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Prognostic factors predicting an unprovoked seizure recurrence in children and adults following a first unprovoked seizure (Review)

Adan G, Neligan A, Nevitt SJ, Bonnett LJ, Sander JW, Marson AG

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[Prognosis Review]

Prognostic factors predicting an unprovoked seizure recurrence in children and adults following a first unprovoked seizure

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ABSTRACT

Background

Assessing the risk of seizure recurrence after a first unprovoked seizure remains a clinical challenge but is essential for counselling, especially given its impact on driving, employment, and treatment decisions. The International League Against Epilepsy now allows for an 'operational' diagnosis of epilepsy after a single unprovoked seizure, based on an individual's recurrence risk. This shift highlights the need for more precise tools to predict seizure risk and guide accurate diagnosis and management.

Objectives

To identify which prognostic factors predict the risk of subsequent unprovoked seizures and the development of epilepsy at any time following a first unprovoked seizure, a cluster of seizures within 24 hours, or a first episode of status epilepticus – regardless of seizure type.

Search methods

We searched the following databases between 12 and 15 December 2022, with no language restrictions: CENTRAL, MEDLINE, SCOPUS, ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform.

Selection criteria

We included retrospective and prospective cohort studies and randomised controlled trials (RCTs) that assessed prognostic factors for seizure recurrence following a first unprovoked seizure. Eligible studies reported on at least one index prognostic factor (including demographic variables such as age and sex, clinical features such as seizure type, and investigation results such as electroencephalogram (EEG) and neuroimaging) and assessed seizure recurrence outcomes. Prognostication began at the time of the initial seizure, with outcomes assessed at a minimum of six months' follow-up.

Data collection and analysis

Two review authors screened titles and abstracts identified through searches and removed irrelevant articles. We extracted data using a data extraction form. We conducted separate meta-analyses to pool odds ratios (ORs), risk ratios (RRs), and hazard ratios (HRs) reported from univariable regression analyses in the included studies.

We conducted meta-analyses using a random-effects, generic inverse-variance model, which accounted for any between-study heterogeneity in the prognostic effect. We summarised the meta-analysis by the pooled estimate (the average prognostic factor effect), its 95% confidence interval (CI), the I^2 (heterogeneity) estimates, and a 95% prediction interval for the predictive effect in a single population.

Two review authors independently extracted data and assessed risk of bias using the Quality In Prognosis Studies (QUIPS) tool. We adapted the GRADE framework to assess the certainty of evidence for each prognostic factor–outcome association. We rated evidence certainty as high, moderate, low, or very low, based on study phase, internal validity, effect size and precision, heterogeneity, generalisability, and reporting bias.

Main results

We included 23 studies (5918 participants). Cohort sizes varied from 50 to 1885 participants (median 134).

Most studies were cohort designs (15 prospective, seven retrospective), with one RCT. Median follow-up was 35 months (range six to 283 months). Seven studies included participants on anti-seizure medication (ASM) after their first seizure; 16 did not. Eight studies were adult-only, 12 paediatric-only, and three included both age groups. Using the QUIPS tool, nine studies (39%) had a low risk of bias, 11 (48%) unclear, and three (13%) high.

Abnormal EEG (RR 1.90, 95% CI 1.60 to 2.25; $P = 0.022$, $I^2 = 55.4\%$; 9 studies, 1904 participants; HR 1.45, 95% CI 1.17 to 1.79; $P = 0.018$, $I^2 = 75\%$; 3 studies, 939 participants) probably increases the risk of seizure recurrence (moderate-certainty evidence for RR; low-certainty for HR). Low-certainty evidence suggests abnormal brain imaging (RR 2.19, 95% CI 1.74 to 2.76; $P = 0.085$, $I^2 = 54.6\%$; 4 studies, 890 participants), nocturnal seizures (HR 1.41, 95% CI 1.13 to 1.75; $P = 0.674$, $I^2 = 0\%$; 3 studies, 967 participants; RR 1.23, 95% CI 1.04 to 1.47; $P = 0.017$, $I^2 = 70.7\%$; 4 studies, 1248 participants), family history of epilepsy (RR 1.47, 95% CI 1.16 to 1.85; $P = 0.423$, $I^2 = 0\%$; 6 studies, 1290 participants), and Todd's paresis (RR 1.48, 95% CI 1.02 to 2.13; $P = 0.102$, $I^2 = 56.2\%$; 3 studies, 836 participants) may increase seizure recurrence, but findings remain uncertain due to limitations in study quality, consistency, and precision.

Very low-certainty evidence means we are uncertain about associations of febrile seizures (RR 1.02, 95% CI 0.82 to 1.28; $P = 0.516$, $I^2 = 0\%$; 3 studies, 841 participants), focal neurological deficit (HR 1.21, 95% CI 0.92 to 1.60; $P = 0.028$, $I^2 = 67\%$; 4 studies, 981 participants), status epilepticus (RR 1.05, 95% CI 0.81 to 1.36; $P = 0.0507$, $I^2 = 56.4\%$; 5 studies, 1456 participants), male sex (RR 1.14, 95% CI 0.94 to 1.39; $P = 0.190$, $I^2 = 39.8\%$; 3 studies, 738 participants), initial focal seizures (OR 1.19, 95% CI 0.77 to 1.85; $P = 0.004$, $I^2 = 88.1\%$; 2 studies, 473 participants), and age under 16 years (OR 1.80, 95% CI 1.16 to 2.79; $I^2 = 0\%$; 5 cohorts, 522 participants; low-certainty evidence but RR 0.69, 95% CI 0.47 to 1.01; $I^2 = 37.9\%$; 3 studies, 480 participants; very low-certainty evidence) with seizure recurrence, due to significant inconsistency, imprecision, indirectness, and risk of bias across studies.

Authors' conclusions

We aimed to identify prognostic factors predicting seizure recurrence after a first unprovoked seizure. Considerable heterogeneity and inconsistency in how the included studies defined, measured, and reported prognostic factors significantly limited our analyses and led to downgrading of the evidence due to imprecision and methodological variability. These limitations highlight the need for standardisation. Future studies would benefit from adherence to an international core outcome set currently under development, which will standardise reporting and collection of prognostic factor data, enhancing comparability and reliability. Identifying high-risk cohorts remains critical for guiding clinical decisions, shaping healthcare policy, and enabling recruitment into trials of disease-modifying treatments.

PLAIN LANGUAGE SUMMARY

What factors increase the risk of a seizure following a first unprovoked seizure (one with no clear cause)?

Key messages

- Abnormal results for a test that records brain activity (an electroencephalogram or EEG) are probably associated with an increased risk of having another seizure.
- Other factors, such as abnormal brain scans, seizures during sleep (nocturnal seizures), Todd's paresis (weakness after a seizure), or a family history of epilepsy, may also increase the risk, but the evidence is less certain.
- We need higher-quality studies to help doctors more accurately predict who will have further seizures after a first unprovoked seizure.

What are unprovoked seizures?

A seizure is a sudden surge of electrical activity in the brain. It can cause shaking, stiffening of the body, staring, confusion, or a loss of awareness. An unprovoked seizure is a seizure that occurs without an immediate or obvious cause, such as a fever, infection, or recent injury. It may be a sign of an underlying condition like epilepsy.

Why are unprovoked seizures a concern?

Many people will have a single seizure in their lifetime — around 1 in 20 by the age of 85. After this first seizure, doctors often cannot tell who will go on to have more. This uncertainty makes it difficult to make decisions about driving, working, or starting treatment.

Doctors need reliable ways to predict seizure risk after a first unprovoked seizure, to help guide diagnosis and treatment. This is especially important because a diagnosis of epilepsy can now be made after one seizure in some people, if the chance of more seizures is high.

What did we want to find out?

We wanted to find out if certain features — either of the person, their first seizure, or results from medical tests — could help predict whether they would have another seizure. We looked at:

- personal characteristics, such as age, sex, and family history of epilepsy;
- medical tests, including brain scans (magnetic resonance imaging (MRI) or computed tomography (CT)) or EEGs (brain wave tests);
- seizure features, including whether the seizure happened during sleep or lasted a long time.

What did we do?

We searched for good-quality studies that followed people after a first unprovoked seizure to see if they went on to have more. We included studies that followed people for at least six months and included at least 30 participants.

We then combined the results of the studies to find out how strong the evidence was for each possible risk factor.

What did we find?

We found 23 studies involving 5918 people. Some studies included adults, some children, and some both. The strength of the evidence for each risk factor varied.

Main results

- Abnormal electroencephalogram (EEG): people with abnormal EEG results probably have a higher risk of another seizure.

The following factors may increase the risk of seizure recurrence:

- abnormal brain scan (imaging);
- Todd's paresis (temporary weakness after a seizure);
- family history of epilepsy;
- seizures during sleep (nocturnal seizures).

We are very uncertain if the following factors increase the risk of seizure recurrence:

- focal neurological signs (problems affecting a specific body part, caused by a problem in a specific area of the brain);
- febrile seizures (seizures that occur during a fever) in childhood;
- status epilepticus (when a seizure doesn't stop on its own, or repeated seizures without regaining full consciousness between them);
- focal seizures (a seizure that starts in one part of the brain);
- male sex.

There is conflicting evidence about whether being younger than 16 is a risk factor: some studies suggest higher risk, others suggest lower risk. Overall, the evidence is uncertain.

What are the limitations of the evidence?

Many studies measured and reported results differently, making them hard to compare. Some were small or did not adjust for all important factors. Most were done in high-income countries, so the findings may not apply everywhere.

Larger, high-quality studies that measure and report on seizure risk factors in the same way would help doctors make better predictions.

How can patients and carers use this information?

Understanding which features may be linked to having more seizures can help patients and families have informed discussions with their doctors. This can support decisions around treatment, driving, school, work, and daily life.

How current is this review?

The review includes studies published up to December 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Prognostic factors predicting an unprovoked seizure recurrence in children and adults following a first unprovoked seizure

Prognostic factor (definition)	Meta-analysis, # study groups (# participants)	Meta-analysis relative effect (95% CI)	Certainty of the evidence (GRADE)	Comments (rating of factors considered)
Febrile seizures (history of febrile convulsions before first unprovoked seizure)	3 studies (841)	RR 1.02 (0.82 to 1.28)	⊕⊕⊕⊕ Very low^a	Febrile seizures may have little to no association with an increased risk of seizure recurrence, but the evidence is very uncertain.
Febrile seizures (as above)	2 studies (700)	HR 1.18 (0.76 to 1.82)	⊕⊕⊕⊕ Very low^b	
Focal neurological deficit (persistent focal deficits at time of first seizure)	4 studies (981)	HR 1.21 (0.92 to 1.60)	⊕⊕⊕⊕ Very low^c	Focal neurological deficit may be associated with a higher risk of seizure recurrence after a first unprovoked seizure; however, the evidence is very uncertain.
Todd's paresis (transient postictal weakness)	3 studies (836)	RR 1.48 (1.02 to 2.13)	⊕⊕⊕⊕ Low^d	Todd's paresis may increase the risk of seizure recurrence after a first unprovoked seizure, but the certainty of the evidence is limited.
Status epilepticus (seizure lasting > 30 minutes or repeated seizures without recovery)	5 studies (1456)	RR 1.05 (0.81 to 1.36)	⊕⊕⊕⊕ Very low^e	The evidence is very uncertain about whether status epilepticus increases the risk of seizure recurrence following a first unprovoked seizure.
Family history of epilepsy (first-degree relative with epilepsy)	4 studies (1012)	HR 1.35 (1.03 to 1.76)	⊕⊕⊕⊕ Low^f	Family history of epilepsy may be associated with a higher risk of seizure recurrence, but the certainty of the evidence is limited.
Family history of epilepsy (as above)	6 studies (1290 participants)	RR 1.47 (1.16 to 1.85)	⊕⊕⊕⊕ Low^g	
Male sex (male sex at time of first seizure)	3 studies (738)	RR 1.14 (0.94 to 1.39)	⊕⊕⊕⊕ Very low^h	Male sex may have little to no association with seizure recurrence, but the evidence is very uncertain due to inconsistent results and imprecise estimates.
Focal seizures (seizure with focal onset)	3 studies (773)	HR 0.90 (0.72 to 1.13)	⊕⊕⊕⊕ Very lowⁱ	Focal seizures may have little to no association with seizure recurrence, but the evidence is very uncertain.
Focal seizures (as above)	2 studies (473)	OR 1.19 (0.77 to 1.85)	⊕⊕⊕⊕ Very low^j	
Focal seizures (as above)	3 studies (455)	RR 1.09 (0.76 to 1.56)	⊕⊕⊕⊕ Very low^k	

Abnormal imaging (structural brain abnormality on MRI or CT)	3 studies (939)	HR 1.09 (0.84 to 1.42)	⊕⊕○○ Low^l	Abnormal imaging may be associated with increased seizure recurrence, but overall the evidence is uncertain.
Abnormal imaging (as above)	4 studies (890)	RR 2.19 (1.74 to 2.76)	⊕⊕○○ Low^m	
Abnormal EEG (epileptiform discharges or focal slowing)	9 studies (1904)	RR 1.90 (1.60 to 2.25)	⊕⊕⊕○ Moderateⁿ	Abnormal EEG findings probably increase the risk of seizure recurrence (RR, moderate-certainty evidence). Time-to-event data (HR) support this association, but the evidence is less certain due to inconsistency and imprecision.
Abnormal EEG (as above)	3 studies (939)	HR 1.45 (1.17 to 1.79)	⊕⊕○○ Low^o	
Nocturnal seizures (seizure occurring during sleep)	3 studies (967)	HR 1.41 (1.13 to 1.75)	⊕⊕○○ Low^p	Nocturnal seizures may increase the risk of seizure recurrence (RR 1.23), but this finding is based on low-certainty evidence.
Nocturnal seizures (as above)	4 studies (1248)	RR 1.23 (1.04 to 1.47)	⊕⊕○○ Low^q	
Age < 16 years (age at time of first seizure)	3 studies, five cohorts (522)	OR 1.80 (1.16 to 2.79)	⊕⊕○○ Low^r	Being under 16 years of age may be associated with an increased risk of seizure recurrence (OR). The effect estimate suggests an increased risk and the confidence interval does not include a decreased risk, but the evidence is limited by risk of bias and inconsistency (low-certainty evidence).
Age < 16 years (as above)	3 studies (480)	RR 0.69 (0.47 to 1.01)	⊕○○○ Very low^t	The evidence is very uncertain about whether being under 16 years of age affects the risk of seizure recurrence (RR). The confidence interval includes the possibility of both a decreased effect and no effect (very low-certainty evidence).

CI: confidence interval; **CT:** computed tomography; **EEG:** electroencephalogram; **HR:** hazard ratio; **MRI:** magnetic resonance imaging; **OR:** odds ratio; **RR:** risk ratio.

^aDowngraded three levels: once for indirectness (variable or unclear classification of febrile seizures across studies), once for imprecision (wide confidence interval and low number of events), and once for risk of bias (unclear or moderate concerns across included studies).

^bDowngraded three levels: once for indirectness (unclear clinical applicability and seizure definitions), once for imprecision (wide confidence interval and low participant numbers), and once for risk of bias (moderate risk and limited methodological transparency across studies).

^cDowngraded three levels: once for inconsistency (heterogeneity in results across studies), once for imprecision (wide confidence interval and low event numbers), and once for risk of bias (concerns related to study design and moderate risk across included studies).

^dDowngraded two levels: once for inconsistency (moderate heterogeneity across studies; $I^2 = 56.2\%$) and once for imprecision (confidence interval includes values suggesting both benefit and no effect, with a limited number of events).

^eDowngraded three levels: once for inconsistency (moderate heterogeneity across studies; $I^2 = 56.4\%$), once for imprecision (confidence interval includes no effect and spans both potential benefit and harm), and once for risk of bias (most included studies had moderate risk of bias and lacked clarity in methodology).

^fDowngraded two levels: once for inconsistency (moderate heterogeneity across studies; $I^2 = 51.4\%$) and once for imprecision (confidence interval includes no effect and suggests limited precision due to modest sample size).

^gDowngraded two levels: once for risk of bias (several studies with moderate or unclear methodological quality) and once for imprecision (confidence interval borders on clinically meaningful effect with limited total number of events).

^hDowngraded three levels: once for inconsistency (moderate heterogeneity; $I^2 = 39.8\%$ and variable effect directions), once for imprecision (confidence interval includes no effect and sample size is relatively small), and once for risk of bias (unclear or moderate methodological concerns in the included studies).

ⁱDowngraded three levels: once for inconsistency (high heterogeneity; $I^2 = 82.7\%$ and mixed effect directions), once for imprecision (confidence interval includes no effect and limited number of participants), and once for risk of bias (several studies had unclear or moderate risk of bias and insufficient reporting).

^jDowngraded three levels: once for inconsistency (high heterogeneity; $I^2 = 88.1\%$ and conflicting effect directions), once for imprecision (wide confidence interval crossing no effect with small sample size), and once for risk of bias (unclear or moderate methodological concerns across studies).

^kDowngraded three levels: once for inconsistency (moderate heterogeneity; $I^2 = 48.3\%$ with inconsistent directions of effect), once for imprecision (wide confidence interval including no effect), and once for risk of bias (methodological limitations and lack of clarity in study design across included studies).

