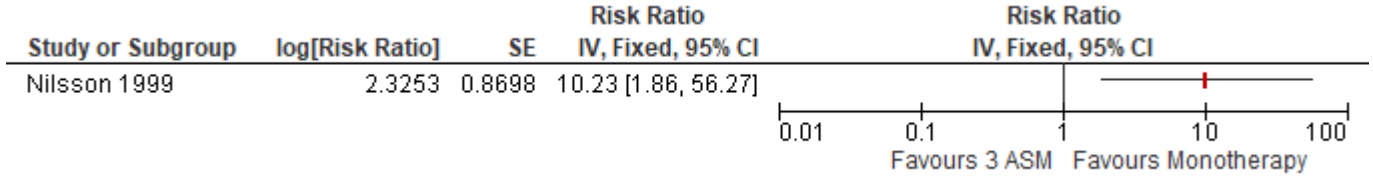


Figure 50: Anti-seizure medication therapy – Polytherapy (> 3 anti-seizure medications)

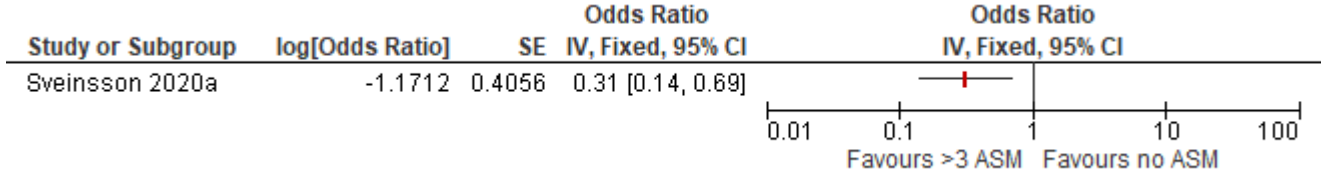


Figure 51: Three to four anti-seizure medications

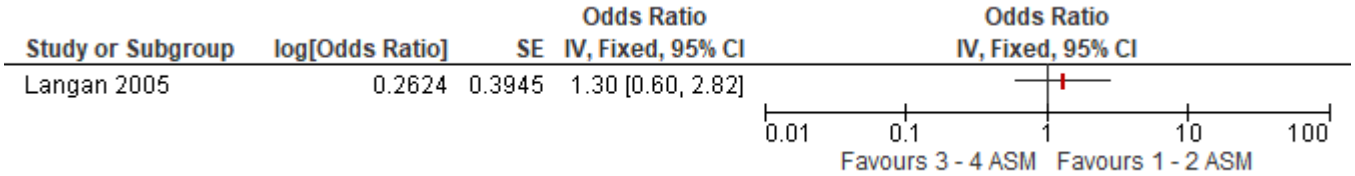


Figure 52: Over four anti-seizure medications

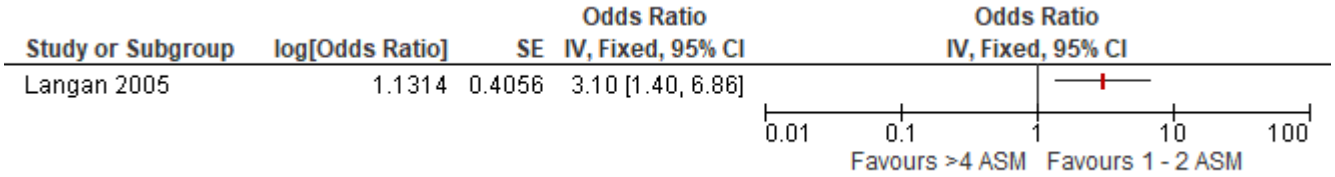


Figure 53: No anti-seizure medications

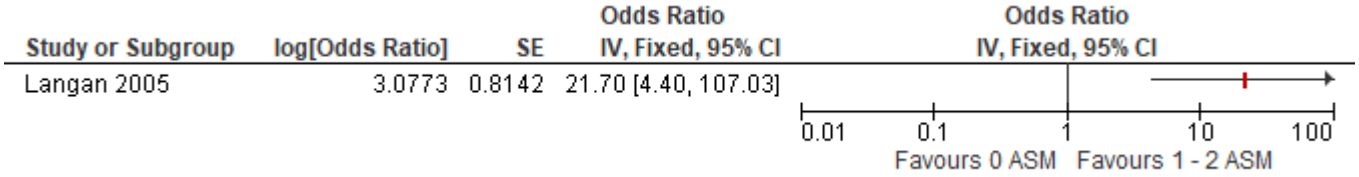


Figure 54: Monotherapy – Carbamazepine

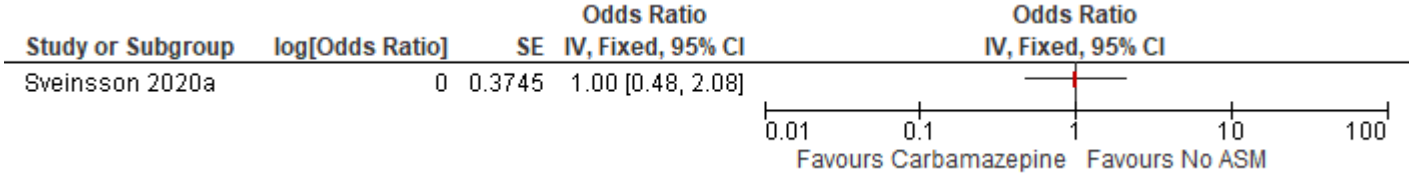


Figure 55: Monotherapy – Carbamazepine

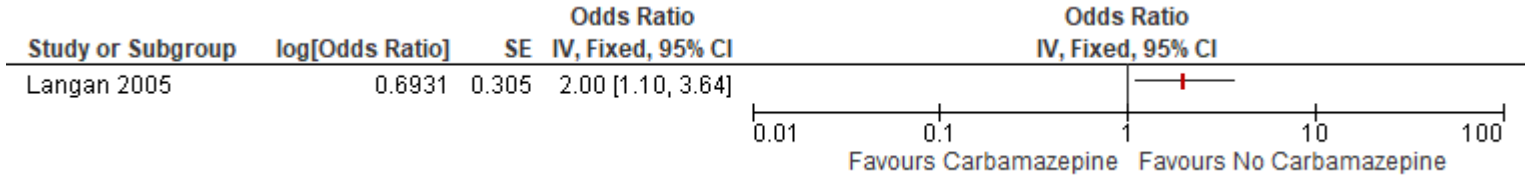


Figure 56: Monotherapy – Lamotrigine

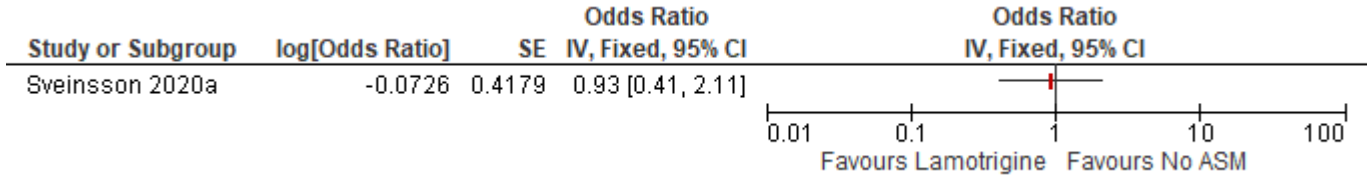