^lDowngraded two levels: once for imprecision (confidence interval includes no effect and crossed clinically important thresholds), and once for inconsistency (moderate heterogeneity and variation in study effects).

^mDowngraded two levels: once for inconsistency (moderate heterogeneity ($I^2 = 54.6\%$) and variation in effect sizes), and once for imprecision (wide confidence interval approaching the threshold of clinical relevance).

ⁿDowngraded one level: for inconsistency (moderate heterogeneity across studies; $I^2 = 55.4\%$).

^oDowngraded two levels: once for inconsistency (substantial heterogeneity ($I^2 = 75\%$)), and once for imprecision (limited number of studies and small sample size).

^pDowngraded two levels: once for indirectness (variation in how nocturnal seizures were defined and assessed), and once for inconsistency (substantial heterogeneity ($I^2 = 70.7\%$), suggesting variability in effects).

^qDowngraded two levels: once for inconsistency (substantial heterogeneity ($I^2 = 70.7\%$) indicating variability in effects), and once for imprecision (confidence interval borders on clinical thresholds, and sample size is limited).

^rDowngraded two levels: once for imprecision (confidence interval includes both meaningful harm and no effect), and once for indirectness (variation in age definitions and subgroup analysis reduced applicability).

^sDowngraded three levels: once for inconsistency (conflicting effect directions between RR and OR analyses), once for imprecision (confidence interval includes potential benefit and harm), and once for indirectness (differences in study design and age categorisation).

BACKGROUND

Description of the health condition and context

An epileptic seizure is a clinical manifestation of abnormal, synchronous, excessive discharge in the cerebral cortex (Fisher 2014). An epileptic seizure, depending on the underlying aetiology and preceding mechanism, can be categorised as either 'provoked' or 'unprovoked'. A provoked seizure, also referred to as an acute symptomatic seizure, is one that occurs within seven days of a stroke, traumatic brain injury, anoxic encephalopathy, or intracranial surgery. It may also occur at the time of first identification of a subdural haematoma, in the presence of an active central nervous system (CNS) infection, or during an active phase of multiple sclerosis or other autoimmune diseases. In addition, a diagnosis of acute symptomatic seizure should be made in the presence of severe metabolic derangements (documented within 24 hours by specific biochemical or haematologic abnormalities), drug or alcohol intoxication and withdrawal, or exposure to well-defined epileptogenic drugs (Beghi 2010). An unprovoked seizure is a seizure or a cluster of seizures within 24 hours without a clear precipitating cause (Hauser 2008). Clinically differentiating between provoked and unprovoked seizures carries significant clinical implications. When an individual presents with an initial seizure, the clinician's first task is to discern the nature of the episode. In cases of provoked seizures, the main clinical goal is to identify and address the causative factor to prevent recurrence. In contrast, individuals with unprovoked seizures need to be considered carefully as they are predisposed to developing epilepsy, unlike people who have a provoking cause for their presentation.

A single unprovoked seizure can completely transform the lives of individuals and their families. This life-changing event is common, occurring in at least one in 20 people at some stage (Sander 2003). Unprovoked seizures precipitate increased uncertainty, fear, and anxiety about the future. The first unprovoked seizure can have serious implications for driving, employment, and continued education in both adults and children. Clinicians caring for these individuals and their families must reduce this uncertainty and provide counselling appropriate to someone's individualised risk of recurrence. As highlighted in our earlier review (Neligan 2023), providing a personalised probability of seizure recurrence is possible, but remains crude based on existing evidence. Focussing on individual prognostic factors routinely available in most modern healthcare settings may allow for a more focused approach to a personalised prognostic assessment. Appropriate support can then be provided accordingly, addressing the well-established significant psychosocial burden that a first unprovoked seizure has on people (Heaney 2008).

Epilepsy was traditionally diagnosed following two unprovoked seizures occurring more than 24 hours apart. In 2014, the International League Against Epilepsy (ILAE) adopted an 'operational' set of diagnostic criteria for epilepsy. According to this 'operational' definition, epilepsy can be diagnosed following the first unprovoked seizure so long as the risk of recurrence is greater than 60% at 10 years (Fisher 2014). This evolution of the diagnostic criteria has heightened the need for accurate prognostication of seizure recurrence risk. Consequently, identifying reliable prognostic factors and biomarkers has become more critical than ever. Identifying those at the highest risk of seizures is essential for timely diagnosis, enabling prompt treatment and, potentially,

boosting the recruitment of individuals at increased risk in studies of novel anti-seizure medications (ASMs).

Description of prognostic factors

This review focusses on prognostic factor studies, aiming to identify factors that predict the risk of seizure recurrence following a first unprovoked seizure. Understanding prognostic factors is essential to improving clinical decision-making and patient counselling. Clarifying which factors are associated with seizure recurrence may help clinicians better inform patients about their prognosis, influence management strategies, and guide decisions on treatment initiation, lifestyle changes, driving eligibility, and employment or education implications.

The review explores the following prognostic factors, given their potential relationship with seizure recurrence.

- Age at seizure onset: prognosis may differ significantly between children (one month to 16 years) and adults (> 16 years). Young age at onset could relate to underlying genetic or developmental disorders, whereas adult onset might suggest structural or acquired aetiologies.
- Sex: biological sex might influence seizure recurrence through hormonal differences, genetic predisposition, or differing susceptibilities to specific epileptogenic triggers.
- Seizure semiology (type of seizure): the initial type or characteristics of a seizure may reflect the underlying epileptogenic mechanism, affecting the likelihood of subsequent seizures.
- Family history of epilepsy: a familial predisposition could indicate a genetic susceptibility or shared environmental risk factors that increase the likelihood of recurrence.
- Nocturnal seizure onset: seizures occurring predominantly during sleep may indicate particular epilepsy syndromes with a known tendency for recurrence.
- Relevant past medical history: previous medical events such as febrile seizures, traumatic brain injury, or central nervous system infections may cause lasting neurological changes, increasing seizure recurrence risk.
- Abnormal electroencephalogram (EEG) findings: EEG abnormalities, particularly epileptiform discharges, strongly suggest increased cortical excitability and hence a higher risk of further seizures.
- Abnormal magnetic resonance imaging (MRI) findings: imaging abnormalities, such as hippocampal sclerosis, cortical dysplasia, dysembryoplastic neuroepithelial tumours (DNET), or cavernomas, indicate structural brain lesions known to increase seizure recurrence.
- Presence of comorbidities: conditions such as learning disabilities can reflect underlying developmental brain disorders associated with increased epilepsy risk and recurrence likelihood.
- Specific subpopulations and aetiologies: certain subpopulations, including people with traumatic brain injury, cerebrovascular disease, or neurodegenerative conditions, may have distinct recurrence risks based on specific neuropathological changes.
- Impact of early treatment initiation (anti-seizure medications – ASMs): initiation of ASMs following the first seizure could

modify the recurrence risk, highlighting the importance of early management decisions.

- Genetic abnormalities: pre-identified genetic mutations (such as those seen in KRT1 gene-related cavernomas, CDKL5 deficiency disorder, or PCDH19 epilepsy) may imply a higher inherent risk of seizure recurrence due to known pathogenic mechanisms.

Health outcomes

The risk factors listed above are believed to potentially influence the risk of subsequent, unprovoked seizures of any type and have been examined in previous studies, such as the Medical Research Council's Multicentre trial for Early epilepsy and Single Seizures (MESS) study (Marson 2005). In particular, it has been shown that an abnormal EEG, abnormal neuroimaging, or both are associated with an increased risk of further seizures. However, the impact of specific neuroimaging findings or underlying aetiologies on seizure recurrence – especially when considered alongside EEG patterns or other risk factors – remains less well understood.

Why it is important to do this review

Identifying and validating prognostic factors for seizure recurrence after a first unprovoked seizure is critically important for both clinicians and patients. Accurate prognosis helps guide management, informs shared decision-making, and can assist in the appropriate and timely diagnosis of epilepsy. Despite existing research, significant uncertainty remains around these prognostic factors, and evidence is fragmented and inconsistent. Conducting this review addresses the current gap by systematically summarising and synthesising available evidence, thereby enabling clearer clinical guidelines and identifying gaps for future research.

OBJECTIVES

To identify which prognostic factors predict the risk of subsequent unprovoked seizures and the development of epilepsy at any time following a first unprovoked seizure, a cluster of seizures within 24 hours, or a first episode of status epilepticus – regardless of seizure type.

METHODS

This review has been conducted within the framework of the Cochrane Prognosis Methods Group and reported in line with the PRISMA guidelines (Page 2021). We based the Methods section on the exemplar Cochrane prognosis review protocol for prognostic factors (Hayden 2014), and the general protocol template of the Cochrane Prognosis Methods Group.

Criteria for considering studies for this review

- Population: children (one month to 16 years) and adults (> 16 years) with a previous unprovoked epileptic seizure of any semiology.
- Index prognostic factors: the index factors considered in this review were prognostic factors associated with an increased risk of seizure recurrence following a first unprovoked seizure, detailed in 'Types of prognostic or predictive factors' below.
- Comparator prognostic factor: not applicable.

- Outcome: the primary outcome is a recurrence of a further unprovoked seizure of any semiology and the identification of prognostic factors that predict such an outcome.
- Timing: any seizure recurrence of any semiology, more than 24 hours from the index seizure, in studies with a minimum of six months of follow-up, with no upper time limit for inclusion.
- Settings: hospital outpatient or community settings.

Types of studies

We included retrospective and prospective cohort studies of all age groups, excluding those in the neonatal period (< one month of age), in people with a single unprovoked seizure (of any semiology), followed up for a minimum of six months, with no upper limit of follow-up, and with the study endpoint being (an unprovoked) seizure recurrence, death, or loss to follow-up. To be included, studies must have had at least 30 participants (West 2019). We also considered well-conducted case-control studies where prognostic factors were clearly defined (see 'Assessment of risk of bias in included studies'). We included randomised controlled trials (RCTs) that provided relevant univariable prognostic data, thus contributing valuable evidence given the paucity of data. We considered both published and unpublished studies. We imposed no language restrictions in the selection of studies.

Targeted population

Population and clinic cohorts of people over one month of age, presenting with a single unprovoked seizure of any semiology, with a follow-up period of at least six months.

We excluded people with seizures that occurred as a result of an acute precipitant or provoking factor or in close temporal proximity to an acute neurological insult (such as a head injury or acute cerebrovascular accident) since they are not considered epileptic in aetiology (acute symptomatic seizures; Beghi 2010). Similarly, we excluded people with situational seizures, such as febrile convulsions, which occur in young children in the context of a high temperature.

If a study included both eligible (single unprovoked seizure) and ineligible participants (situational or acute symptomatic seizures), we included the study only if data on eligible participants were reported separately or if we could extract relevant data specifically for the eligible subgroup. Where subgroup data were unavailable or unclear, we excluded the study.

Types of prognostic or predictive factors

We considered the following prognostic factors for predicting seizure recurrence.

- Age of seizure onset: age at the time of the first unprovoked seizure, categorised as childhood (one month to 16 years) or adulthood (> 16 years).
- Sex: biological sex categorised as male or female.
- Seizure semiology: clinical manifestation and classification of the initial seizure, as defined by the International League Against Epilepsy (ILAE) classifications.
- EEG findings: electroencephalogram (EEG) results categorised as abnormal if demonstrating epileptiform discharges or focal slowing. Adequate measurement included clearly defined EEG

abnormalities based on standard EEG guidelines and expert interpretation.

- MRI findings: abnormal magnetic resonance imaging (MRI) findings relevant to seizure recurrence, including specific lesions such as hippocampal sclerosis, cortical dysplasia, dysembryoplastic neuroepithelial tumours (DNET), and cavernomas. Adequate measurement included imaging interpreted and classified according to established radiological criteria.
- Comorbidities: the presence of clinically diagnosed comorbid conditions such as learning disabilities, assessed through standardised clinical assessments or clearly documented medical histories.
- Specific subpopulations or aetiologies: participants with clearly defined conditions such as traumatic brain injury, cerebrovascular disease, or neurodegenerative disorders, confirmed through clinical history or diagnostic imaging.
- Impact of treatment: initiation of anti-seizure medications (ASMs) following the initial seizure, with clear documentation of whether participants received treatment or remained untreated.
- Genetic abnormalities: pre-identified genetic abnormalities such as mutations associated with conditions like multiple cavernomas, CDKL5 deficiency disorder, or PCDH19 epilepsy, confirmed by genetic testing.

The prognostic factors were measured at the time of the first seizure (baseline), and the outcomes were predicted over a minimum follow-up period of six months, with no upper limit of follow-up.

Types of outcomes to be predicted

The primary outcome is the occurrence of a second (unprovoked) epileptic seizure more than 24 hours after the original seizure of any type. We analysed this as the proportion of people who had a further seizure in any period, with an evaluation of the impact of the individual predictive factors on this outcome.

Search methods for identification of studies

Electronic searches

We searched the following databases with no language restrictions:

- CENTRAL via the Cochrane Register of Studies Online (CRS Web, 13 December 2022), using the strategy outlined in [Appendix 1](#);
- MEDLINE Ovid (1946 to 12 December 2022), using the strategy outlined in [Appendix 2](#);
- SCOPUS (1823 to 13 December 2022), using the subject and citation strategies outlined in [Appendix 3](#);
- ClinicalTrials.gov (15 December 2022), using the strategy outlined in [Appendix 4](#);
- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; 15 December 2022), using the strategy outlined in [Appendix 5](#).

To avoid duplication of effort, we used the same search for this review and the overall prognosis review ([Neligan 2023](#)). We anticipated that several of the studies included in this earlier review would not be eligible for this review.

Searching other resources

We searched for additional relevant studies in the reference lists of included studies and any relevant systematic reviews identified in the search.

Data collection

Selection of studies

We conducted the initial screening of titles and abstracts identified through electronic searches and removed irrelevant articles. We then obtained full-text articles of all potentially relevant studies, or those whose relevance could not be determined from the abstract. Two review authors (AN, GA) independently assessed these full-text articles for eligibility. We resolved any disagreements through discussion or, if required, in consultation with a third review author (AM).

We did not contact study authors to determine study eligibility. When studies were reported in multiple publications or reports, we collated all relevant reports under a single study ID so that the study, rather than the individual report, was the unit of interest in the review.

We have illustrated the study selection process in a PRISMA study flow diagram ([Page 2021](#)).

Data extraction and management

We extracted data from the included studies using a standardised extraction form developed in accordance with the CHARMS checklist (checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies; [Moons 2014](#)). We piloted this form on several studies and made appropriate edits.

Working independently, two review authors (GA, AN) extracted data from all studies, unless explicitly stated otherwise. A third review author (LB) independently checked the extracted data for accuracy. As AN and JWS were co-authors of one included study ([Bell 2016](#)), two other review authors (GA, LB) exclusively performed all data extraction and subsequent analysis of this study. Similarly, as LB and AM were co-authors of another included study ([Bonnett 2010](#)), GA and AN exclusively performed data extraction and analysis relating to this study. We resolved any disagreements through discussion or, if necessary, by consulting a fourth review author (AGM).

Where data were missing or unclear, we contacted study authors to request additional information or clarification.

List of data extracted, where available

- Date of first seizure and date(s) of subsequent seizure(s)
- Age at seizure onset
- Sex
- Seizure semiology (e.g. focal onset, generalised onset, impairment of consciousness)
- EEG results, including the presence or absence of epileptiform abnormalities or specific EEG patterns
- Neuroimaging results, including specific abnormalities such as hippocampal sclerosis, cortical dysplasia, dysembryoplastic neuroepithelial tumours (DNET), or cavernomas

- Relevant past medical history, including febrile seizures, traumatic brain injury, or central nervous system infections
- Family history of epilepsy
- Presence of comorbidities, such as learning disabilities
- Specific subpopulations or individuals with particular aetiologies (e.g. traumatic brain injury, cerebrovascular disease, or neurodegenerative conditions)
- Anti-seizure medication (ASM) therapy initiation status (initiated or not)
- Pre-identified genetic abnormalities (e.g. CDKL5 deficiency disorder, PCDH19 epilepsy, or genetic markers such as the KRT1 gene)
- Follow-up duration and outcomes, specifically seizure recurrence, death, or loss to follow-up

Assessment of risk of bias in included studies

Two authors (GA, AN) independently assessed the risk of bias in each included study using the QUality In Prognosis Studies (QUIPS) tool (Hayden 2013; see Appendix 6). This tool is specifically designed for assessing the risk of bias in studies of prognostic factors, and includes six domains:

- study participation;
- study attrition;
- prognostic factor measurement;
- outcome measurement;
- adjustment for other prognostic factors;
- statistical analysis and reporting.

In line with Cochrane recommendations for prognostic factor reviews (Boutron 2024, section 7.6.2), we replaced the standard 'confounding' domain with 'adjustment for other prognostic factors' to reflect the review's focus on covariate adjustment rather than confounding per se. We made no additional modifications to the QUIPS tool.

Before formal assessment, we conducted a pilot test of the QUIPS tool to ensure consistent interpretation and application of each domain amongst review authors. We resolved any disagreements between assessors through discussion to reach consensus without needing involvement from a third review author. Working independently, GA and LB assessed the risk of bias of the Bell 2016 study, which AN co-authored, to mitigate potential bias.

We rated each risk of bias domain as low, unclear, or high. We considered studies to have an overall low risk of bias if most QUIPS domains (i.e. at least four of six) were rated as low risk and none were rated as high risk. This rule was prespecified and applied consistently across all studies.

Due to resource and time constraints, we did not systematically contact study authors for additional methodological details to inform our risk of bias assessments. Thus, our judgements were based solely on information available in the published articles. We acknowledge this may introduce uncertainty in certain domains; consequently, we rated these domains conservatively.

We included all eligible studies in the primary analysis regardless of their risk of bias rating.

Measures of association or predictive performance measures to be extracted

We extracted odds ratios (ORs), risk ratios (RRs), and hazard ratios (HRs) from univariable or multivariable regression analyses if reported. For consistency, ORs, RRs, and HRs from univariable regression analyses were used for meta-analysis only.

Statistical significance

We defined statistical significance as a P value of less than 0.05. All reported confidence intervals (CIs) are 95%; therefore, we considered estimates with confidence intervals not including the null value (i.e. CI did not cross 1 for HR, RR, or OR) as statistically significant.

Dealing with missing data

We included studies investigating the relationship between prognostic factors and the risk of seizure recurrence. If only multivariable effect estimates were reported, we contacted study authors to request the corresponding univariable data. If authors did not respond after 30 days, we excluded those studies from the review.

Assessment of heterogeneity

We anticipated clinical and statistical heterogeneity between studies due to the broad inclusion criteria for study design and participant populations. Consequently, we used a random-effects model for the meta-analysis.

We considered the clinical heterogeneity of included studies based on the study design, study duration, potential biases of the study, the participant population, the definition and measurement of the prognostic factor used (including any cut-off points), and the outcome measurement.

To assess statistical heterogeneity across studies in each synthesis, we inspected forest plots and quantified heterogeneity statistically using the I^2 statistic and τ^2 (the estimate of between-study variance; Snell 2016).

Assessment of reporting deficiencies

We planned to examine publication bias for each prognostic factor meta-analysis, provided there were at least 10 studies, by visually examining asymmetry on funnel plots and testing for asymmetry at the 10% level, using Egger's test for HRs (Debray 2018; Egger 1997), and Peters' test for ORs (Harbord 2009; Sterne 2011).

Data synthesis

Data synthesis and meta-analysis approaches

We estimated effect sizes based on the dichotomous data for the univariable relationship between each prognostic factor and the outcome. We pooled these effect sizes where study designs, participant populations, and prognostic factor definitions and cut-offs were sufficiently homogenous to synthesise.

We conducted meta-analyses using STATA version 18, with a random-effects, generic inverse-variance meta-analysis model, which accounted for any between-study heterogeneity in the prognostic effect. We summarised the meta-analysis by the pooled estimate (the average prognostic factor effect), its 95% CI, the

estimates of I^2 (heterogeneity), and a 95% prediction interval for the prognostic impact in a single population (Riley 2011).

For studies or prognostic factors where it was not possible or appropriate to perform a meta-analysis due to insufficient homogeneity, we followed the Synthesis Without Meta-analysis (SWiM) guidelines (Campbell 2020). In these cases, we narratively summarised the results, providing descriptive information on the size and direction of effects reported in individual studies, highlighting similarities and differences amongst the studies, and discussing potential reasons for observed differences or heterogeneity. With this narrative approach, we aimed to ensure transparency and provide context for findings not amenable to quantitative synthesis, facilitating interpretation and informing future updates of this review.

Subgroup analysis and investigation of heterogeneity

We intended to explore potential sources of heterogeneity by performing subgroup analyses based on prespecified effect modifiers, including study design (prospective versus retrospective), age group (adults versus children, as defined by individual studies), and seizure type (e.g. focal versus generalised). We chose these effect modifiers because differences in study methodology, participant age, and seizure characteristics could plausibly influence prognostic outcomes and contribute to between-study heterogeneity. However, subgroup analyses require at least two studies per subgroup to allow meaningful statistical synthesis. We defined 'sufficient data' as the availability of at least two studies per subgroup reporting the same prognostic factor, measured consistently, and expressed using the same effect measure (HR, RR, or OR). Due to insufficient data meeting these criteria within each subgroup category, we were unable to perform the planned subgroup analyses in this review.

Due to considerable heterogeneity in how individual studies measured prognostic factors and reported outcomes (using different statistical measures such as HR, RR, OR), we did not perform separate subgroup meta-analyses based on study design (prospective versus retrospective), participant age groups (adults versus children), or seizure types (e.g. focal, nocturnal). While some meta-analyses individually met the numerical criterion (at least two studies per subgroup), the included studies did not consistently use identical effect measures, definitions, and reporting methods to allow meaningful synthesis and robust interpretation. Future updates of this review should aim to include additional high-quality studies with more uniform reporting standards to enable robust subgroup analyses.

Sensitivity analysis

A sensitivity analysis was not required as no data transformation was part of the review process.

Certainty of the evidence and summary of findings

We used an approach adapted from the GRADE framework to assess the overall certainty of the evidence for each prognostic factor and outcome (Guyatt 2011; Hayden 2013; Hugué 2013; Iorio 2015). We rated the certainty of evidence as high, moderate, low, or very low based on five domains: risk of bias, inconsistency, indirectness, imprecision, and publication/reporting bias.

We incorporated the overall risk of bias judgment from the QUIPS assessment into the risk of bias domain of the GRADE framework, explicitly using it to inform certainty of the evidence ratings and downgrading decisions, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Boutron 2024, section 7.5; Higgins 2024a, section 8.2.4; Higgins 2024b, section 23.1.2), and consistent with MECIR standard C56 (Higgins 2023).

Downgrading decisions were made for each domain and documented in footnotes of the summary of findings (SoF) table. We followed the narrative guidance for interpreting prognostic findings, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2024).

Working independently, two review authors (GA and AN) performed GRADE assessments. We resolved any discrepancies through discussion, with input from a third author (LB) where required.

Due to the limited number of studies available for each prognostic factor, we did not perform subgroup or sensitivity analyses based on risk of bias ratings.

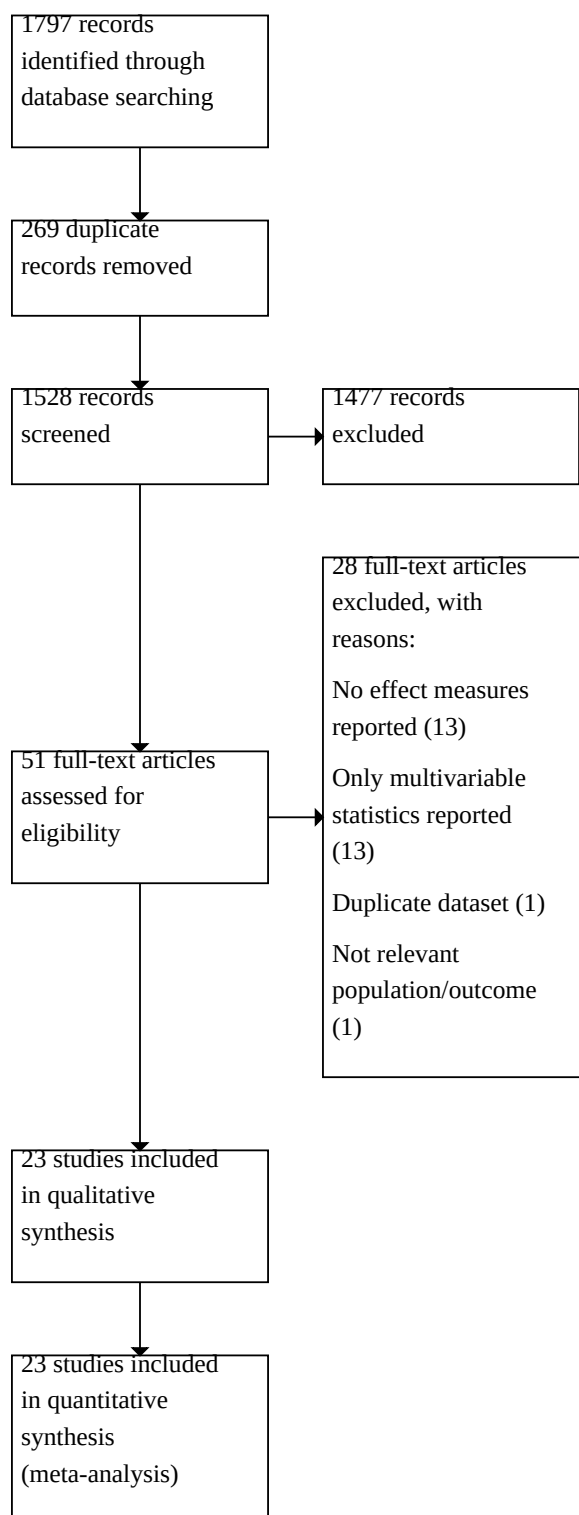
RESULTS

Description of studies

Results of the search

We identified a total of 1797 records through our search. After excluding duplicates (269 records) and non-relevant records based on title and abstract screening, we assessed 51 full-text records (Figure 1). Of these, we excluded 28 full-text articles with reasons (Characteristics of excluded studies); the remaining 23 articles were reports of 23 unique studies (see Included studies for overview and Characteristics of included studies for details).

Figure 1. PRISMA flow diagram illustrating the study selection process, including identification, screening, eligibility, and inclusion of studies.



We identified no studies currently awaiting classification or ongoing studies eligible for inclusion.

Excluded studies

Following full-text screening, we excluded 28 studies as they did not meet the eligibility criteria for this review. The most common reasons for exclusion were:

- no effect measures reported (13);
- only multivariable statistics reported (13) (Additional [Table 1](#));
- duplicate dataset (1);
- inappropriate study population (e.g. the seizure was provoked or acute symptomatic) (1).

A full list of excluded studies, along with the specific reasons for their exclusion, is available in the [Characteristics of excluded studies](#) table.

Included studies

Studies are described in detail in the [Characteristics of included studies](#) table. Twenty-three studies with 5918 participants met the inclusion criteria for the review ([Al-Momani 2020](#); [Baldin 2017](#); [Bell 2016](#); [Bonnett 2010](#); [Chen 2016](#); [Daoud 2004](#); [Hauser 1990](#); [Hesdorffer 2007](#); [Hui 2001](#); [Kanemura 2015](#); [Machado 2021](#); [Mahler 2015](#); [Mizorogi 2015](#); [Pang 2022](#); [Qadri 2017](#); [Ramos Lizana 2000](#); [Ramos Lizana 2009](#); [Sathirapanya 2020](#); [Schreiner 2003](#); [Scotoni 2004](#); [Shinnar 2000](#); [Takami 2021](#); [Winckler 2004](#)). The size of the cohorts varied, with a median (range) of 134 (50 to 1885) participants.

Study designs

Fifteen studies were prospective cohort studies ([Baldin 2017](#); [Bell 2016](#); [Chen 2016](#); [Daoud 2004](#); [Kanemura 2015](#); [Mizorogi 2015](#); [Pang 2022](#); [Qadri 2017](#); [Ramos Lizana 2000](#); [Ramos Lizana 2009](#); [Schreiner 2003](#); [Scotoni 2004](#); [Shinnar 2000](#); [Takami 2021](#); [Winckler 2004](#)), seven were retrospective cohort studies ([Al-Momani 2020](#); [Hauser 1990](#); [Hesdorffer 2007](#); [Hui 2001](#); [Machado 2021](#); [Mahler 2015](#); [Sathirapanya 2020](#)), and one was a randomised controlled trial (RCT) ([Bonnett 2010](#)). Although our inclusion criteria specified observational cohort studies, we included the RCT as it provided relevant univariable prognostic data, thus contributing valuable evidence given the paucity of data.

Study characteristics

Four studies were from the USA ([Baldin 2017](#); [Hauser 1990](#); [Hesdorffer 2007](#); [Shinnar 2000](#)); two from the United Kingdom ([Bell 2016](#); [Bonnett 2010](#)); three from Brazil ([Machado 2021](#); [Scotoni 2004](#); [Winckler 2004](#)); three from Japan ([Kanemura 2015](#); [Mizorogi 2015](#); [Takami 2021](#)); two from China ([Chen 2016](#); [Hui 2001](#)); two from Jordan ([Al-Momani 2020](#); [Daoud 2004](#)); two from Spain ([Ramos Lizana 2000](#); [Ramos Lizana 2009](#)); and one each from Australia ([Pang 2022](#)), Germany ([Schreiner 2003](#)), India ([Qadri 2017](#)), Sweden ([Mahler 2015](#)), and Thailand ([Sathirapanya 2020](#)).

The median follow-up duration was 35 months, ranging from six months ([Mahler 2015](#); [Qadri 2017](#)) to 283 months ([Bell 2016](#)).

Participants

The included studies had similar proportions of male and female participants (median 57.3% male, interquartile range (IQR) 54.5% to 61.5%). Sixteen studies did not involve routine prescription of anti-seizure medication (ASM) following a first seizure ([Al-Momani](#)

[2020](#); [Baldin 2017](#); [Bell 2016](#); [Chen 2016](#); [Daoud 2004](#); [Hesdorffer 2007](#); [Hui 2001](#); [Kanemura 2015](#); [Mahler 2015](#); [Mizorogi 2015](#); [Qadri 2017](#); [Schreiner 2003](#); [Scotoni 2004](#); [Shinnar 2000](#); [Takami 2021](#); [Winckler 2004](#)), while seven studies did include participants who received ASM after the first seizure ([Bonnett 2010](#); [Hauser 1990](#); [Machado 2021](#); [Pang 2022](#); [Ramos Lizana 2000](#); [Ramos Lizana 2009](#); [Sathirapanya 2020](#)).

Eight studies included only adults (≥ 16 years) ([Baldin 2017](#); [Bell 2016](#); [Bonnett 2010](#); [Hui 2001](#); [Mahler 2015](#); [Pang 2022](#); [Sathirapanya 2020](#); [Schreiner 2003](#)), 12 included only children (< 16 years) ([Al-Momani 2020](#); [Daoud 2004](#); [Kanemura 2015](#); [Machado 2021](#); [Mizorogi 2015](#); [Qadri 2017](#); [Ramos Lizana 2000](#); [Ramos Lizana 2009](#); [Scotoni 2004](#); [Shinnar 2000](#); [Takami 2021](#); [Winckler 2004](#)), and three included both adults and children ([Chen 2016](#); [Hauser 1990](#); [Hesdorffer 2007](#)).

Prognostic factors

Studies examined various prognostic factors, including febrile seizures, focal neurological deficit, Todd's paresis, status epilepticus, family history of epilepsy, sex, focal onset seizures, abnormal brain imaging, abnormal EEG, nocturnal seizures, and age.

Outcomes

All studies evaluated seizure recurrence as the primary outcome. We conducted meta-analyses for prognostic factors reported by at least two studies using consistent statistical measures (hazard ratio (HR), risk ratio (RR), odds ratio (OR)). We excluded studies reporting only multivariable results without univariable data if no additional data were provided after contacting study authors. The multivariable data extracted are presented in Additional [Table 1](#). These exclusions are listed in the [Characteristics of excluded studies](#) table, including reasons for exclusion.

Definitions of prognostic factors assessed

- Febrile seizure refers to a seizure occurring in the context of a febrile illness in the absence of central nervous system infection or acute electrolyte imbalance, typically in children aged six months to five years, prior to the first unprovoked seizure. Febrile seizures that occurred before the first unprovoked seizure were explicitly considered as potential prognostic factors in the included studies and were included in our analysis.
- Focal neurological deficit refers to any persistent neurological abnormality identified upon clinical neurological examination following the initial unprovoked seizure episode.
- Todd's paresis refers to a transient, focal neurological deficit presenting as unilateral weakness occurring immediately after the initial seizure.
- Status epilepticus refers to continuous seizure activity lasting at least five minutes or recurrent seizures without recovery in between, occurring as the presenting epileptic event.
- Family history of epilepsy refers to a documented diagnosis of epilepsy in at least one first-degree relative (parent, sibling, or offspring).
- Sex refers to the biological sex of the individual experiencing the first unprovoked seizure, categorised as male or female.
- Focal onset seizures refer to seizures characterised by clinical or electroencephalographic evidence of localised onset in a specific cerebral hemisphere or brain region during the initial seizure.

- Abnormal brain imaging refers to structural cerebral abnormalities identified through neuroimaging techniques (MRI or computed tomography (CT)) conducted in proximity to the time of the first unprovoked seizure.
- Abnormal EEG refers to electroencephalographic findings indicating interictal epileptiform abnormalities or abnormal background rhythms, recorded following the first unprovoked seizure.
- Nocturnal seizures refer to seizures occurring exclusively or predominantly during sleep, including when the initial unprovoked seizure was nocturnal.
- Age refers to the chronological age of the individual at the time of experiencing their first unprovoked seizure.