Figure 57: Monotherapy – Valproic Acid

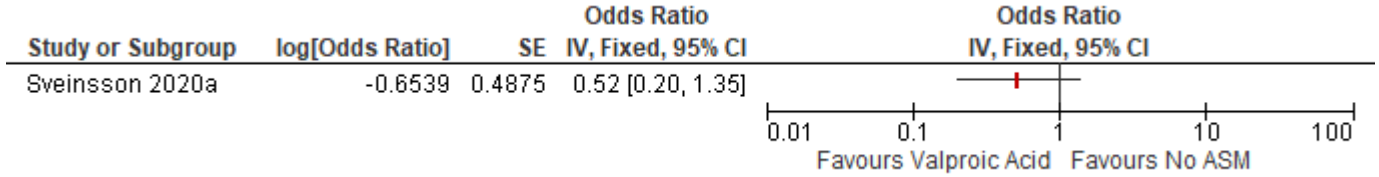


Figure 58: Monotherapy – Phenytoin

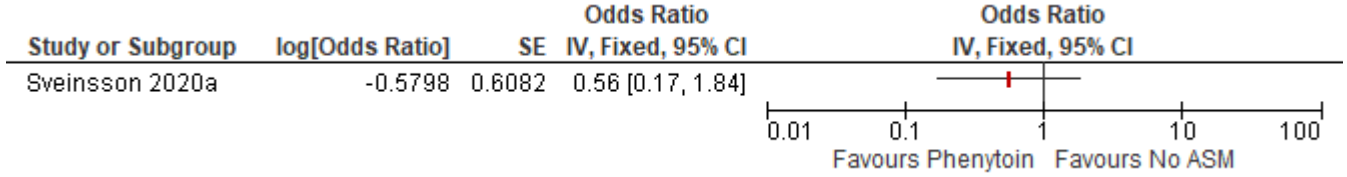


Figure 59: Monotherapy – Levetiracetam

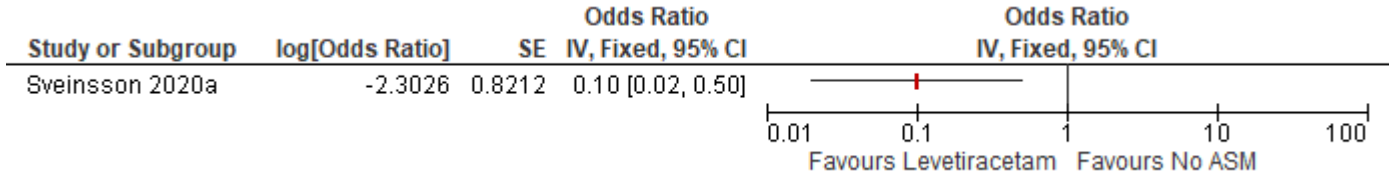


Figure 60: Monotherapy – Oxcarbazepine

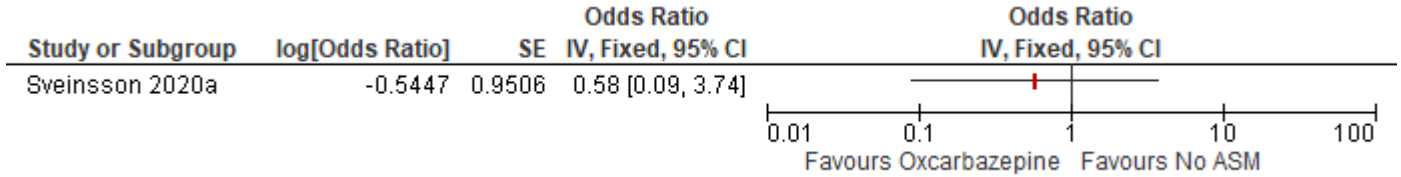


Figure 61: Monotherapy – Topiramate

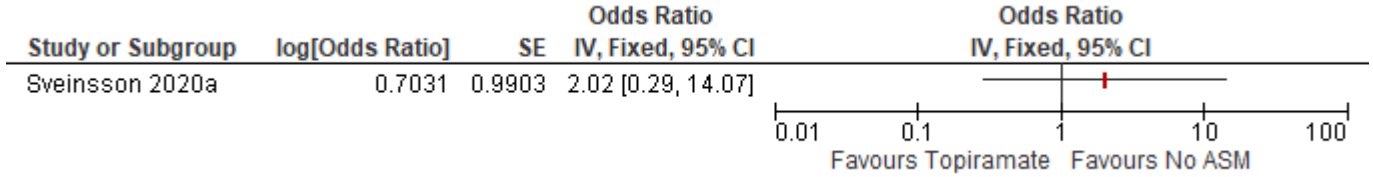


Figure 62: Monotherapy – Other anti-seizure medication

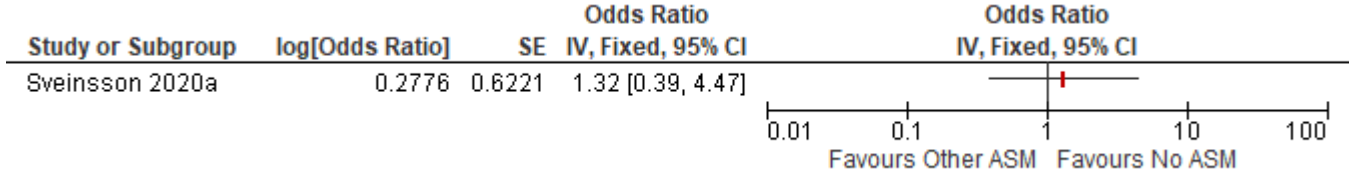


Figure 63: Nonadherence

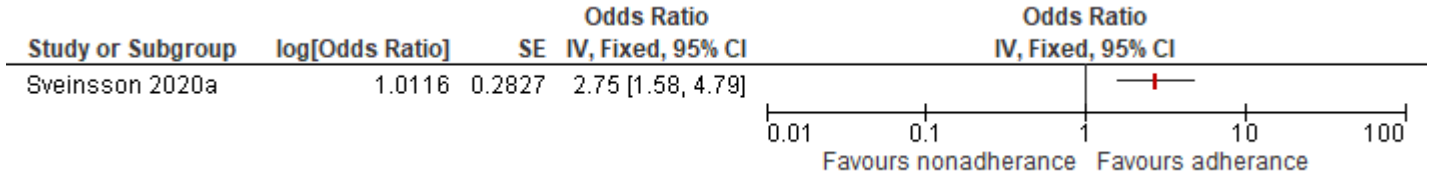


Figure 64: One to two changes in dose of antiseizure medication (per year)

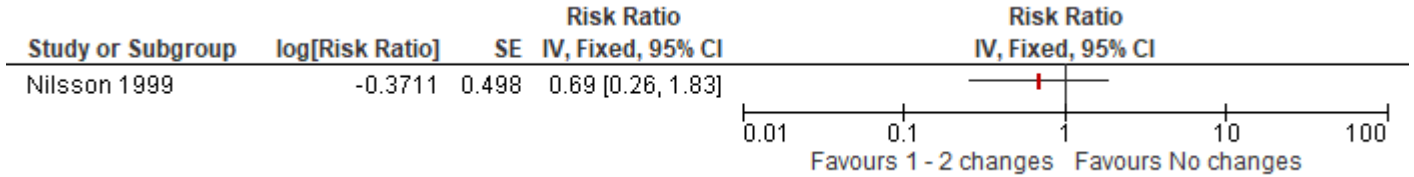


Figure 65: Three to five changes in dose of antiseizure medication (per year)

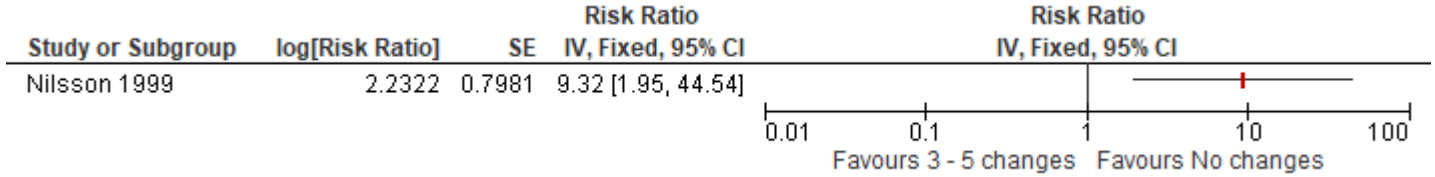


Figure 66: Antipsychotic medication

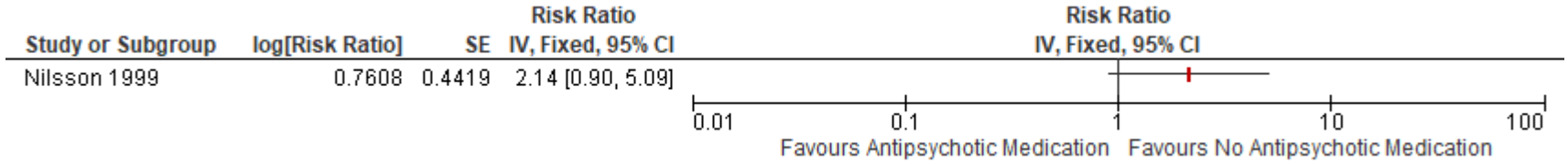


Figure 67: Anxiolytic medication

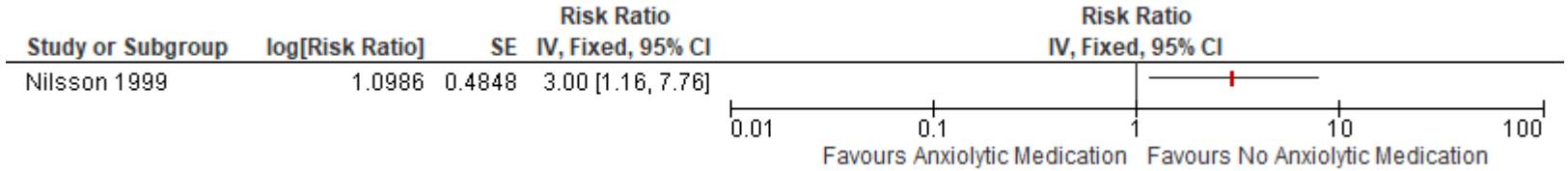


Figure 68: Asthma

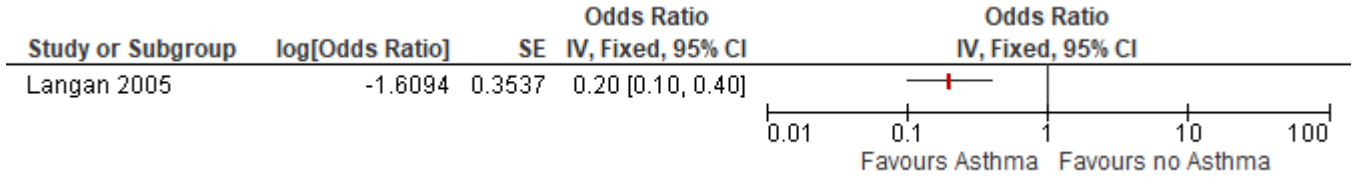


Figure 69: Sharing household but not a bedroom

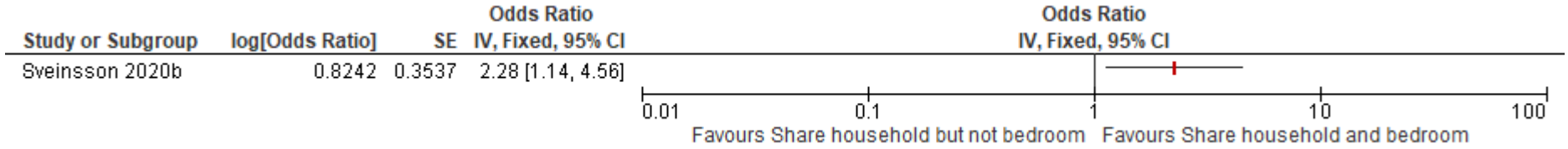


Figure 70: Living alone

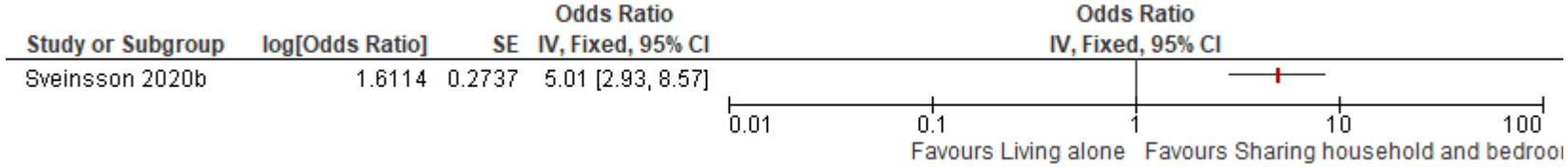


Figure 71: Secondary education

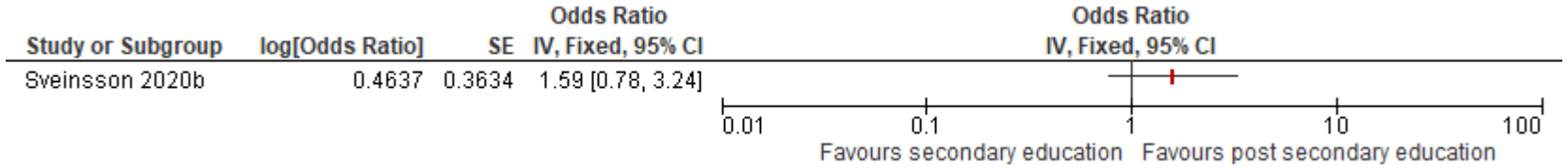


Figure 72: Primary education

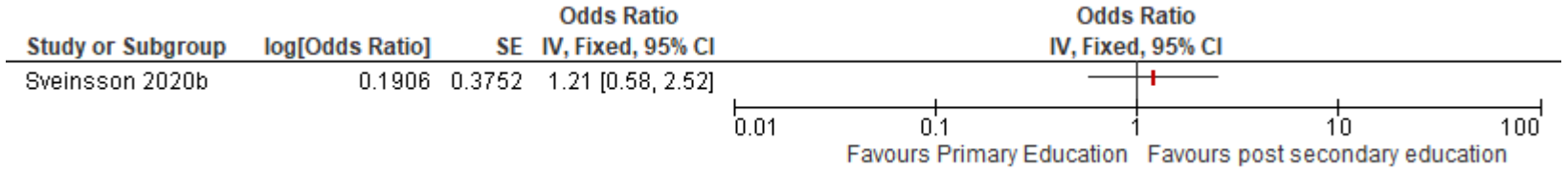


Figure 73: Same room supervision at night

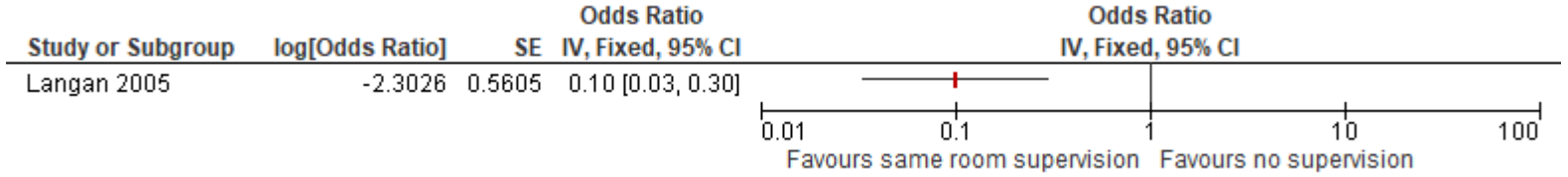
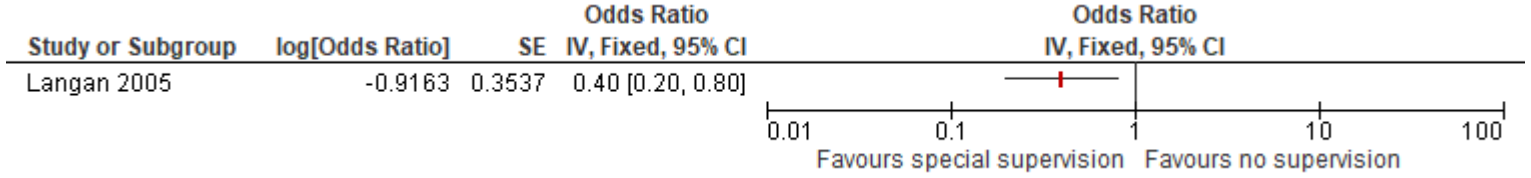


Figure 74: Special supervision at night (regular checks throughout the night or the use of a listening device)



Appendix F GRADE tables

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

Table 85: one to five seizures per month

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		
one to five seizures per month Male (follow-up 1 - 5 years)												
1	Observational study	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	OR 3.40 (0.5 to 23.12)	- -	⊕OOO VERY LOW[4]	CRITICAL
one to five seizures per month Female (follow-up 1 - 5 years)												
1	Observational study	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	OR 5.70 (0.6 to 54.15)	- -	⊕OOO VERY LOW[4]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Outcomes adjusted for number of seizures (per month) and number of tonic clonic seizures (per year)

Table 86: Over five seizures per month

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		
Over five seizures per month Male (follow-up 1 - 5 years)												
1	Observational study	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	OR 1.0 (0.1 to 10)	- -	⊕OOO VERY LOW[4]	CRITICAL
Over five seizures per month Female (follow-up 1 - 5 years)												
1	Observational study	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 7.40 (1.3 to 42.12)	- -	⊕⊕OO LOW[4]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Outcomes adjusted for number of seizures (per month) and number of tonic clonic seizures (per year)

Table 87: One to three tonic-clonic seizures per year

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**		
One to three tonic-clonic seizures per year Male (follow-up 1 - 5 years)												
1	Observational study	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	OR 4.30 (0.5 to 36.98)	-	⊕OOO VERY LOW[4]	CRITICAL
One to three tonic-clonic seizures per year Female (follow-up 1 - 5 years)												

1	Observational study	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 11.20 (1.6 to 78.39)	-	⊕⊕OO LOW[4]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Outcomes adjusted for number of seizures (per month) and number of tonic clonic seizures (per year)

Table 88: Over three tonic-clonic seizures per year