We were unable to find suitable studies reporting data on several prognostic factors we initially identified as of interest, detailed in the protocol for this study ([Adan 2021](#)). These included specific

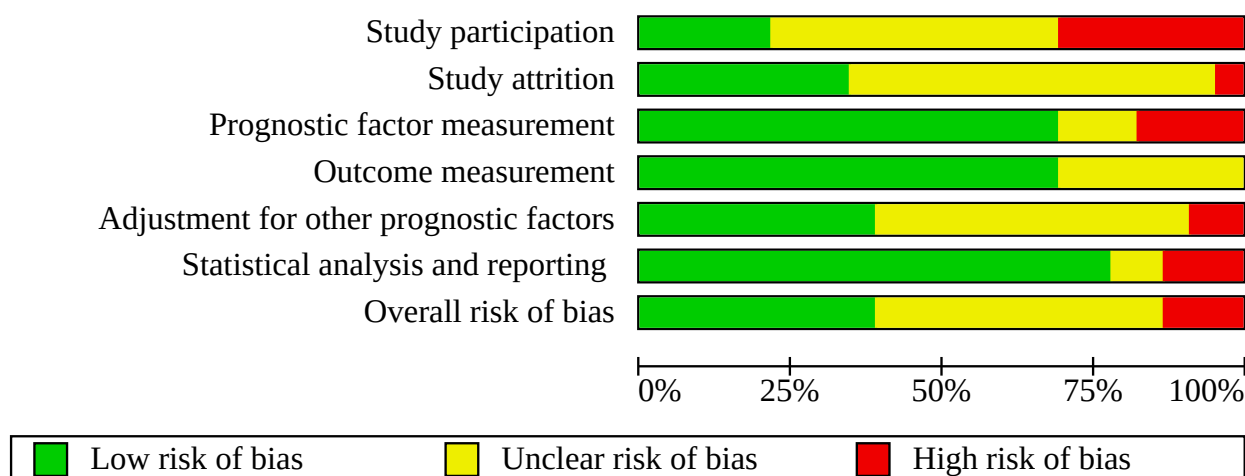
genetic abnormalities, comorbidities such as learning disabilities, clearly defined subpopulations (e.g. traumatic brain injury or neurodegenerative disorders), and the impact of anti-seizure medication initiation after a first seizure. The absence of data on these factors represents important gaps in current knowledge, highlighting areas that require further investigation in future prognostic research.

Risk of bias assessment of included studies

We assessed the risk of bias across six domains using the QUIPS tool for each of the included studies. [Figure 2](#) summarises the risk of bias assessment by study. We assessed nine studies (39%) as having an overall low risk of bias, 11 (48%) as unclear risk, and three (13%) as high risk. Full risk of bias assessments are provided in the [Characteristics of included studies](#) table. [Figure 3](#) presents a summary of the proportion of studies rated as low, unclear, or high risk of bias in each domain.

Figure 2. Summary of the risk of bias assessment across included studies, categorising each study by domain and level of bias risk.

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Adjustment for other prognostic factors	Statistical analysis and reporting	Overall risk of bias
Al-Momani 2020	?	+	+	?	+	+	?
Baldin 2017	+	+	?	+	+	+	?
Bell 2016	+	?	+	+	+	+	+
Bonnett 2010	?	?	+	+	+	+	+
Chen 2016	+	?	+	+	?	+	+
Daoud 2004	+	?	+	+	+	+	+
Hauser 1990	+	+	+	+	?	+	?
Hesdorffer 2007	+	?	+	+	+	+	+
Hui 2001	+	?	+	?	?	+	?
Kanemura 2015	?	+	+	?	+	?	?
Machado 2021	?	?	+	?	?	+	?
Mahler 2015	+	?	+	?	?	?	+
Mizorogi 2015	?	+	?	+	?	+	?
Pang 2022	+	?	+	+	+	+	?
Qadri 2017	?	+	+	?	?	+	+
Ramos Lizana 2000	?	+	+	+	?	+	+
Ramos Lizana 2009	?	+	+	+	?	+	+
Sathirapanya 2020	+	?	+	?	?	+	?
Schreiner 2003	?	+	?	+	?	+	?
Scotoni 2004	?	?	+	+	+	+	+
Shinnar 2000	?	?	+	+	+	+	+
Takami 2021	+	?	+	+	?	+	?
Winckler 2004	+	?	+	+	+	+	+

Figure 3. Distribution of risk of bias categories across all included studies, visualised as a bar chart.

We noted several recurring methodological limitations across the included studies that may affect the overall validity of the review's findings.

- Prognostic factor measurement: many studies lacked clarity or standardisation in how they defined and measured prognostic factors (e.g. EEG or imaging abnormalities), limiting comparability across studies.
- Adjustment for other prognostic factors: a considerable number of studies did not adjust for relevant confounders or provide univariable data that were directly extractable, increasing the risk of biased estimates.
- Outcome measurement: there was variation in how seizure recurrence was defined and measured, including differences in follow-up duration and whether anti-seizure medication initiation influenced outcome definition.
- Statistical analysis and reporting: reporting of effect measures was inconsistent, with some studies presenting only multivariable results without specifying the covariates included in the model.

These limitations contributed to our downgrading the certainty of the evidence across several prognostic factors, and we took them into account when interpreting the overall strength of the findings.

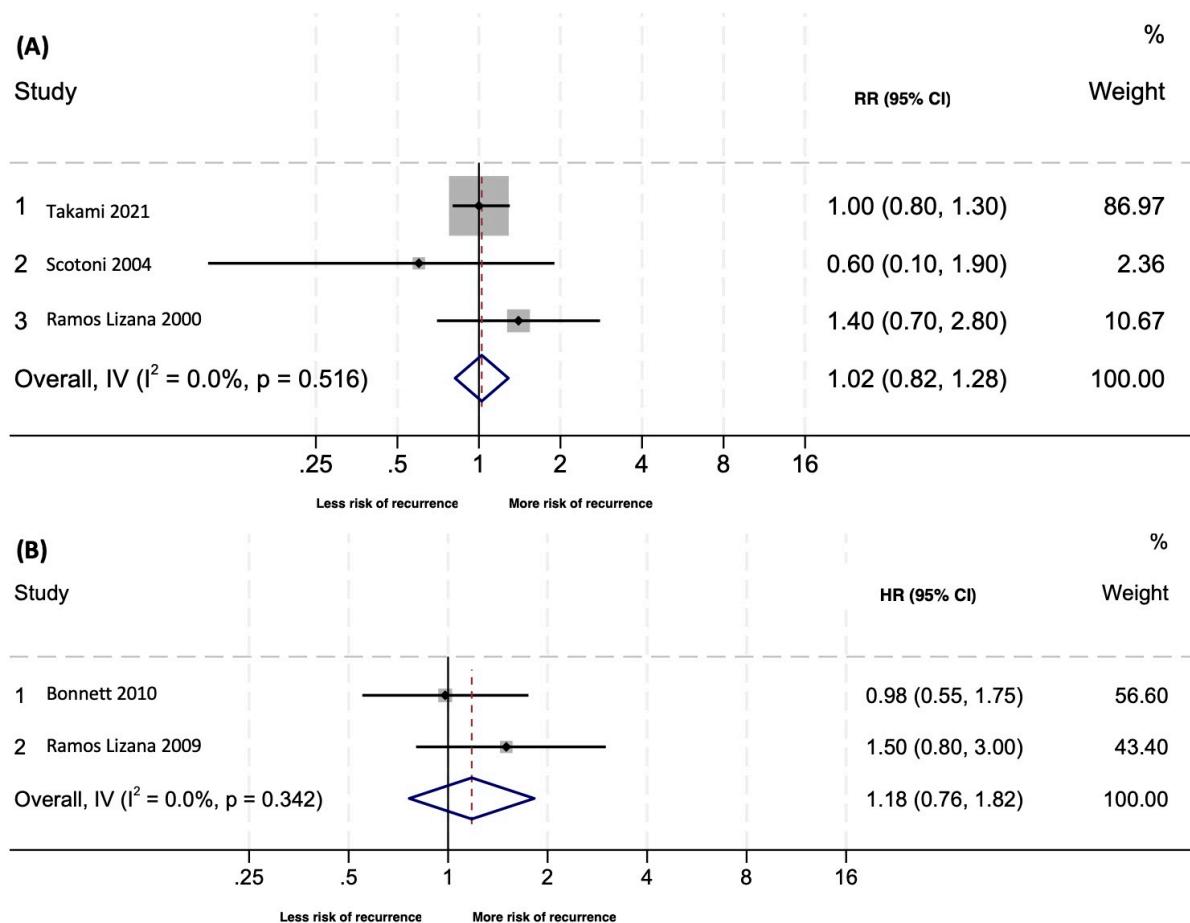
Findings

All 23 included studies provided sufficient data to contribute to at least one meta-analysis. We only performed a meta-analysis of a prognostic factor if at least two studies provided sufficient univariable outcome data. We conducted 22 meta-analyses, involving 13 different prognostic factors: febrile seizures, focal neurological deficit, Todd's paresis, status epilepticus, family history of epilepsy, male sex (with female sex as the reference group), focal seizures, abnormal brain imaging, abnormal EEG, nocturnal seizures, and age under 16 years (with age ≥ 16 years as the reference group). We performed meta-analyses of HR, RR, and OR separately but collated the results into the same figure to allow comparison across studies despite differences in how data were reported.

Febrile seizures

Five studies (1541 participants) provided usable data on febrile seizures. Two studies (700 participants) allowed a meta-analysis using HR (HR 1.18, 95% confidence interval (CI) 0.76 to 1.82; 95% prediction interval (PI) 0.76 to 1.83; $P = 0.342$, $I^2 = 0.0\%$, $\tau^2 = 0.0\%$; 2 studies, 700 participants; very low-certainty evidence; [Figure 4](#)). Three studies (841 participants) allowed a meta-analysis using RR (RR 1.02, 95% CI 0.82 to 1.28; PI 0.82 to 1.28; $P = 0.516$, $I^2 = 0.0\%$, $\tau^2 = 0.0\%$; 3 studies, 841 participants; very low-certainty evidence; [Figure 4](#)). The evidence is very uncertain about whether febrile seizures are associated with seizure recurrence.

Figure 4. (A) Forest plot of risk ratio (RR) of febrile seizures as a prognostic factor for seizure recurrence. (B) Forest plot of hazard ratio (HR) of febrile seizures as a prognostic factor for seizure recurrence. Figure generated using STATA version 18 based on meta-analysis results. The reported P value refers to heterogeneity between studies, not the significance of the pooled effect estimate.

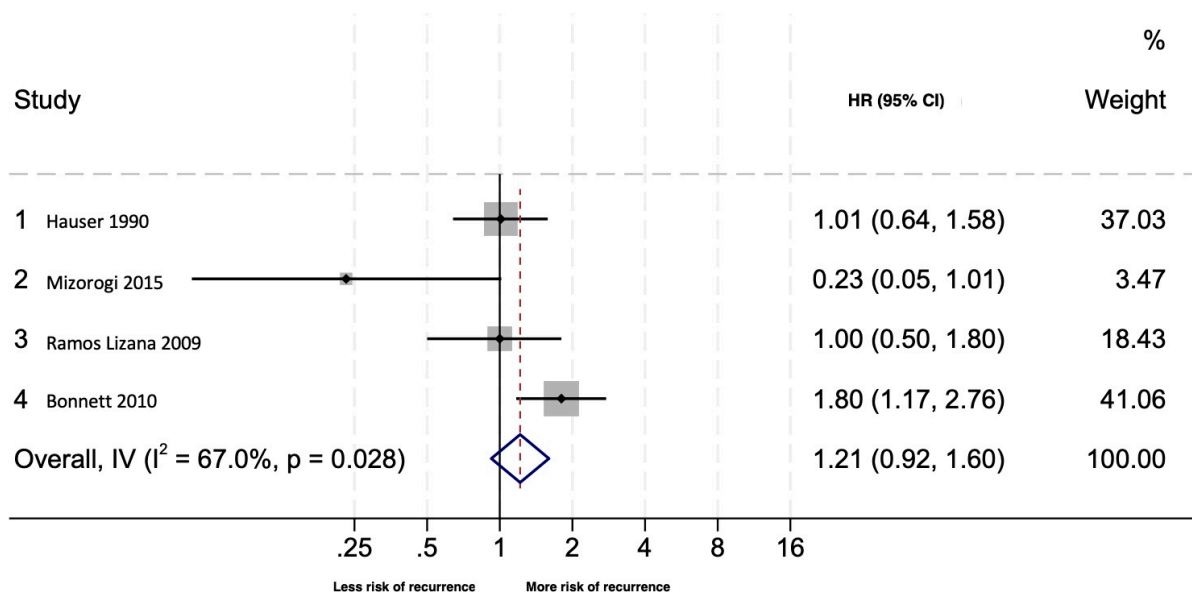


Focal neurological deficit

Four studies (981 participants) provided usable HR data (HR 1.21, 95% CI 0.92 to 1.60; PI 0.35 to 4.24; $P = 0.028$, $I^2 = 67\%$, $\tau^2 = 0.1839\%$;

4 studies, 981 participants; very low-certainty evidence; [Figure 5](#)). The evidence is very uncertain about whether focal neurological deficit is associated with an increased risk of seizure recurrence.

Figure 5. Forest plot of hazard ratio (HR) of focal neurological deficit as a prognostic factor for seizure recurrence. Figure generated using STATA version 18 based on meta-analysis results. The reported P value refers to heterogeneity between studies, not the significance of the pooled effect estimate.



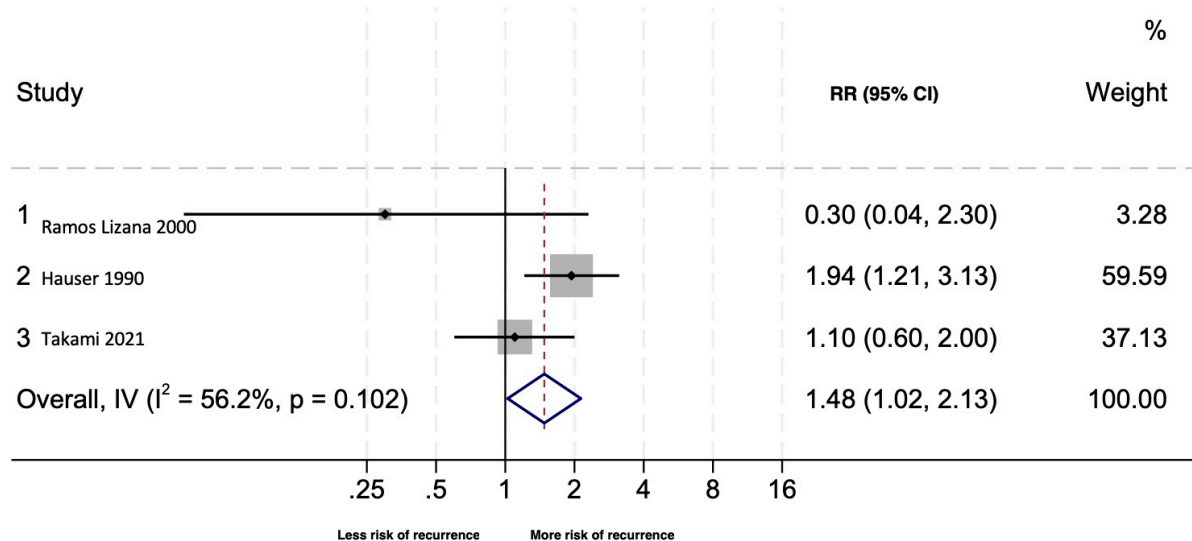
Mizorogi 2015 reported a contradictory finding, suggesting focal neurological deficits were associated with decreased seizure recurrence risk, contrasting significantly with the positive associations observed in Hauser 1990, Ramos Lizana 2009, and Bonnett 2010. Mizorogi and colleagues' retrospective, single-centre design, specialised adult epilepsy patient cohort, stricter diagnostic criteria, and potentially differing seizure definitions likely contributed to this discrepancy. Inclusion of this study introduced significant heterogeneity ($I^2 = 67\%$) and diluted the pooled results, shifting effect estimates toward null, thus increasing

uncertainty regarding focal neurological deficit as a prognostic factor for seizure recurrence.

Todd's paresis

Three studies (836 participants) provided RR data (RR 1.48, 95% CI 1.02 to 2.13; PI 0.64 to 3.45; $P = 0.102$, $I^2 = 56.2\%$, $\tau^2 = 0.1511\%$; 3 studies, 836 participants; low-certainty evidence; Figure 6). Todd's paresis may increase the risk of seizure recurrence, but the certainty of the evidence is low.

Figure 6. Forest plot of risk ratio (RR) of Todd's paresis as a prognostic factor for seizure recurrence. Figure generated using STATA version 18 based on meta-analysis results. The reported P value refers to heterogeneity between studies, not the significance of the pooled effect estimate.



The inclusion of [Ramos Lizana 2000](#), due to it reporting a weaker association between Todd's paresis and seizure recurrence, reduced the overall pooled estimate, introducing greater uncertainty and heterogeneity into the meta-analysis. This resulted in wider confidence intervals and a lower level of certainty regarding the prognostic relevance of Todd's paresis. The discrepancy observed between [Ramos Lizana 2000](#) and the studies by [Hauser 1990](#) and [Takami 2021](#) regarding Todd's paresis may be explained by differences in study populations (paediatric-only in Spain versus mixed or different paediatric cohorts elsewhere), variability in the definitions and classification of Todd's paresis, differences in seizure aetiologies, and variations in healthcare

practices influencing seizure management across study settings. These factors likely contributed to heterogeneity in observed recurrence risks and the reduced predictive power of Todd's paresis reported by Ramos Lizana and colleagues compared to the other two studies.

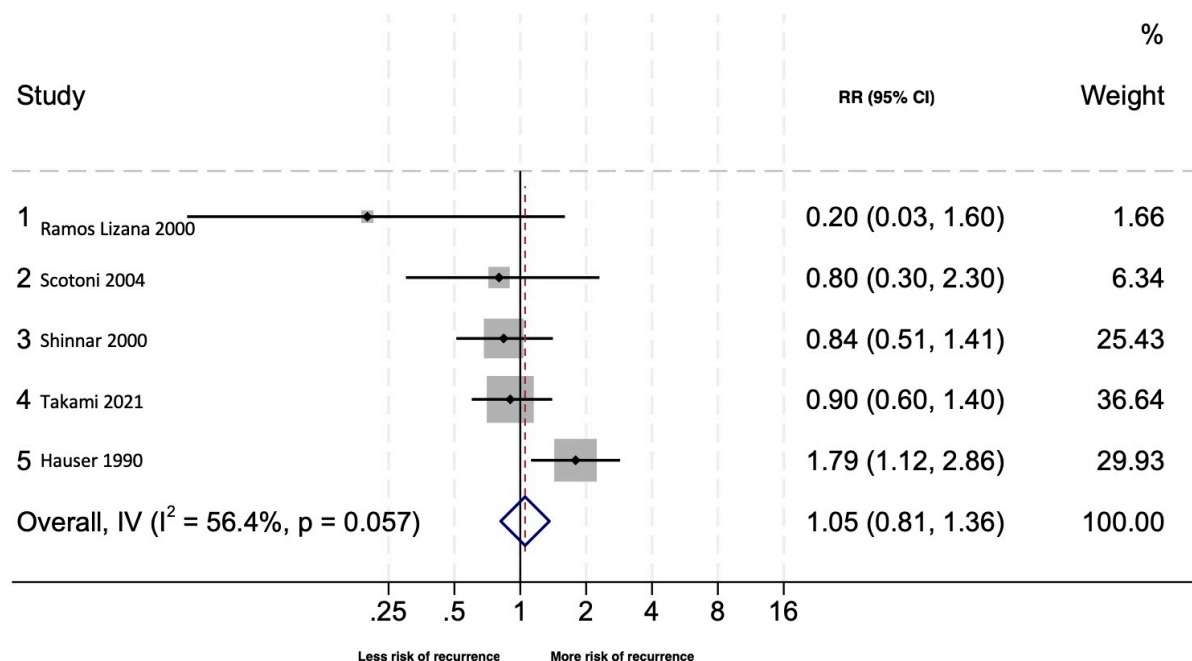
Status epilepticus

Five studies (1456 participants) provided RR data (RR 1.05, 95% CI 0.81 to 1.36; PI 0.28 to 3.47; $P = 0.057$, $I^2 = 56.4\%$, $\tau^2 = 0.1088\%$; 5 studies, 1456 participants; very low-certainty evidence; [Figure 7](#)). The evidence is very uncertain about whether status epilepticus increases the risk of seizure recurrence.

Figure 7. Forest plot of risk ratio (RR) of status epilepticus as a prognostic factor for seizure recurrence.

Figure generated using STATA version 18 based on meta-analysis results.

The reported P value refers to heterogeneity between studies, not the significance of the pooled effect estimate.



Family history of epilepsy

Ten studies (2306 participants) reported usable information on the association between family history of epilepsy and seizure recurrence. Four studies (1012 participants) provided HR data (HR 1.35, 95% CI 1.03 to 1.76; PI 0.30 to 6.01; $P = 0.104$, $I^2 = 51.4\%$;

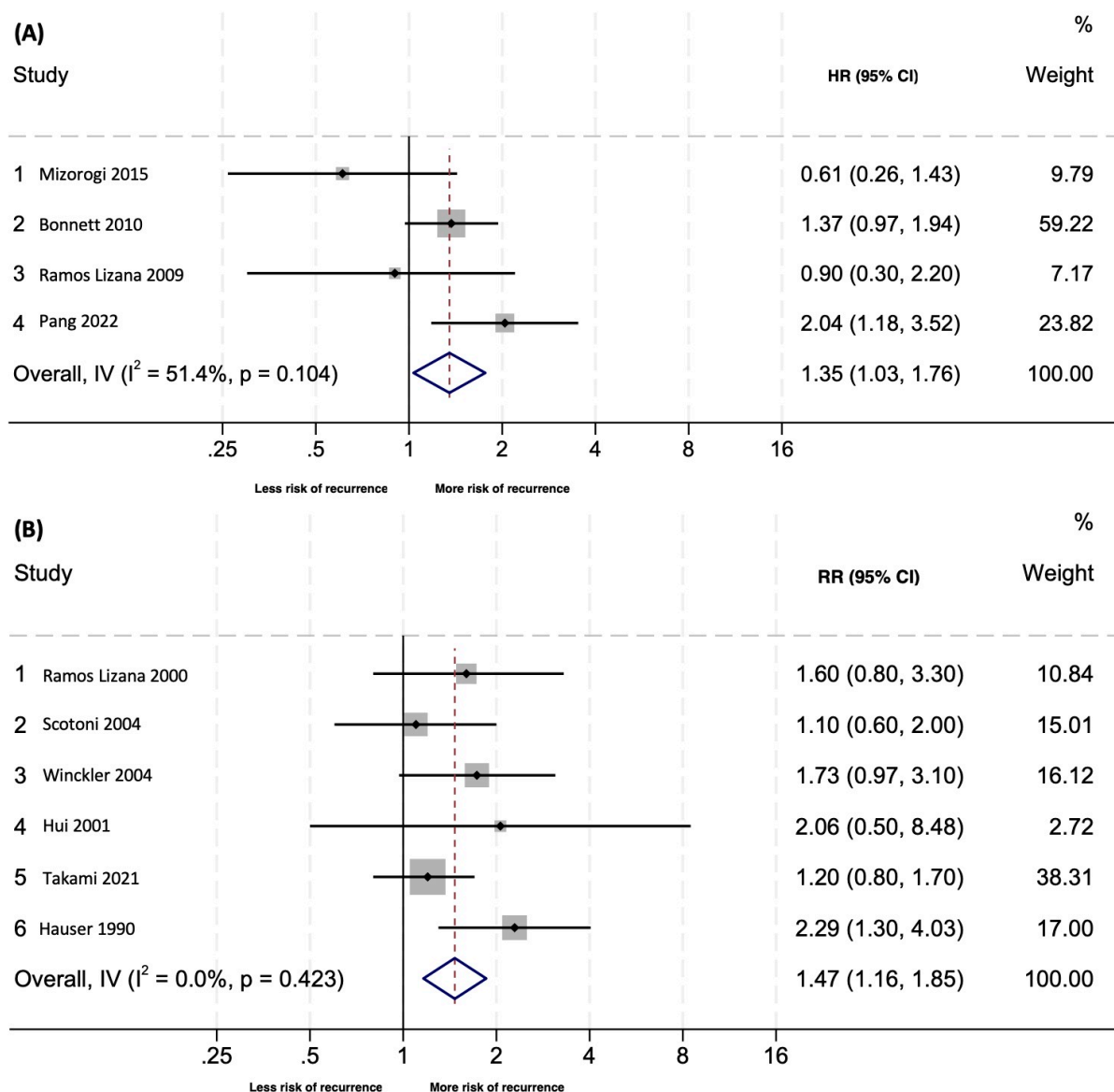
$\tau^2 = 0.1017\%$; 4 studies, 1012 participants; low-certainty evidence; [Figure 8](#)). Six studies (1290 participants) provided RR data (RR 1.47, 95% CI 1.16 to 1.85; PI 1.16 to 1.86; $P = 0.423$, $I^2 = 0\%$, $\tau^2 = 0.0\%$; 6 studies, 1290 participants; low-certainty evidence; [Figure 8](#)). A family history of epilepsy may be associated with a higher risk of seizure recurrence, but the evidence is limited.

Figure 8. (A) Forest plot of hazard ratio (HR) of family history of epilepsy as a prognostic factor for seizure recurrence.

(B) Forest plot of risk ratio (RR) of family history of epilepsy as a prognostic factor for seizure recurrence.

Figure generated using STATA version 18 based on meta-analysis results.

The reported P value refers to heterogeneity between studies, not the significance of the pooled effect estimate.



Male sex

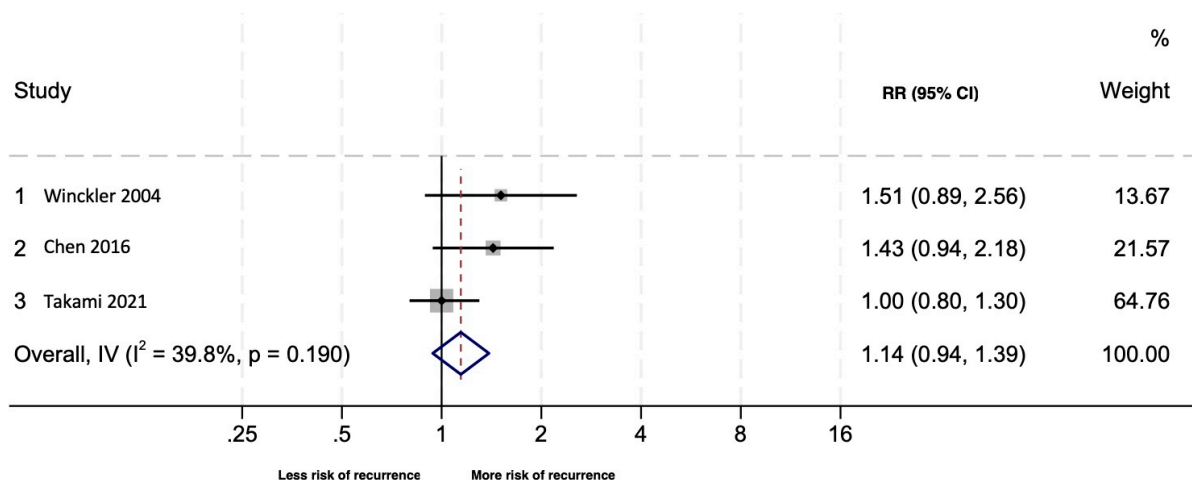
Three studies (738 participants) provided RR data (RR 1.14, 95% CI 0.94 to 1.39; PI 0.83 to 1.56; $P = 0.190$, $I^2 = 39.8\%$, $\tau^2 = 0.0255\%$;

3 studies, 738 participants; very low-certainty evidence; [Figure 9](#)). The evidence is very uncertain about whether male sex influences seizure recurrence.

Figure 9. Forest plot of risk ratio (RR) of male sex as a prognostic factor for seizure recurrence.

Figure generated using STATA version 18 based on meta-analysis results.

The reported P value refers to heterogeneity between studies, not the significance of the pooled effect estimate.

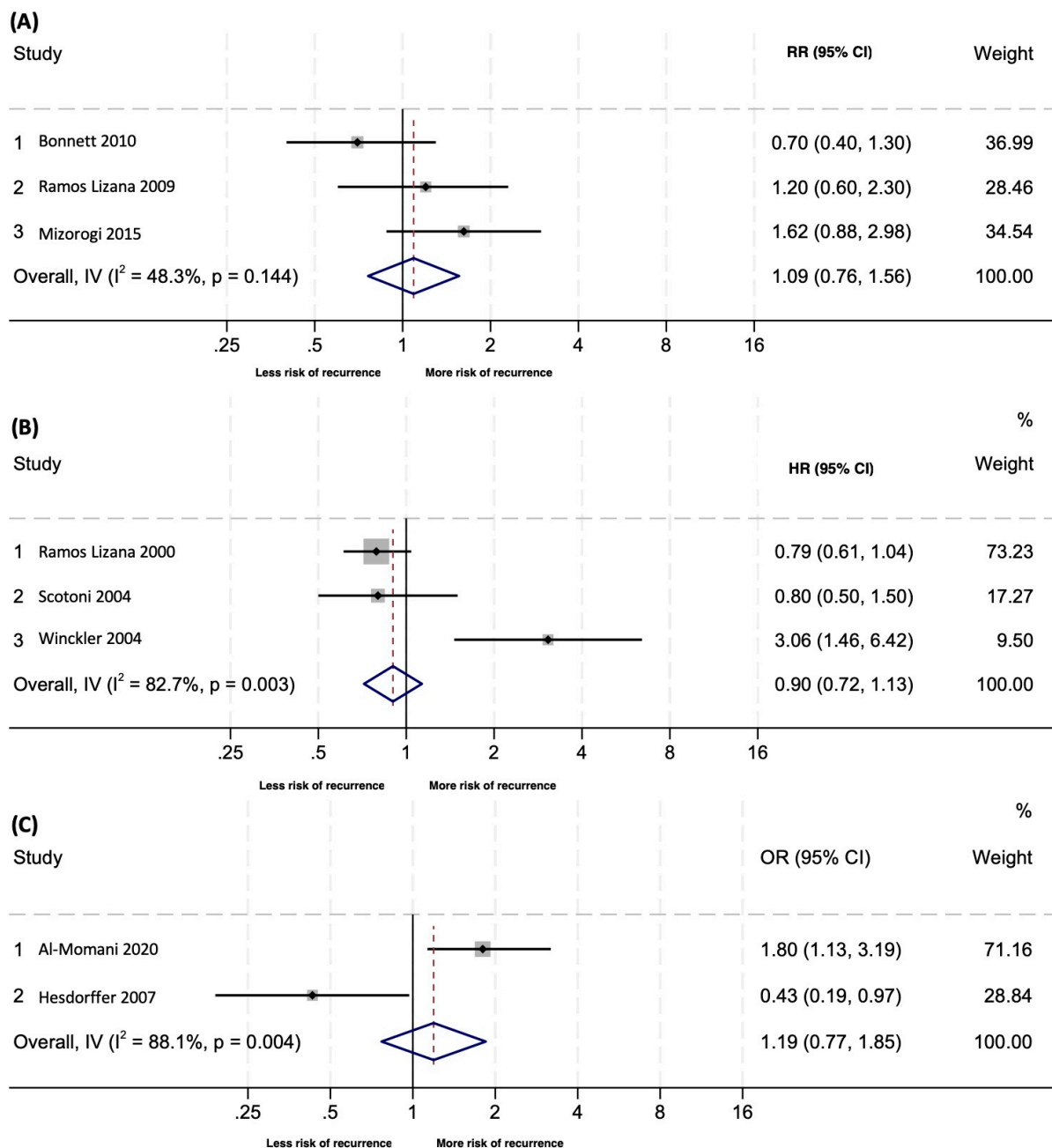


Focal seizures

Eight studies (1701 participants) reported usable data on the association between focal seizures and seizure recurrence.

- Two studies (473 participants) provided OR data (OR 1.19, 95% CI 0.77 to 1.85; PI 0.18 to 8.07; $P = 0.004$, $I^2 = 88.1\%$, $\tau^2 = 0.9034\%$; 2 studies, 473 participants; very low-certainty evidence; [Figure 10](#)).
- Three studies (773 participants) provided HR data (HR 0.90, 95% CI 0.72 to 1.13; PI 0.30 to 2.72; $P = 0.003$, $I^2 = 82.7\%$, $\tau^2 = 0.3060\%$; 3 studies, 773 participants; very low-certainty evidence; [Figure 10](#)).
- Three studies (455 participants) provided RR data (RR 1.09, 95% CI 0.76 to 1.56; PI 0.54 to 2.20; $P = 0.144$, $I^2 = 48.3\%$, $\tau^2 = 0.0943\%$; 3 studies, 455 participants; very low-certainty evidence; [Figure 10](#)).

Figure 10. (A) Forest plot of risk ratio (RR) of focal seizures as a prognostic factor for seizure recurrence. (B) Forest plot of hazard ratio (HR) of focal seizures as a prognostic factor for seizure recurrence. (C) Forest plot of odds ratio (OR) of focal seizures as a prognostic factor for seizure recurrence. Figure generated using STATA version 18 based on meta-analysis results. The reported P value refers to heterogeneity between studies, not the significance of the pooled effect estimate.