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**		
Over three tonic-clonic seizures per year Male (follow-up 1 - 5 years)												
1	Observational study	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	OR 3.30 (0.5 to 21.78)	-	⊕OOO VERY LOW[4]	CRITICAL
Over three tonic-clonic seizures per year Female (follow-up 1 - 5 years)												
1	Observational study	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 28.00 (3.8 to 206.31)	-	⊕⊕OO LOW[4]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Outcomes adjusted for number of seizures (per month) and number of tonic clonic seizures (per year)

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

Table 89: Seizure frequency

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		
Seizure frequency (follow-up >5 years)												
1	Observational study	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	OR 2.50 (0.9 to 6.95)	-	⊕OOO VERY LOW[4]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Outcomes adjusted for Age at onset, Duration of disease, Aura, Family history of epilepsy, Psychiatric conditions, Epilepsy classification, Seizure frequency, Seizure related to lesion on MR imaging, Number of ASMs, Type of ASM

Table 90: Number of anti-seizure medications

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		
Number of ASM (follow-up >5 years)												

1	Observational study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 1.80 (1.1 to 2.95)	-	⊕OOO VERY LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Outcomes adjusted for Age at onset, Duration of disease, Aura, Family history of epilepsy, Psychiatric conditions, Epilepsy classification, Seizure frequency, Seizure related to lesion on MR imaging, Number of ASMs, Type of ASM

Table 91: Non-adherence of medications

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**		
Nonadherence (follow-up >5 years)												
1	Observational study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 3.32 (3.11 to 3.54)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Outcomes adjusted for adherence status, gender, age, race, use of ASM polytherapy, epilepsy related comorbidities

Table 92: Untreated epilepsy

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**		
Untreated Epilepsy (follow-up >5 years)												

1	Observational study	serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	-	-	HR 0.92 (0.84 to 1.01)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed the null line
[3] Outcomes adjusted for adherence status, gender, age, race, use of ASM polytherapy, epilepsy related comorbidities

Table 93: Polytherapy

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**		
Polytherapy (follow-up >5 years)												
1	Observational study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.75 (0.69 to 0.82)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Outcomes adjusted for adherence status, gender, age, race, use of ASM polytherapy, epilepsy related comorbidities