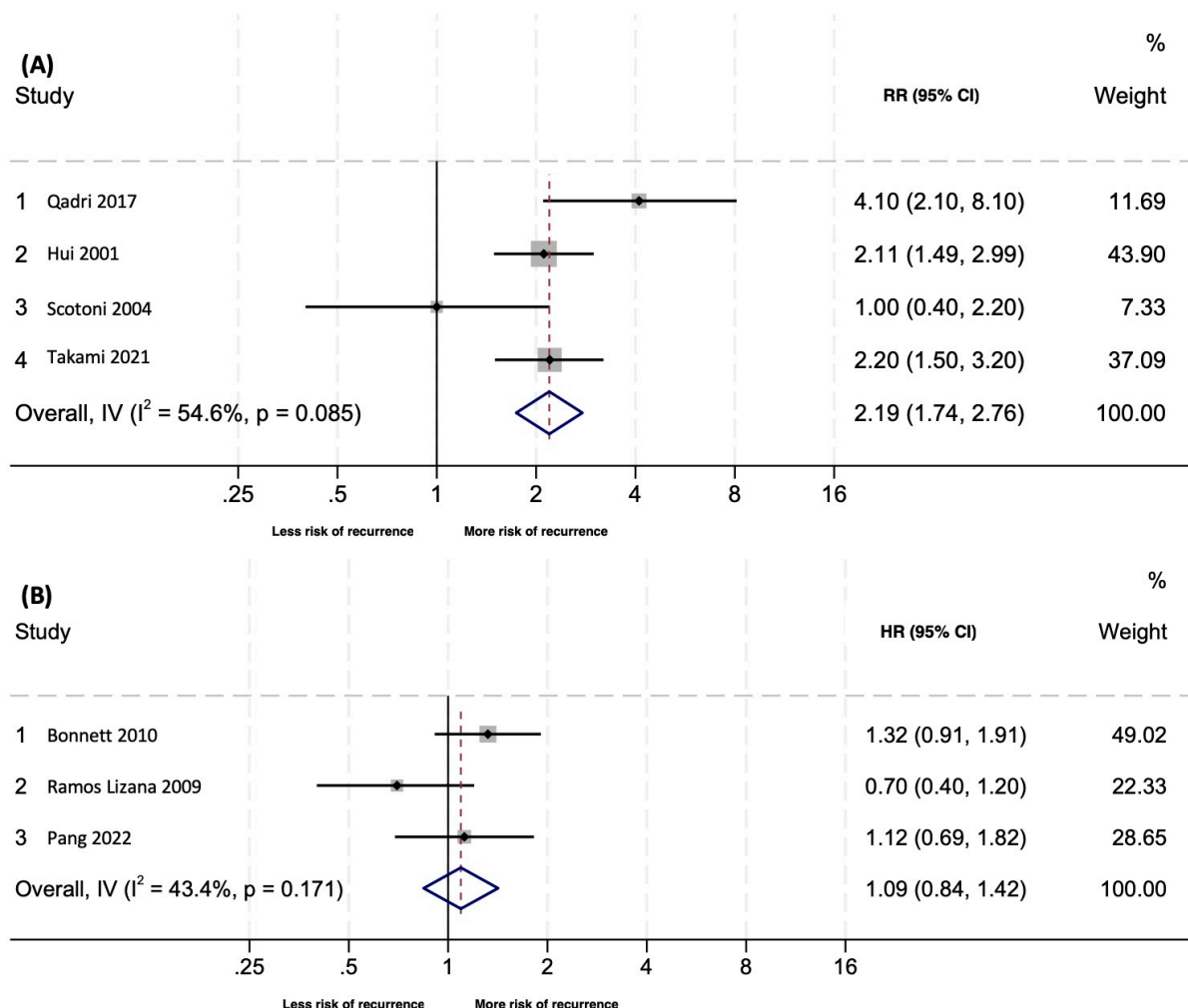
The evidence is very uncertain about whether focal seizures are associated with seizure recurrence.

Abnormal imaging

Seven studies (1769 participants) reported usable data on the association between abnormal imaging and seizure recurrence.

- Three studies (939 participants) provided HR data (HR 1.09, 95% CI 0.84 to 1.42; PI 0.67 to 1.77; $P = 0.171$, $I^2 = 43.4\%$, $\tau^2 = 0.0428\%$; 3 studies, 939 participants; low-certainty evidence; [Figure 11](#)).
- Four studies (890 participants) provided RR data (RR 2.19, 95% CI 1.74 to 2.76; PI 1.21 to 3.95; $P = 0.085$, $I^2 = 54.6\%$, $\tau^2 = 0.0769\%$; 4 studies, 890 participants; low-certainty evidence; [Figure 11](#)).

Figure 11. (A) Forest plot of risk ratio (RR) of abnormal brain imaging as a prognostic factor for seizure recurrence. (B) Forest plot of hazard ratio (HR) of abnormal brain imaging as a prognostic factor for seizure recurrence. Figure generated using STATA version 18 based on meta-analysis results. The reported P value refers to heterogeneity between studies, not the significance of the pooled effect estimate.



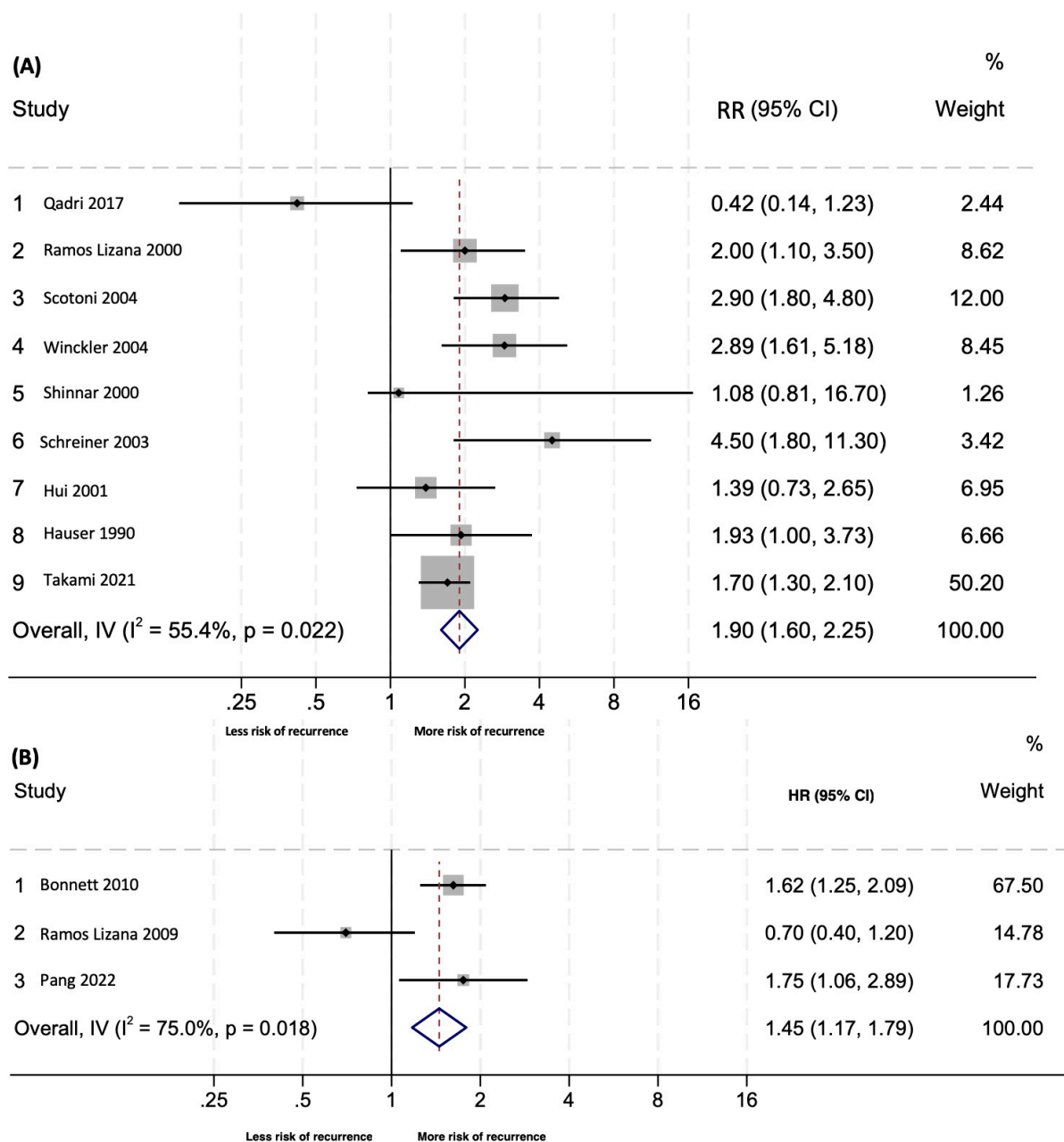
Abnormal imaging may be associated with an increased risk of seizure recurrence, but the certainty of the evidence is low.

Abnormal EEG

Twelve studies (2843 participants) reported usable data on the association between abnormal EEG and seizure recurrence.

- Nine studies (1904 participants) provided RR data (RR 1.90, 95% CI 1.60 to 2.25; PI 0.98 to 3.67; $P = 0.022$, $I^2 = 55.4\%$, $\tau^2 = 0.1054\%$; 9 studies, 1904 participants; moderate-certainty evidence; [Figure 12](#)).
- Three studies (939 participants) provided HR data (HR 1.45, 95% CI 1.17 to 1.79; PI 0.67 to 3.13; $P = 0.018$, $I^2 = 75\%$, $\tau^2 = 0.1419\%$; 3 studies, 939 participants; low-certainty evidence; [Figure 12](#)).

Figure 12. (A) Forest plot of risk ratio (RR) of abnormal EEG as a prognostic factor for seizure recurrence. (B) Forest plot of hazard ratio (HR) of abnormal EEG as a prognostic factor for seizure recurrence. Figure generated using STATA version 18 based on meta-analysis results. The reported P value refers to heterogeneity between studies, not the significance of the pooled effect estimate.



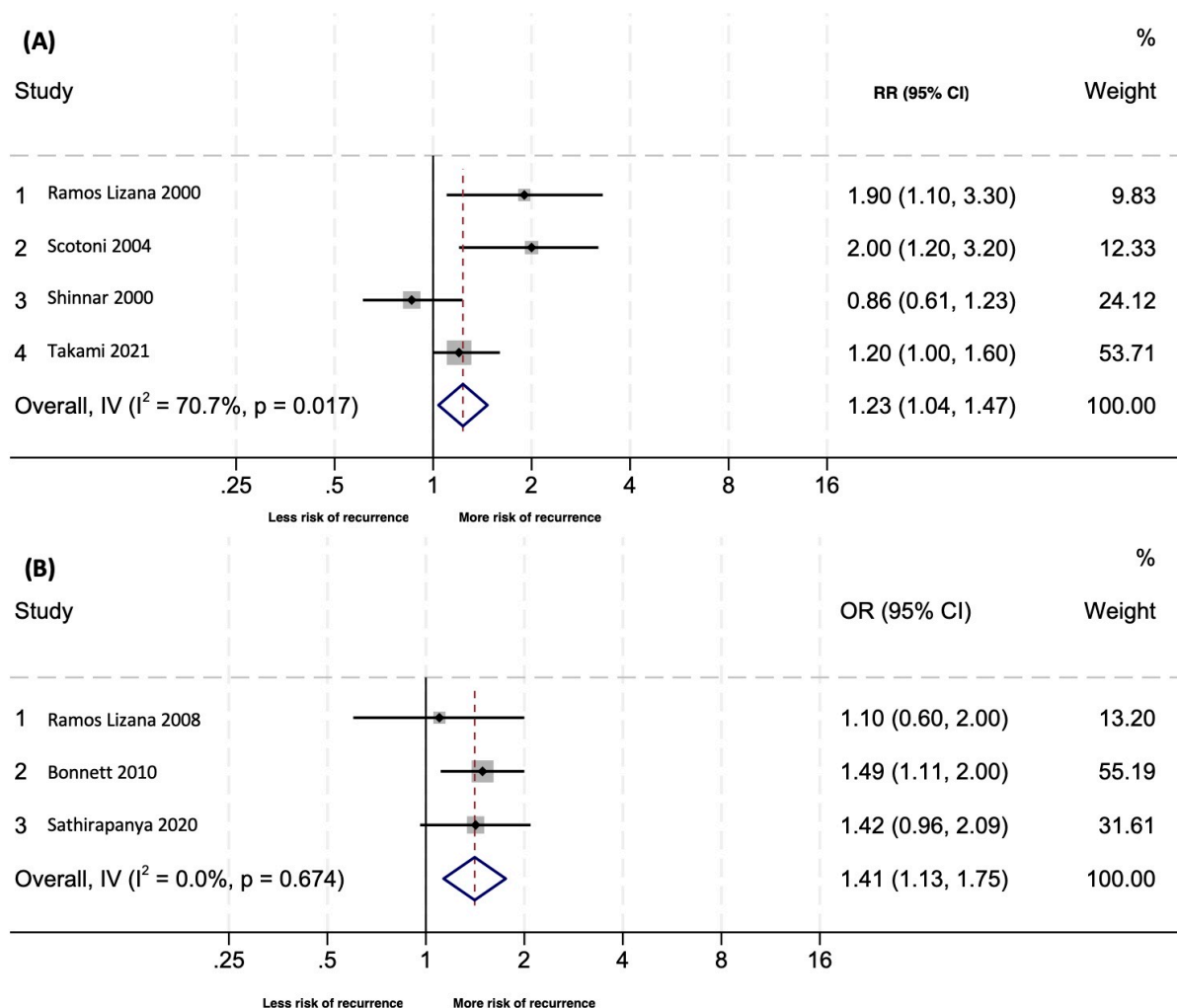
Abnormal EEG findings probably increase the risk of seizure recurrence (RR, moderate-certainty evidence). Time-to-event data (HR) support this association, but the evidence is less certain due to inconsistency and imprecision.

Nocturnal seizures

Seven studies (2215 participants) reported usable data on the association between nocturnal seizures and seizure recurrence.

- Three studies (967 participants) provided HR data (HR 1.41, 95% CI 1.13 to 1.75; PI 1.13 to 1.75; $P = 0.674$, $I^2 = 0\%$, $\tau^2 = 0.0\%$; 3 studies, 967 participants; low-certainty evidence; [Figure 13](#)).
- Four studies (1248 participants) provided RR data (RR 1.23, 95% CI 1.04 to 1.47; PI 0.67 to 2.26; $P = 0.017$, $I^2 = 70.7\%$, $\tau^2 = 0.0888\%$; 4 studies, 1248 participants; low-certainty evidence; [Figure 13](#)).

Figure 13. (A) Forest plot of risk ratio (RR) of nocturnal seizures as a prognostic factor for seizure recurrence. (B) Forest plot of odds ratio (OR) of nocturnal seizures as a prognostic factor for seizure recurrence. Figure generated using STATA version 18 based on meta-analysis results. The reported P value refers to heterogeneity between studies, not the significance of the pooled effect estimate.



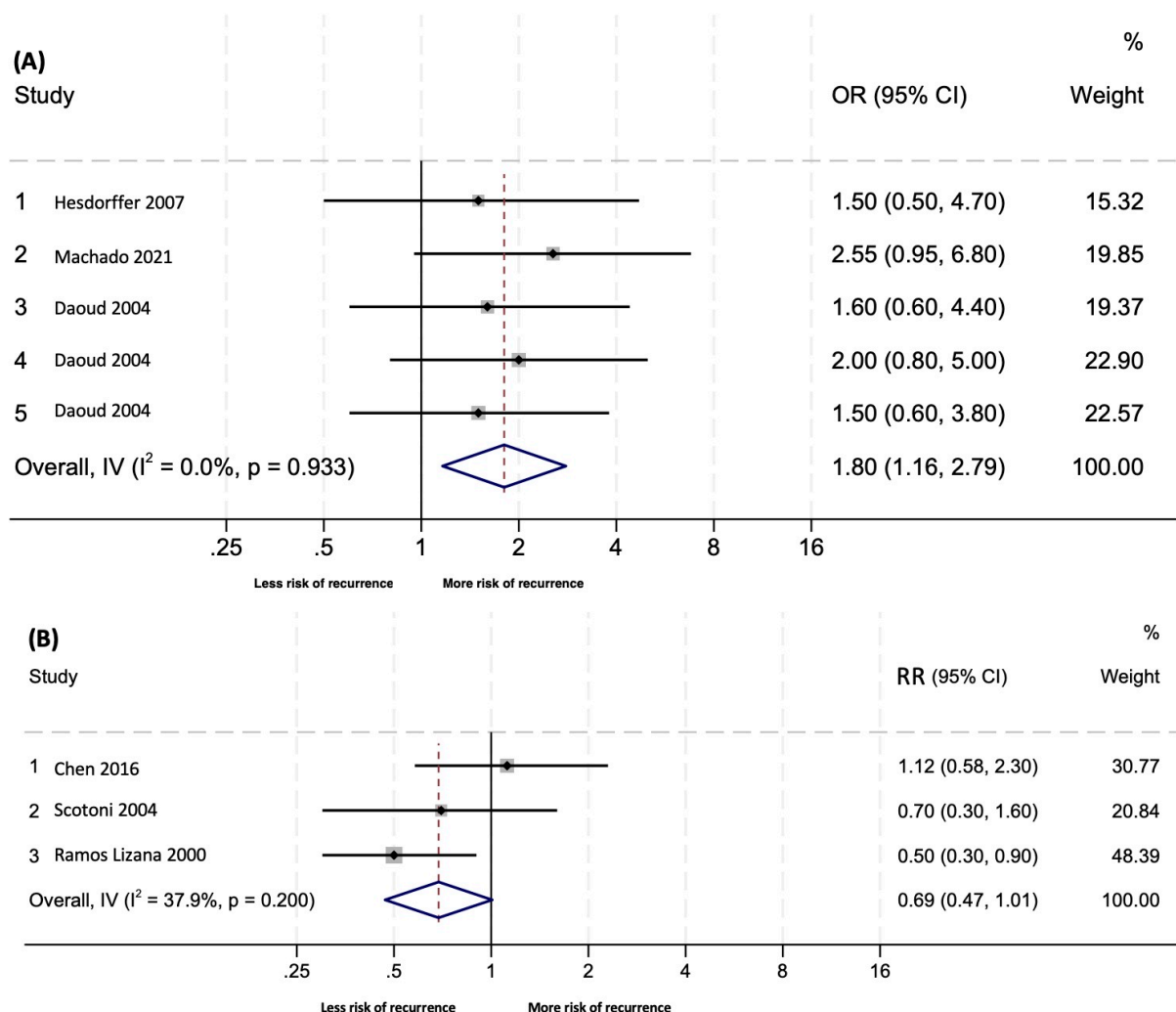
Nocturnal seizures may increase the risk of seizure recurrence, but the certainty of the evidence is low.

Age under 16 years

Eight cohorts from six studies (1002 participants) provided usable data on the association between age under 16 years and seizure recurrence.

- Five cohorts from three studies (522 participants) provided OR data (OR 1.80, 95% CI 1.16 to 2.79; PI 1.16 to 2.79; $I^2 = 0.0\%$, $\tau^2 = 0.0\%$; 5 cohorts, 522 participants; low-certainty evidence; [Figure 14](#)).
- Three studies (480 participants) provided RR data (RR 0.69, 95% CI 0.47 to 1.01; PI 0.36 to 1.33; $I^2 = 37.9\%$, $\tau^2 = 0.0739\%$; 3 studies, 480 participants; very low-certainty evidence; [Figure 14](#)).

Figure 14. (A) Forest plot of odds ratio (OR) of age < 16 as a prognostic factor for seizure recurrence. (B) Forest plot of risk ratio (RR) of age < 16 as a prognostic factor for seizure recurrence. Figure generated using STATA version 18 based on meta-analysis results. The reported P value refers to heterogeneity between studies, not the significance of the pooled effect estimate.



The evidence is uncertain (low certainty) based on odds ratio (OR) analysis, and very uncertain (very low certainty) based on risk ratio (RR) analysis, about whether being under 16 years of age influences the risk of seizure recurrence after a first unprovoked seizure. The differences in certainty reflect imprecision and inconsistency across analyses, as well as the direction and strength of association varying, depending on the statistical measure used.

DISCUSSION

Summary of main results

As highlighted in our previous systematic review (Neligan 2023), significant clinical uncertainty remains in predicting recurrence following a first unprovoked seizure. Whilst that review focused on providing clinicians and individuals with recurrence rates at specific time points, the purpose of this review was to utilise routinely collected clinical prognostic factors and demographic data to enable refined prognostication regarding seizure recurrence. We included 23 studies, all contributing data

suitable for meta-analyses. Despite methodological and clinical heterogeneity, meaningful synthesis was achievable.

Abnormal electroencephalogram (EEG) findings probably increase the risk of seizure recurrence (moderate-certainty evidence). Other prognostic factors – including focal neurological deficit, Todd's paresis, status epilepticus, family history of epilepsy, male sex, focal onset seizures, nocturnal seizures, abnormal imaging, febrile seizures, and age under 16 – had low- or very low-certainty evidence. These factors may be associated with seizure recurrence, but the evidence is uncertain due to wide confidence intervals and inconsistent results. Age showed conflicting associations depending on the statistical measure used (risk ratio (RR) or odds ratio (OR)), adding further uncertainty.

Summary of findings 1 provides detailed effect sizes and certainty assessments. Abnormal EEG was the strongest predictor identified, though uncertainty remains regarding other factors. These findings should therefore be interpreted cautiously, with EEG considered

the primary method of assessment, supplemented by additional clinical information.

Comparison with other studies or reviews

Despite clinical importance, few large-scale, well-designed studies have examined seizure recurrence prognostic factors. The MRC Multicentre trial for Early epilepsy and Single Seizures (MESS) developed a prognostic model subsequently externally validated, yet it lacked the detailed granularity necessary for modern personalised clinical care (Bonnnett 2022; Kim 2006). Generally, prior research has focused on epilepsy diagnosis and surgery outcomes, as well as narrative reviews (Berg 1991; Rizvi 2017). The recent evidence review by the National Institute for Health and Care Excellence (NICE) reinforced the critical need for robust prognostic tool development and validation (NICE 2022).

Certainty of evidence available

The certainty of evidence was generally low or very low, except for abnormal EEG (moderate certainty). Whilst risks of bias and publication bias were minimal, we substantially downgraded the evidence for most factors analysed due to inconsistency, indirectness, imprecision, and limited event numbers.

Limitations of the review process

We followed a systematic approach with well-defined inclusion criteria and used the QUIPS tool specifically tailored for prognostic studies (Hayden 2013; Appendix 6). Significant heterogeneity amongst the included studies limited data pooling. Studies used varied statistical analyses and inconsistent effect measures (HRs, ORs, RRs), significantly constraining meta-analytic possibilities. We contacted authors for univariable data, but responses were limited, necessitating the exclusion of studies from pooled analyses.

Heterogeneity of outcome reporting (HR, OR, RR) influenced meta-analysis results, notably for age under 16. Limited study numbers prevented conclusive explanations regarding discrepancies arising from either heterogeneity or statistical approaches. Further restriction to a single statistical measure would have severely reduced the available evidence.

Overall completeness and applicability of evidence

Although several important prognostic factors were identified, notable gaps remain. Limited granularity prevented detailed categorisation of EEG abnormalities (e.g. focal spikes, generalised spike-wave discharges) and specific epileptogenic brain lesions (e.g. mesial temporal sclerosis, focal cortical dysplasia). Our reliance on study authors' definitions of first unprovoked seizures and acute symptomatic seizures introduced uncertainties (Beghi 2010). More stringent verification would severely restrict available data, emphasising the urgent need for standardised definitions and outcome measures, supported by initiatives such as Mitchell and colleagues' epilepsy core outcome set development (Mitchell 2022). Furthermore, included studies, predominantly from high-income countries and hospital settings, limit global generalisability and primary care applicability. Addressing these gaps requires prospective, community-based studies with standardised methodology and reporting.

Several prognostic factors that we initially identified in our protocol as being of clinical interest were ultimately not included in

meta-analyses due to a lack of suitable data (Adan 2021). These included specific genetic abnormalities (e.g. SCN1A mutations), comorbidities such as learning disabilities, well-defined clinical subgroups such as individuals with traumatic brain injury or neurodegenerative disorders, and the impact of initiating anti-seizure medications following a first seizure. The absence of consistently reported or comparable data on these factors across the included studies limited our ability to assess their prognostic value. This highlights a substantial gap in the current evidence base and underscores the need for future primary studies to collect and report data on a wider range of clinically relevant prognostic factors in a consistent and standardised manner.

Quantitative synthesis debate and impact of anti-seizure medications

We recognise the substantial methodological and clinical heterogeneity in the included studies, notably the combination of retrospective and prospective designs, variable anti-seizure medication (ASM) initiation practices, and inconsistent reporting. Despite this, quantitative synthesis provided pragmatic estimates relevant to real-world clinical practice. Including studies with participants prescribed ASMs reflected clinical realities, though potentially attenuating apparent impacts of prognostic factors like status epilepticus. Clearer reporting of ASM initiation in future studies would improve analytical clarity.

Subgroup analyses based on ASM treatment were precluded due to insufficient and inconsistent reporting of treatment details and outcomes. Future studies should consistently report ASM initiation to allow meaningful subgroup analyses, enhancing prognostic clarity.

Collinearity amongst prognostic factors

Potential collinearity, particularly between focal neurological deficits and abnormal imaging, may have influenced predictor effects, inflating or masking true associations. Our aggregate data level limited collinearity assessment, highlighting the necessity for future individual patient-level data studies. Clinicians interpreting these results should consider possible prognostic factor interdependencies in clinical decision-making.

AUTHORS' CONCLUSIONS

Implications for practice

Stratifying individuals according to their risk of seizure recurrence after a first unprovoked seizure remains a challenge in clinical practice, but is important for counselling patients and families about recurrence risk. Accurate stratification can influence key decisions regarding driving, employment, education, and the initiation of treatment for epilepsy. The International League Against Epilepsy's (ILAE) operational definition of epilepsy – allowing diagnosis after a single seizure if recurrence risk is sufficiently high – underlines the need for reliable prognostic information (Fisher 2014).

Current evidence suggests that electroencephalogram (EEG) may be the most consistently predictive factor and may therefore play a central role in informing risk discussions. Other factors identified, such as abnormal brain imaging or seizure occurrence during sleep, may also contribute to clinical decision-making when considered alongside the broader clinical picture.

Given the limitations and uncertainties in the evidence base, caution may be warranted in placing substantial weight on prognostic factors beyond EEG findings. These factors are likely best interpreted in the context of individual patient characteristics rather than used to guide generalised predictions.

Improved risk stratification may also support the identification of high-risk groups for inclusion in future trials of disease-modifying therapies, with the potential to influence the long-term course of epilepsy.

Implications for research

There is a clear need for high-quality, prospective research studies that systematically and consistently report prognostic factors following a first unprovoked seizure. Current deficiencies and heterogeneity in evidence, particularly in defining and measuring prognostic factors, have limited the ability to perform comprehensive data synthesis and develop validated prognostic models.

Future research should prioritise the establishment of a core set of prognostic factors that are clearly defined, consistently measured, and routinely reported across studies. The emerging international core outcome set for seizure-related studies represents an important step towards this goal and will enable future systematic reviews and meta-analyses to perform more meaningful pooled analyses (Mitchell 2022; Mitchell 2024).

Additionally, research should explore and validate new biomarkers for epilepsy and seizure recurrence, including blood, EEG, and imaging biomarkers (Adan 2022; Eriksson 2021; Klotz 2021). Prospective studies designed for multivariable analyses would

provide a robust framework for evaluating the predictive value of these biomarkers alongside established prognostic factors.

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- Sign-off Editor (final editorial decision): Francesco Brigo, Innovation, Research and Teaching Service (SABES-ASDAA), Teaching Hospital of the Paracelsus Medical Private University, Bolzano, Italy;
- Managing Editors (selected peer reviewers, provided editorial guidance to authors, edited the article): Luisa Fernandez Mauleffinch and Gail Quinn, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Jessenia Hernandez, Cochrane Central Editorial Service;
- Copy Editor (copy editing and production): Faith Armitage, Cochrane Central Production Service;
- Peer-reviewers (provided comments and recommended an editorial decision): Clare Miles, Cochrane Evidence Production and Methods Directorate (methods review); Johanna AA Damen, Cochrane Netherlands (methods review); Lucas Lozano-García, Epilepsy Surgery Group - Instituto Neurológico de Colombia, Medellín, Colombia (clinical/content review); Phil Käding, Certified Expert in Drug Development and GMP-based production (consumer review); and Jo Platt, Central Editorial Information Specialist (search review). One additional reviewer provided clinical/content review but chose not to be publicly acknowledged.

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CHARACTERISTICS OF STUDIES**Characteristics of included studies** [ordered by study ID]**Al-Momani 2020****Study characteristics**

Notes	Jordanian retrospective cohort study Paediatric study: 1 month to 16 years Excluded: previous febrile seizures, absences, myoclonus 290 participants 5-year follow-up 57.9% male sex Funding: no funding information stated
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Item	Authors' judgement	Support for judgement
Study participation	Unclear	Retrospective case review
Study attrition	No	Retrospective study, missing data and incomplete data regarding investigations
Prognostic factor measurement	No	Mixed modalities of prognostic factors (imaging - uses CT, MRI and US)
Outcome measurement	Unclear	Incomplete follow-up data

Al-Momani 2020 (Continued)

Adjustment for other prognostic factors	Yes	Univariable and multivariable analysis conducted
Statistical analysis and reporting	Yes	Appropriate statistical methods applied, including modelling of data
Overall risk of bias	Unclear	Moderate

Baldin 2017

Study characteristics

Notes	USA prospective cohort study Adult cohort No mention of ASMs or seizure types 52 participants 2-year follow-up 53.9% male sex Funding: study funded by the Epilepsy Society of Australia
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Item	Authors' judgement	Support for judgement
Study participation	No	Ascertainment methods different for each recruiting site. Poor response rate from those who agreed to take part
Study attrition	Yes	No dropouts reported in the study
Prognostic factor measurement	Unclear	No prognostic factors of seizure recurrence reported
Outcome measurement	Yes	Outcomes are well-defined
Adjustment for other prognostic factors	Yes	Multiple adjustments made for varying factors
Statistical analysis and reporting	Yes	Reasonable statistical methodology applied to data
Overall risk of bias	Unclear	Moderate

Bell 2016

Study characteristics

Notes	British prospective cohort All age cohort 302 participants but missing data in 22 participants (324-22) 23.6 years of follow-up 46% male sex Funding: no specific funding declared. Authors state no financial support was received for this study
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Bell 2016 (Continued)

Item	Authors' judgement	Support for judgement
Study participation	Yes	Prospective well-characterised participants for all categories
Study attrition	Unclear	High dropout rate but prolonged follow-up period mitigates this
Prognostic factor measurement	Yes	Multiple variables measured
Outcome measurement	Yes	Clear definition of outcome and measurement
Adjustment for other prognostic factors	Yes	Multiple adjustments
Statistical analysis and reporting	Yes	Appropriate analysis applied to the data
Overall risk of bias	Yes	Low

Bonnett 2010

Study characteristics

Notes	British multicentre RCT Paediatric and adult ASM given and recurrence reported separately 1443 participants 18 months follow-up 63% male sex Funding: funded by the National Institute for Health Research (NIHR), Health Technology Assessment (HTA) Programme
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Item	Authors' judgement	Support for judgement
Study participation	Unclear	Only patients where there was equipose re: starting treatment were included
Study attrition	Unclear	Sizable proportion refused randomisation and another number were lost to follow-up
Prognostic factor measurement	Yes	Multiple risk factors measured
Outcome measurement	Yes	Very clear outcome measurement
Adjustment for other prognostic factors	Yes	Multiple adjustments made
Statistical analysis and reporting	Yes	Excellent stats reporting
Overall risk of bias	Yes	Low

Prognostic factors predicting an unprovoked seizure recurrence in children and adults following a first unprovoked seizure (Review)

Chen 2016

Study characteristics

Notes	Chinese prospective cohort study Ages of participant: 3 to 77 years No ASMs Excluded: absences, myoclonus and unspecified seizures SE included 134 participants 24-month follow-up 66% male sex Funding: this study was supported by grants from the National Science Council (NSC 99-2314-B-038-017-MY3) and Taipei Medical University (TMU100-AE1-B07)
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Item	Authors' judgement	Support for judgement
Study participation	Yes	Representative sample, consecutive patients, single centre but very clear inclusion criteria
Study attrition	Unclear	Difficult to ascertain patients lost to follow-up from description
Prognostic factor measurement	Yes	Very well-defined and well-documented
Outcome measurement	Yes	Very clear outcomes
Adjustment for other prognostic factors	Unclear	Unclear if controlled for variables that could affect outcomes
Statistical analysis and reporting	Yes	Appropriate analysis performed
Overall risk of bias	Yes	Low

Daoud 2004

Study characteristics

Notes	Jordanian prospective cohort study Paediatric cohort: 3 months to 14 years No ASMs Excluded: absences, myoclonus and infantile spasms SE included 265 participants 3-year follow-up 56.6% male sex Funding: not reported in the manuscript
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Item	Authors' judgement	Support for judgement
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Daoud 2004 (Continued)

Study participation	Yes	Consecutive patients from large teaching hospitals, representative of wider population
Study attrition	Unclear	Unclear re: dropout rates
Prognostic factor measurement	No	All patients did not have uniform investigations, e.g. EEG and brain imaging, due to cost limitations
Outcome measurement	Yes	Detailed reporting of recurrence at several time points that are well described
Adjustment for other prognostic factors	No	No adjustments undertaken
Statistical analysis and reporting	No	Univariable analysis only; no multivariable analysis performed
Overall risk of bias	No	High

Hauser 1990
Study characteristics

Notes	USA prospective cohort All ages included ASMs given (80%) Focal and generalised seizures included SE included 208 participants 22-month follow-up No mention of gender Funding: supported in part by grant NS 12592 from the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), National Institutes of Health
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Item	Authors' judgement	Support for judgement
Study participation	No	Very narrow inclusion criteria - recruitment had to be within 24 hours
Study attrition	Yes	20 participants out of 208 withdrew from the study
Prognostic factor measurement	Yes	Well described
Outcome measurement	Yes	Well represented
Adjustment for other prognostic factors	Unclear	Some attempt to adjust made
Statistical analysis and reporting	Yes	Appropriate methods used
Overall risk of bias	Unclear	Moderate

Hesdorffer 2007

Study characteristics

Notes	<p>USA retrospective registry. Case-control study</p> <p>All ages included</p> <p>Acute vs unprovoked seizures in stroke, TBI and CNS infections. Stroke (101); TBI (37); CNS infection (10). All seizures including focal aware seizures are included. Only first seizure included if associated with CVA, TBI or CNS infections</p> <p>SE (25.7%) included</p> <p>148 participants</p> <p>10-year follow-up</p> <p>No proportional data on gender provided</p> <p>Funding: supported by grant NS 31146 from the National Institute of Neurological Disorders and Stroke (NINDS)</p>
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Item	Authors' judgement	Support for judgement
Study participation	Yes	Representative of wider population
Study attrition	Unclear	Case-control database study
Prognostic factor measurement	Yes	The study clearly defines a range of prognostic factors, applies them consistently, and uses them appropriately in both univariate and multivariate analyses
Outcome measurement	Yes	Well-described and defined outcomes with time points clearly set out
Adjustment for other prognostic factors	Yes	Multiple adjustments made
Statistical analysis and reporting	Yes	Well-described and represented
Overall risk of bias	Yes	Low