Table 94: Alzheimer's disease

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**		
Alzheimer's Disease (follow-up >5 years)												
1	Observational study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 1.7 (1.54 to 1.88)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

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

[2] Outcomes adjusted for adherence status, gender, age, race, use of ASM polytherapy, epilepsy related comorbidities

Table 95: Brain tumour

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		
Brain Tumour (follow-up >5 years)												
1	Observational study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 1.58 (1.39 to 1.8)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Outcomes adjusted for adherence status, gender, age, race, use of ASM polytherapy, epilepsy related comorbidities

Table 96: Meningitis

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		
Meningitis (follow-up >5 years)												
1	Observational study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 1.34 (1.08 to 1.66)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Outcomes adjusted for adherence status, gender, age, race, use of ASM polytherapy, epilepsy related comorbidities

Table 97: Stroke

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		
Stroke (follow-up >5 years)												
1	Observational study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 1.3 (1.22 to 1.39)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Outcomes adjusted for adherence status, gender, age, race, use of ASM polytherapy, epilepsy related comorbidities

Table 98: Charlson Comorbidity Index

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**		
Charlson Comorbidity Index (follow-up >5 years)												
1	Observational study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 1.19 (1.18 to 1.2)	-	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Outcomes adjusted for adherence status, gender, age, race, use of ASM polytherapy, epilepsy related comorbidities

Table 99: CNS infections

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**		
CNS infection (follow-up >5 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 6.10 (4.1 to 9.08)	-	⊕⊕OO LOW[3]	CRITICAL

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

[3] Outcomes adjusted for age, gender, CNS infections, metastatic cancer, renal disease, solid tumours without metastasis, anoxic brain injury, cardiac arrhythmias, encephalopathy, depression, paraplegia, diabetes without complications, peripheral vascular disease, traumatic brain and head injuries

Table 100: Metastatic Cancer

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		
Metastatic Cancer (follow-up >5 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 3.70 (2.2 to 6.22)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Outcomes adjusted for age, gender, CNS infections, metastatic cancer, renal disease, solid tumours without metastasis, anoxic brain injury, cardiac arrhythmias, encephalopathy, depression, paraplegia, diabetes without complications, peripheral vascular disease, traumatic brain and head injuries

Table 101: Solid Tumour (no metastasis)

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		
Solid tumour (no metastasis) (follow-up >5 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 2.0 (1.1 to 3.64)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Outcomes adjusted for age, gender, CNS infections, metastatic cancer, renal disease, solid tumours without metastasis, anoxic brain injury, cardiac arrhythmias, encephalopathy, depression, paraplegia, diabetes without complications, peripheral vascular disease, traumatic brain and head injuries

Table 102: Depression

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		
Depression (follow-up >5 years)												
1	Observational study	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 0.20 (0.1 to 0.4)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Outcomes adjusted for age, gender, CNS infections, metastatic cancer, renal disease, solid tumours without metastasis, anoxic brain injury, cardiac arrhythmias, encephalopathy, depression, paraplegia, diabetes without complications, peripheral vascular disease, traumatic brain and head injuries

Table 103: Diabetes (no complications)

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 (no complications) (follow-up > 5 years)												
1	Observational study	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 1.40 (1 to 1.96)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Outcomes adjusted for age, gender, CNS infections, metastatic cancer, renal disease, solid tumours without metastasis, anoxic brain injury, cardiac arrhythmias, encephalopathy, depression, paraplegia, diabetes without complications, peripheral vascular disease, traumatic brain and head injuries

Table 104: Peripheral vascular disease

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**		
Peripheral Vascular Disease (follow-up > 5 years)												

1	Observational study	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 0.50 (0.3 to 0.83)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Outcomes adjusted for age, gender, CNS infections, metastatic cancer, renal disease, solid tumours without metastasis, anoxic brain injury, cardiac arrhythmias, encephalopathy, depression, paraplegia, diabetes without complications, peripheral vascular disease, traumatic brain and head injuries

Table 105: Traumatic brain and head injury

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**		
Traumatic Brain and Head Injury (follow-up >5 years)												
1	Observational study	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 5.10 (2.8 to 9.29)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Outcomes adjusted for age, gender, CNS infections, metastatic cancer, renal disease, solid tumours without metastasis, anoxic brain injury, cardiac arrhythmias, encephalopathy, depression, paraplegia, diabetes without complications, peripheral vascular disease, traumatic brain and head injuries

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

Table 106: Abnormal neurological examination

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Children f/u >5 years**	**Control**	**Relative (95% CI)**	**Absolute**		

Abnormal Neurological Examination (follow-up >5 years)												
1	Observational study	very serious[2]	no serious inconsistency	serious[1]	no serious imprecision	none	-	-	HR 12.80 (1.4 to 116.96)	-	⊕OOO VERY LOW[3]	CRITICAL

[1] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[2] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[3] Adjusted for neurologic examination, cognitive function, previous status epilepticus, mode of onset, aetiology, usage of ≥ 2 ASM's, seizure frequency, intractable at last follow up

Table 107: Abnormal cognitive function

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Children f/u >5 years**	**Control**	**Relative (95% CI)**	**Absolute**		
Abnormal Cognitive Function (follow-up >5 years)												
1	Observational study	very serious[2]	no serious inconsistency	serious[1]	serious[3]	none	-	-	HR 3.78 (0.42 to 34.02)	-	⊕OOO VERY LOW[4]	CRITICAL

[1] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[2] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Adjusted for neurologic examination, cognitive function, previous status epilepticus, mode of onset, aetiology, usage of ≥ 2 ASM's, seizure frequency, intractable at last follow up

Table 108: Status Epilepticus (ever)

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

1	Observational study	very serious[2]	no serious inconsistency	serious[1]	serious[3]	none	-	-	HR 1.34 (0.48 to 3.74)	-	⊕OOO VERY LOW[4]	CRITICAL

[1] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[2] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Adjusted for neurologic examination, cognitive function, previous status epilepticus, mode of onset, aetiology, usage of ≥ 2 ASM's, seizure frequency, intractable at last follow up

Table 109: Metabolic / Structural Aetiology

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Children f/u >5 years**	**Control**	**Relative (95% CI)**	**Absolute**		
Metabolic / Structural Aetiology (follow-up >5 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	HR 2.62 (0.69 to 9.95)	-	⊕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 non-modifiable confounders
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Adjusted for neurologic examination, cognitive function, previous status epilepticus, mode of onset, aetiology, usage of ≥ 2 ASM's, seizure frequency, intractable at last follow up

F.4 Mixed population of children <18 years and adults >18 years (follow up 1 - 5 years)

Table 110: Tumour aetiology

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u <5 years)	Control	Relative (95% CI)	Absolute		
Tumour Aetiology (follow-up 1 - 5 years)												
1	Observational study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	-	-	HR 4.67 (1.76 to 12.39)	-	⊕⊕⊕O MODERATE[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed the null line
[3] Adjusted for age of onset, frequency, imaging, type of seizure, aetiology, medication, age, gender

Table 111: Vascular lesion aetiology

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u <5 years)	Control	Relative (95% CI)	Absolute		
Vascular lesion Aetiology (follow-up 1 - 5 years)												
1	Observational study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 1.37 (0.46 to 4.08)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed the null line
[3] Adjusted for age of onset, frequency, imaging, type of seizure, aetiology, medication, age, gender

Table 112: Trauma aetiology

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u <5 years)	Control	Relative (95% CI)	Absolute		
Trauma Aetiology (follow-up 1 - 5 years)												
1	Observational study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.81 (0.22 to 2.98)	- -	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed the null line
[3] Adjusted for age of onset, frequency, imaging, type of seizure, aetiology, medication, age, gender

Table 113: Infection aetiology

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u <5 years)	Control	Relative (95% CI)	Absolute		
Infection Aetiology (follow-up 1 - 5 years)												
1	Observational study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 1.18 (0.15 to 9.28)	-	⊕⊕OO LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed the null line
[3] Adjusted for age of onset, frequency, imaging, type of seizure, aetiology, medication, age, gender

F.5 Mixed population of children <18 years and adults >18 years (follow up > 5 years)

Table 114: Seizure frequency - >10 seizures per year (at baseline)

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Seizure frequency - >10 seizures per year (at baseline) (follow-up >5 years)												
1	Observational study	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	OR 5.90 (2.2 to 15.82)	-	⊕OOO VERY LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Adjusted for age at onset, duration of epilepsy, type of epilepsy, causes of epilepsy, living conditions, highest education

Table 115: Seizures prior to SUDEP

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Seizure free prior to SUDEP (follow-up >5 years)												
1	Observational study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 9.50 (3 to 30.08)	-	⊕OOO VERY LOW[3]	CRITICAL
								0%		-		

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Adjusted for age at onset, duration of epilepsy, type of epilepsy, causes of epilepsy, living conditions, highest education

Table 116: Seizure frequency – (3 – 12 seizures past year)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		

Seizure frequency – (3 – 12 seizures past year) (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	RR 4.47 (1.33 to 15.02)	-	⊕OOO VERY LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 117: six to ten tonic-clonic seizures (previous 3 months)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed (f/u >5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
six to ten tonic-clonic seizures (previous 3 months) (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	OR 0.70 (0.2 to 2.45)	-	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Adjusted for History of generalized tonic clonic seizures, No of tonic clonic seizures in previous 3 months, Total number of anti-seizure medications, Carbamazepine usage, Supervision, Asthma

Table 118: eleven to twenty tonic-clonic seizures (previous 3 months)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed (f/u >5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
eleven to twenty tonic-clonic seizures (previous 3 months) (follow-up >5 years)												

1	observational study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 19.40 (1.7 to 221.4)	-	⊕OOO VERY LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Adjusted for history of GTCS, number of TCS in the previous 3 months, number of ASMs, carbamazepine usage, supervision level, asthma

Table 119: Twenty-one to fifty tonic-clonic seizures (previous 3 months)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed (f/u >5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
Twenty-one to fifty tonic-clonic seizures (previous 3 months) (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 14.60 (1.3 to 163.96)	-	⊕OOO VERY LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Adjusted for history of GTCS, number of TCS in the previous 3 months, number of ASMs, carbamazepine usage, supervision level, asthma

Table 120: Over fifty tonic-clonic seizures (previous 3 months)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed (f/u >5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
Over fifty tonic-clonic seizures (previous 3 months) (follow-up 5 years)												

1	observational study	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	OR 11.70 (0.3 to 456.31)	-	⊕OOO VERY LOW[4]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Adjusted for history of GTCS, number of TCS in the previous 3 months, number of ASMs, carbamazepine usage, supervision level, asthma

Table 121: History of generalized tonic-clonic seizures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed (f/u >5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
History of generalized tonic-clonic seizures (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 13.80 (6.6 to 28.85)	-	⊕OOO VERY LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Adjusted for history of GTCS, number of TCS in the previous 3 months, number of ASMs, carbamazepine usage, supervision level, asthma

Table 122: Focal seizures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed (f/u >5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
Focal seizures (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[1]	none	-	-	OR 1.34 (0.77 to 2.33)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed the null line
[2] Adjusted for age at onset, duration of epilepsy, type of epilepsy, causes of epilepsy, living conditions, highest education

Table 123: Focal and generalized seizures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Focal and generalized seizures (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[1]	none	-	-	OR 1.42 (0.49 to 4.12)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed the null line
[2] Adjusted for age at onset, duration of epilepsy, type of epilepsy, causes of epilepsy, living conditions, highest education

Table 124: Undetermined seizures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Undetermined seizures (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	OR 3.51 (1.44 to 8.56)	-	⊕⊕⊕⊕ HIGH[1]	CRITICAL

[1] Adjusted for age at onset, duration of epilepsy, type of epilepsy, causes of epilepsy, living conditions, highest education

Table 125: Substance abuse

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Substance abuse	Control	Relative (95% CI)	Absolute		
Substance abuse - Substance abuse												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	0%	OR 2.07 (1.07 to 4)	-[1]	⊕⊕⊕⊕ HIGH	CRITICAL

Table 126: Alcohol dependence/alcoholism

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alcohol dependence	Control	Relative (95% CI)	Absolute		
Alcohol dependence (follow up >5 years) (follow-up 5 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	0%	OR 2.3 (1.02 to 5.19)	-	⊕⊕⊕O MODERATE	CRITICAL
Alcoholism (follow up >5 years)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	-	0%	OR 1.42 (0.68 to 2.97)	-	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed the null line
[2] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias

Table 127: Local symptomatic seizures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Local symptomatic seizures (follow-up >5 years)												

1	observational study	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	RR 1.15 (0.18 to 7.35)	-	⊕OOO VERY LOW[4]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 128: Local cryptogenic seizures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed (f/u >5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
Local cryptogenic seizures (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	RR 1.94 (0.27 to 13.94)	-	⊕OOO VERY LOW[4]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 129: Undetermined seizures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed (f/u >5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
Undetermined seizures (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	RR 1.17 (0.14 to 9.78)	-	⊕OOO VERY LOW[4]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 130: Anti-seizure medication therapy – monotherapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Anti-seizure medication therapy – monotherapy (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[1]	none	-	-	OR 0.79 (0.44 to 1.42)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed the null line
[2] Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 131: Anti-seizure medication therapy – Polytherapy (≥2 medications)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Anti-seizure medication therapy – Polytherapy (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	OR 0.48 (0.26 to 0.89)	-	⊕⊕⊕⊕ HIGH[1]	CRITICAL

[1] Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 132: Anti-seizure medication therapy – Two anti-seizure medications

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Anti-seizure medication therapy – Two anti-seizure medications (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[1]	none	-	-	OR 0.59 (0.31 to 1.12)	-	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed the null line
[2] Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 133: Two anti-seizure medications

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Two anti-seizure medications (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	RR 1.95 (0.65 to 5.58)	-	⊕OOO VERY LOW[4]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Multivariate model includes the same prognostic variables, unclear of other variables in multivariate analysis

Table 134: Three antiseizure medications

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		

Three antiseizure medications (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	RR 10.23 (1.86 to 56.27)	-	⊕OOO VERY LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Multivariate model includes the same prognostic variables, unclear of other variables in multivariate analysis

Table 135: Anti-seizure medication therapy – Polytherapy (> 3 anti-seizure medications)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed (f/u >5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
Anti-seizure medication therapy – Over 3 anti-seizure medications (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	OR 0.31 (0.14 to 0.69)	-	⊕⊕⊕⊕ HIGH[1]	CRITICAL

[1] Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 136: three to four anti-seizure medications

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed (f/u >5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
three to four anti-seizure medications (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	OR 1.30 (0.6 to 2.82)	-	⊕OOO VERY LOW[4]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Adjusted for history of GTCS, number of TCS in previous 3 months, total number of ASM, carbamazepine usage, supervision, asthma

Table 137: Over four anti-seizure medications

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Over four anti-seizure medications (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 3.10 (1.4 to 6.86)	-	⊕OOO VERY LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Adjusted for history of GTCS, number of TCS in previous 3 months, total number of ASM, carbamazepine usage, supervision, asthma

Table 138: No anti-seizure medications

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
No anti-seizure medications (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 21.70 (4.4 to 107.03)	-	⊕OOO VERY LOW[3]	CRITICAL

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

[3] Adjusted for history of GTCS, number of TCS in previous 3 months, total number of ASM, carbamazepine usage, supervision, asthma

Table 139: Monotherapy – Carbamazepine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Monotherapy – Carbamazepine (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[1]	none	-	-	OR 1 (0.48 to 2.08)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed the null line
[2] Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 140: Monotherapy – Carbamazepine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Monotherapy – Carbamazepine (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 2.00 (1.1 to 3.64)	-	⊕OOO VERY LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Adjusted for history of GTCS, number of TCS in previous 3 months, total number of ASM, carbamazepine usage, supervision, asthma

Table 141: Monotherapy – Lamotrigine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Monotherapy – Lamotrigine (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[1]	none	-	-	OR 0.93 (0.41 to 2.11)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed the null line
[2] Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 142: Monotherapy – Valproic Acid

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Monotherapy – Valproic Acid (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[1]	none	-	-	OR 0.52 (0.2 to 1.35)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed the null line
[2] Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 143: Monotherapy – Phenytoin

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Monotherapy – Phenytoin (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[1]	none	-	-	OR 0.56 (0.17 to 1.84)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed the null line
[2] Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 144: Monotherapy – Levetiracetam

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Monotherapy – Levetiracetam (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	OR 0.1 (0.02 to 0.5)	-	⊕⊕⊕⊕ HIGH[1]	CRITICAL

[1] Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 145: Monotherapy – Oxcarbazepine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Monotherapy – Oxcarbazepine (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[1]	none	-	-	OR 0.58 (0.09 to 3.74)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed the null line
[2] Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 146: Monotherapy – Topiramate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Monotherapy – Topiramate (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[1]	none	-	-	OR 2.02 (0.29 to 14.07)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed the null line
[2] Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 147: Monotherapy – Other anti-seizure medication

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Monotherapy – Other anti-seizure medication (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[1]	none	-	-	OR 1.32 (0.39 to 4.47)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed the null line
[2] Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 148: Nonadherence

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Nonadherence (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	OR 2.75 (1.58 to 4.79)	-	⊕⊕⊕⊕ HIGH[1]	CRITICAL

[1] Adjusted for adjusted for matching variables (sex and calendar time), age, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level, history of GTCS, GTCS frequency in the last year and nocturnal GTCS last year

Table 149: One to two changes in dose of antiseizure medication (per year)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
One to two changes in dose of antiseizure medication (per year) (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	RR 0.69 (0.26 to 1.83)	-	⊕OOO VERY LOW[4]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 150: Three to five changes in dose of antiseizure medication (per year)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Three to five changes in dose of antiseizure medication (per year) (follow-up >5 years)												

1	observational study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	RR 9.32 (1.95 to 44.54)	-	⊕OOO VERY LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 151: Antipsychotic medication

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed (f/u >5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
Antipsychotic medication (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	RR 2.14 (0.9 to 5.09)	-	⊕OOO VERY LOW[4]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Downgraded by 1 increment if the confidence interval crossed the null line
[4] Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 152: Anxiolytic medication

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed (f/u >5 years)**	**Control**	**Relative (95% CI)**	**Absolute**		
Anxiolytic medication (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	RR 3.00 (1.16 to 7.76)	-	⊕OOO VERY LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Adjusted for seizure frequency during last year, age in years at epilepsy onset, epilepsy type, number of ASM, changes in dose of ASM per year

Table 153: Asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Asthma (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 0.20 (0.1 to 0.4)	-	⊕OOO VERY LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Adjusted for history of TCS, number of TCS in previous 3 months, total number of anti-seizure medications, carbamazepine usage, supervision, asthma

Table 154: Sharing household but not sharing a bedroom

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Sharing household only (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	OR 2.28 (1.14 to 4.56)	-	⊕⊕⊕⊕ HIGH[1]	CRITICAL

[1] Adjusted for age at onset, duration of epilepsy, type of epilepsy, causes of epilepsy, living conditions, highest education

Table 155: Living alone

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Not sharing household (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	OR 5.01 (2.93 to 8.57)	-	⊕⊕⊕⊕ HIGH[1]	CRITICAL

[1] Adjusted for age at onset, duration of epilepsy, type of epilepsy, causes of epilepsy, living conditions, highest education

Table 156: Secondary education

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Secondary education (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[1]	none	-	-	OR 1.59 (0.78 to 3.24)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed the null line
[2] Adjusted for age at onset, duration of epilepsy, type of epilepsy, causes of epilepsy, living conditions, highest education

Table 157: Primary education

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Primary education (follow-up >5 years)												
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[1]	none	-	-	OR 1.21 (0.58 to 2.52)	-	⊕⊕⊕O MODERATE[2]	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed the null line
[2] Adjusted for age at onset, duration of epilepsy, type of epilepsy, causes of epilepsy, living conditions, highest education

Table 158: Same room supervision at night

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Same room supervision at night (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 0.40 (0.2 to 0.8)	-	⊕OOO VERY LOW[3]	CRITICAL

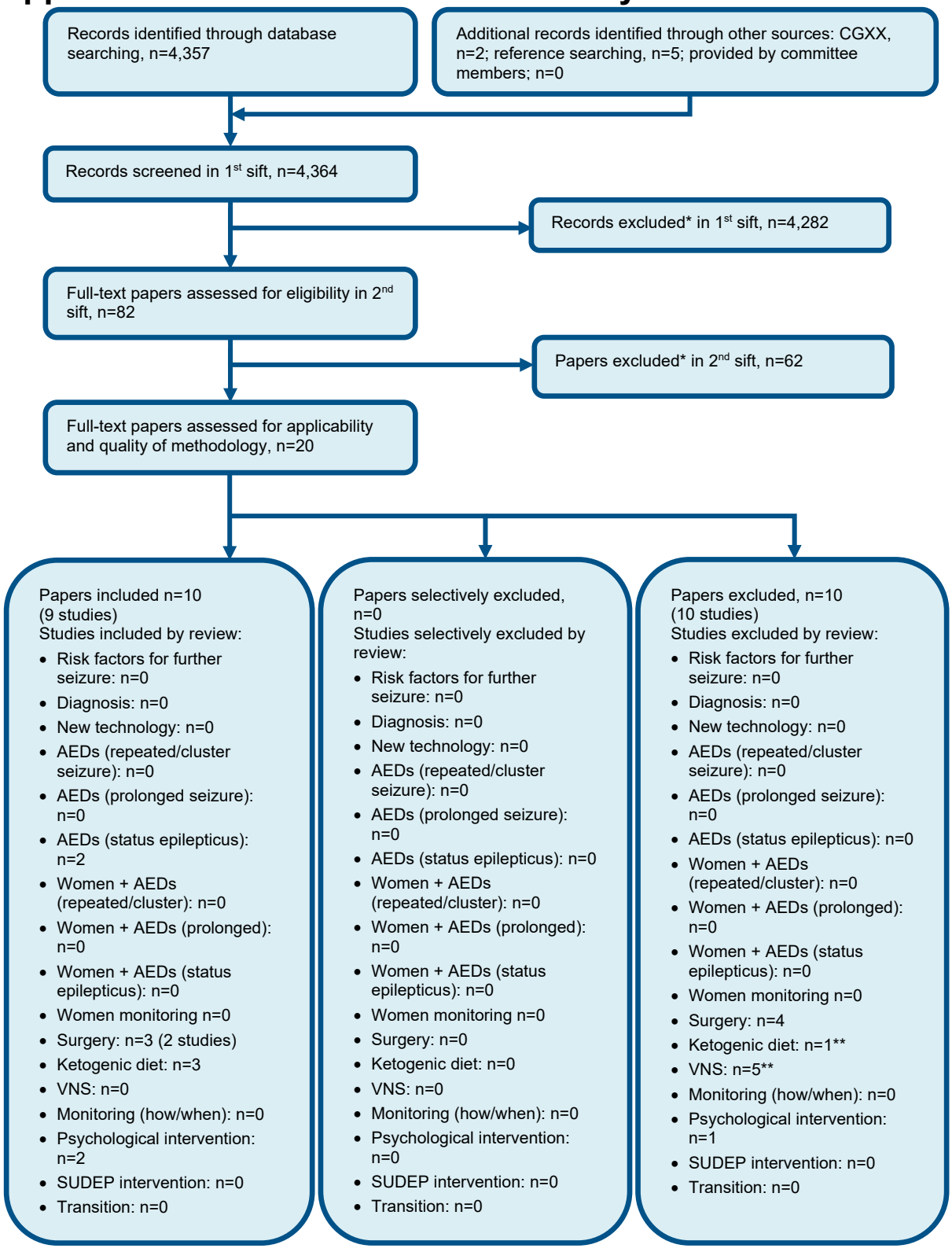
[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Adjusted for history of TCS, number of TCS in previous 3 months, total number of anti-seizure medications, carbamazepine usage, supervision, asthma

Table 159: Special supervision at night (regular checks throughout the night or the use of a listening device)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed (f/u >5 years)	Control	Relative (95% CI)	Absolute		
Special supervision at night (follow-up >5 years)												
1	observational study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	OR 0.10 (0.03 to 0.3)	-	⊕OOO VERY LOW[3]	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at high risk of bias
[2] Downgraded for indirectness as analysis did not adjust for at least two of the non-modifiable confounders
[3] Adjusted for history of TCS, number of TCS in previous 3 months, total number of anti-seizure medications, carbamazepine usage, supervision, asthma

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 160: Studies excluded from the clinical review

Reference	Reason for exclusion
Alvarez 2020[1]	Inappropriate study design – narrative review of prognostic scores for status epilepticus.
Andrade-Machado 2015[2]	Inappropriate comparison – no relevant outcomes for extraction or analysis
Assis 2015[4]	Inappropriate study design – cross sectional study design
Blank 2021[5]	Inappropriate comparison – no relevant outcomes (analysis compares prognostic factors against no epilepsy)
Canoui-Poitrine 2011[6]	Inappropriate comparison – Multivariate analysis does not include modifiable risk factors
Dabla 2018[8]	Inappropriate population – people with epilepsy who sustained injuries; multivariate analysis not for mortality
Fangsaad 2019[9]	Inappropriate population – mixed population with neonates and multivariate analysis not for mortality or SUDEP
Hesdorffer 2011[11]	Inappropriate study design – meta-analysis of four studies; individual papers ordered for analysis
Hesdorffer 2012[12]	Inappropriate study design – meta-analysis of four studies; individual papers ordered for analysis
Hitiris 2007[3]	Inappropriate study design – no multivariate analysis for risk factors for epilepsy related death
Hunt 2003[13]	Inappropriate population – correlation between sleeping position and sudden infant death syndrome
Lamberts 2015[14]	Inappropriate population and study design – correlation between cardiovascular conditions and possible SUDEP in epileptic and non-epileptic population
Li 2009[16]	Inappropriate study design – no modifiable risk factors included within multivariate analysis
Logroscino 2008[17]	Inappropriate population – risk of death after 1st seizure or incident epilepsy
McCabe 2021[18]	Inappropriate study design – analysis of a checklist for SUDEP in the primary care compared to secondary care setting
McCarter 2018[19]	Inappropriate study design – investigation the risk of possible SUDEP in people with obstructive sleep apnoea
Ngugi 2014[21]	Inappropriate study design – population of people with active convulsive epilepsy and people with potentially undiagnosed epilepsy given treatment and monitored
Novak 2015[24]	Inappropriate study design – double blind cross-over trial

Reference	Reason for exclusion
Odom 2018[25]	Inappropriate study design – comparison of a risk score for possible SUDEP
Saetre 2018[27]	Inappropriate study design – Systematic review; references checked
Saxena 2018[28]	Inappropriate study design – Literature review; references checked
Shankar 2018[29]	Inappropriate study design – analysis of a risk score for possible SUDEP
Sillanpaa 2013[31]	Inappropriate study design – no modifiable risk factors included within analysis with unclear methodology
Singh 2013[32]	Inappropriate comparison – cardiovascular risk factors in relation to possible SUDEP
Sveinsson 2017[34]	Inappropriate study design – incidence rates of psychological comorbidities in relation to SUDEP
Sveinsson 2018[33]	Inappropriate study design – incidence rates of SUDEP
Tennis 1995[37]	Inappropriate study design – multivariate analysis not for epilepsy related death or SUDEP
Waddy 2019[38]	Inappropriate population – mortality related to end stage renal failure patients on dialysis and epilepsy

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 161: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	