Hui 2001

Study characteristics

Notes	<p>Chinese retrospective cohort study. Single centre</p> <p>Age: > 14 years</p> <p>GTCS only</p> <p>No ASMs</p> <p>Excluded: absences, myoclonus, infantile spasms</p> <p>SE excluded</p> <p>132 participants</p> <p>27.2 months of follow-up</p> <p>50% male sex</p> <p>Funding: not reported</p>
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Item	Authors' judgement	Support for judgement
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Hui 2001 (Continued)

Study participation	No	Multiple exclusion criteria makes it a non-representative cohort
Study attrition	Unclear	Retrospective, so attrition is unclear
Prognostic factor measurement	Yes	Multiple prognostic factors
Outcome measurement	Unclear	Seizure recurrence until four years
Adjustment for other prognostic factors	Unclear	Some adjustment undertaken
Statistical analysis and reporting	Yes	Appropriate stats - univariable and multivariable, survival curves included
Overall risk of bias	Unclear	Moderate

Kanemura 2015
Study characteristics

Notes	<p>Japanese prospective cohort</p> <p>Single-centre study</p> <p>Paediatric cohort: 1 month to 15 years</p> <p>No ASMs</p> <p>87 participants</p> <p>41% male</p> <p>Minimum 4-year follow-up</p> <p>Eligibility: included individuals with a first unprovoked seizure, including those with prior febrile, neonatal, or post-traumatic seizures</p> <p>Excluded: ambiguous events, acute symptomatic seizures (e.g. with encephalopathy or febrile illness), and cases with structural or progressive brain pathology on MRI as well as SE</p> <p>Funding: not reported</p>
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Item	Authors' judgement	Support for judgement
Study participation	Unclear	Retrospective study, unclear how selection occurred
Study attrition	Yes	Nine children who met the criteria did not have follow-up data
Prognostic factor measurement	Yes	Extensive prognostic factors are described in the paper
Outcome measurement	Unclear	Seizure recurrence at four years given
Adjustment for other prognostic factors	No	No adjustments
Statistical analysis and reporting	Unclear	No survival curves
Overall risk of bias	Unclear	Moderate

Machado 2021

Study characteristics

Notes	Brazilian retrospective cohort Paediatric cohort: 1 month to 14 years ASMs given No specific mention of SE but no cases recorded Included: focal and generalised seizures 74 participants 32.5 months follow-up 55% male sex Funding: no funding statement found in the article
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Item	Authors' judgement	Support for judgement
Study participation	Unclear	Retrospective study
Study attrition	Unclear	No clearly reported dropout rates
Prognostic factor measurement	Yes	High number of prognostic factors collected and presented
Outcome measurement	Unclear	Recurrence rates presented, but not very clearly defined with time points
Adjustment for other prognostic factors	Unclear	Unclear if adjustments were undertaken
Statistical analysis and reporting	No	No univariable or multivariable modelling undertaken and no survival curves presented
Overall risk of bias	Unclear	Moderate

Mahler 2015

Study characteristics

Notes	Retrospective registry study of first unprovoked seizure in Northern Stockholm, Sweden No ASMs All ages Excluded: seizures occurring < 7 days after a TBI were defined as acute symptomatic and not included, unless followed by at least 1 unprovoked seizure > 7 days after the TBI 1885 cases 55% male sex 6 months of follow-up Funding: supported by a grant from the "Friends of the Tel-Aviv Medical Center" (non-commercial funding source)
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Item	Authors' judgement	Support for judgement
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Mahler 2015 (Continued)

Study participation	No	Clearly defined retrospective study, some conflation of single seizure and multiple seizure presentations
Study attrition	Unclear	N/A - retrospective registry study
Prognostic factor measurement	No	Mostly focussed on a single prognostic factor - TBI, only some mention of other factors
Outcome measurement	Unclear	Appropriately defined outcomes and end points for the study but within a very narrow spectrum of TBI
Adjustment for other prognostic factors	Unclear	Some sensitivity checks for possible confounding factors
Statistical analysis and reporting	Unclear	Appropriate statistical reporting with risk ratios stated clearly from univariable statistics but no multivariable model used in the paper
Overall risk of bias	No	High

Mizorogi 2015
Study characteristics

Notes	<p>Japanese prospective cohort</p> <p>Paediatric cohort</p> <p>No ASMs</p> <p>Excluded: absence, myoclonus seizures</p> <p>Focal and generalised seizures included</p> <p>SE excluded</p> <p>73 participants</p> <p>4.6 years of follow-up</p> <p>45% male sex</p> <p>Funding: no funding statement found in the article</p>
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Item	Authors' judgement	Support for judgement
Study participation	Unclear	Clear criteria but some patients excluded e.g. for having organic brain lesions which may not be epileptogenic; also SE excluded
Study attrition	Yes	Less than 10% without follow-up data
Prognostic factor measurement	Unclear	Basic list of factors included
Outcome measurement	Yes	Well documented at various time points
Adjustment for other prognostic factors	Unclear	Unclear if adjustments have been made
Statistical analysis and reporting	Yes	Good and appropriate

Mizorogi 2015 (Continued)

Overall risk of bias	Unclear	Basic list of prognostic factors included. However, it is unclear whether all relevant confounders were measured or appropriately adjusted for in the analysis, and limited detail is provided on the rationale for factor selection.
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Pang 2022
Study characteristics

Notes	Prospective observational study of 239 adults in Australia who had a first unprovoked seizure from sleep only between 2000 and 2011. Patients were reviewed at clinic 3 to 9 months after the index seizure. If there were ongoing seizures, patients were followed up in the epilepsy clinic. If there were no further seizures, patients were discharged and contacted by phone every 1 to 2 years until seizure recurrence or death. ASM given 61% male sex Funding: no funding information provided
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Item	Authors' judgement	Support for judgement
Study participation	No	Only sleep onset unprovoked seizure
Study attrition	Unclear	No mention of study dropout rates
Prognostic factor measurement	Yes	High number of prognostic factors measured and provided in easily accessible format
Outcome measurement	Yes	Clear outcomes and endpoints
Adjustment for other prognostic factors	Yes	Significant variables controlled for in multivariable model
Statistical analysis and reporting	Yes	Appropriate use of statistical analysis and clear reporting of univariable and multivariable statistics
Overall risk of bias	Unclear	Moderate

Qadri 2017
Study characteristics

Notes	Observational prospective study from March 2016 to December 2016 Infants 1 to 12 months presenting to the hospital with first-time seizure Srinagar, India in a tertiary care hospital for children No ASMs given Excluded: infants with any significant perinatal history or with prior history of seizures 50 infants included 58% male sex Funding: no funding information provided
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Qadri 2017 (Continued)

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Consecutive children with first unprovoked seizure recruited prospectively
Study attrition	Yes	Six of 56 infants lost to follow-up and clearly stated
Prognostic factor measurement	No	Very limited prognostic factors measured and reported in the paper
Outcome measurement	Unclear	Clear outcomes and endpoints but short follow-up period
Adjustment for other prognostic factors	Unclear	No mention of confounding factors
Statistical analysis and reporting	No	Only univariable statistics with no mention of a multivariable model
Overall risk of bias	No	High

Ramos Lizana 2000

Study characteristics

Notes

Prospective cohort study
Patients aged less than 14 years with 1 or more unprovoked seizures
Spain
Minimum 6 months of follow-up; average follow-up 3.8 years
ASMs given
Excluded: neonatal convulsions and patients already receiving antiepileptic treatment or who had been examined at other centres
217 patients
61% male sex
Funding: no funding information provided

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Consecutive patients under the age of 14 included; unclear why this cut off was used for a paediatric cohort
Study attrition	Yes	Only three children lost to follow-up out of 217
Prognostic factor measurement	Yes	High number of prognostic factors measured and clearly reported
Outcome measurement	Yes	Clear endpoints defined and reported
Adjustment for other prognostic factors	Unclear	No mention of confounding factors
Statistical analysis and reporting	Yes	Appropriate univariable and multivariable analysis
Overall risk of bias	Yes	Low

Ramos Lizana 2009

Study characteristics

Notes	<p>Prospective cohort study</p> <p>Patients aged 14 years or younger who attended for a first remote symptomatic unprovoked seizure</p> <p>Spain</p> <p>Mean follow-up: 4.1 years</p> <p>ASM given</p> <p>Excluded: neonatal convulsions, patients already on antiepileptic treatment, those who had been examined previously in other centres, and those whose detailed clinical record revealed antecedents of prior seizures</p> <p>63 patients</p> <p>56% male sex</p> <p>Funding: no funding information provided</p>
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Item	Authors' judgement	Support for judgement
Study participation	Unclear	Consecutive patients aged 14 years or younger who attended the unit for a first remote symptomatic unprovoked seizure
Study attrition	Yes	Only one patient lost to follow-up of 63 participants included
Prognostic factor measurement	Yes	Adequate reporting of prognostic factors and a high number of factors measured
Outcome measurement	Yes	Clear study end points defined and reported
Adjustment for other prognostic factors	Unclear	No formal discussion of confounding factors but multivariable model used
Statistical analysis and reporting	Yes	Appropriate statistical analysis and reporting with univariable and multivariable statistics clearly stated
Overall risk of bias	Yes	Low

Sathirapanya 2020

Study characteristics

Notes	<p>Retrospective case note review</p> <p>Patients aged ≥ 15 years who presented to the emergency department with a first seizure</p> <p>Thai study</p> <p>Median follow-up 33.4 months</p> <p>ASM given</p> <p>Excluded: those with a known history of epilepsy and all epilepsy mimics</p> <p>414 cases</p> <p>64.5% male sex</p> <p>Funding: no funding information provided</p>
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Item	Authors' judgement	Support for judgement
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Sathirapanya 2020 (Continued)

Study participation	No	Retrospective case review of patients ≥ 15 year but only those who were admitted for at least 48 hours
Study attrition	Unclear	N/A - retrospective study
Prognostic factor measurement	Yes	High number of prognostic factors that are clearly defined and reported
Outcome measurement	Unclear	Endpoints of study clearly defined and reported
Adjustment for other prognostic factors	Unclear	No formal mention of study confounders
Statistical analysis and reporting	Yes	Appropriate use of univariable and multivariable statistics
Overall risk of bias	Unclear	Retrospective design with selection limited to hospitalised patients staying ≥ 48 hours raises concerns about representativeness. Prognostic factors were reported but with limited detail. Other domains were acceptable, so overall risk of bias is rated as unclear.

Schreiner 2003
Study characteristics

Notes	German prospective cohort Adult cohort > 16 years No ASMs given Excluded: absences and myoclonus Included: all seizure types including SE 157 participants 34 months of follow-up 62% male sex Funding: no funding information provided
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Item	Authors' judgement	Support for judgement
Study participation	Unclear	Adults coming to emergency dept with unprovoked seizure, clear criteria for study however only those with an EEG within 48 hours included, which is not representative of the wider population
Study attrition	Yes	Seven patients lost to follow-up
Prognostic factor measurement	Unclear	Extensive for EEG measures but few other factors considered e.g. imaging
Outcome measurement	Yes	Well presented
Adjustment for other prognostic factors	Unclear	Unclear adjustments made
Statistical analysis and reporting	Yes	Survival curves and multivariable/univariable analysis performed

Schreiner 2003 (Continued)

Overall risk of bias	Unclear	Moderate
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Scotoni 2004

Study characteristics

Notes	<p>Brazilian prospective cohort study</p> <p>Paediatric cohort: 1 month to 17 years</p> <p>No ASMs</p> <p>Excluded: absence, myoclonic seizures, infantile spasms, and symptomatic seizures</p> <p>Included: focal and generalised seizures</p> <p>SE (6%) included</p> <p>213 participants</p> <p>25.7-month follow-up period</p> <p>58% male sex</p> <p>Funding: no funding information provided</p>
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Item	Authors' judgement	Support for judgement
Study participation	Unclear	Clear criteria but excluded absence and myoclonus which will introduce some bias
Study attrition	Unclear	16% of participants had less than six months of follow-up
Prognostic factor measurement	Yes	Extensive
Outcome measurement	Yes	Well reported
Adjustment for other prognostic factors	Yes	Plenty of adjustments
Statistical analysis and reporting	Yes	Appropriate survival curves, univariable and multivariable analyses
Overall risk of bias	Yes	Low

Shinnar 2000

Study characteristics

Notes	<p>USA prospective cohort</p> <p>Age: 1 month to 19 years</p> <p>No ASMs</p> <p>All seizures included</p> <p>No specific mention of SE</p> <p>407 participants</p> <p>9.6 years of follow-up</p> <p>No mention of gender</p> <p>Funding: this work was supported by the National Institutes of Health (NIH) grant NS 31146 from the National Institute of Neurological Disorders and Stroke (NINDS)</p>
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Shinnar 2000 (Continued)

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Clear criteria but excluded absence and myoclonus which will introduce some bias
Study attrition	Unclear	16% of participants had less than six months of follow-up
Prognostic factor measurement	Yes	Extensive
Outcome measurement	Yes	Well reported
Adjustment for other prognostic factors	Yes	Plenty of adjustments
Statistical analysis and reporting	Yes	Appropriate survival curves, univariable and multivariable analyses
Overall risk of bias	Yes	Low

Takami 2021

Study characteristics

Notes	<p>Japanese prospective observational study</p> <p>467 participants</p> <p>Patients aged between 1 month and 16 years who were attended to for their first unprovoked seizures and had an EEG at the Japanese Red Cross Society Himeji Hospital between 1 November 2008 and 31 October 2016</p> <p>No ASMs</p> <p>56.5% male sex</p> <p>Funding: this study was supported by a grant from the Practical Research Project for Rare/Intractable Diseases from the Japan Agency for Medical Research and Development (AMED) (JP20ek0109486)</p>
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Item	Authors' judgement	Support for judgement
Study participation	No	Only children who had an EEG were included in the study
Study attrition	Unclear	No mention of study attrition or dropouts from study
Prognostic factor measurement	Yes	High number of prognostic factors collected as part of study
Outcome measurement	Yes	Clear study end points and outcomes clearly defined
Adjustment for other prognostic factors	Unclear	No formal reporting of study confounders but they do use multivariable models to control for a number of variables
Statistical analysis and reporting	Yes	Appropriate use of univariable and multivariable statistics

Takami 2021 (Continued)

Overall risk of bias	Unclear	Moderate
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Winckler 2004
Study characteristics

Notes	Brazilian prospective cohort study Paediatric cohort: 1 month to 16 years No ASMs All seizure types included No specific mention of SE 109 participants 24 months of follow-up 64.2% male sex Funding: no funding sources mentioned or declared
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Item	Authors' judgement	Support for judgement
Study participation	Yes	Consecutive patients, really clear inclusion and exclusion criteria
Study attrition	Unclear	Not clearly stated
Prognostic factor measurement	Yes	Very extensive collection of factors included
Outcome measurement	Yes	Very clear outcome and risk for epilepsy development given at multiple time points
Adjustment for other prognostic factors	Yes	Multiple adjustments
Statistical analysis and reporting	Yes	Well-reported methods
Overall risk of bias	Yes	Low

ASMs: anti-seizure medications
 CNS: central nervous system
 CT: computed tomography
 CVA: cerebrovascular accident
 GTCS: generalised tonic-clonic seizure
 MRI: magnetic resonance imaging
 RCT: randomised controlled trial
 SE: status epilepticus
 TBI: traumatic brain injury
 US: ultrasound

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abdennadher 2021	No prognostic factor data
Aksu 2022	No effect measures reported
Amagasa 2021	No effect measures reported
Annegers 1986	Only multivariable statistics reported
Arabi 2018	No effect measures reported
Arıcan 2021	No effect measures reported
Bonnett 2022	Duplicate dataset
Boonluksiri 2003	Only multivariable statistics reported
Bora 1995	Only multivariable statistics reported
Boursoulian 2021	No effect measures reported
El Shakankiry 2021	No effect measures reported
Haddad 2021	No effect measures reported
Haltiner 1997	Only multivariable statistics reported
Hopkins 1988	Only multivariable statistics reported
Inaloo 2008	Only multivariable statistics reported
Jason 2018	No effect measures reported
Kho 2006	Only multivariable statistics reported
Lawn 2015	Only multivariable statistics reported
Llauradó 2021	No effect measures reported
Maloney 2021	No effect measures reported
Musicco 1997	Only multivariable statistics reported
Paliwal 2015	Only multivariable statistics reported
Schmidt 2021	No effect measures reported
Verma 2021	No effect measures reported
Woo 2021	Only multivariable statistics reported
Woo 2022	Only multivariable statistics reported
Zelig 2022	No effect measures reported
Zhang 2017	Only multivariable statistics reported

ADDITIONAL TABLES

Table 1. Summary of multivariable analyses reported by excluded studies

Study	Prognostic factor	Effect estimate (OR/HR/RR)	95% CI	P value	Covariates adjusted for
Annegers 1986	Abnormal neurologic exam (idiopathic)	2.30	1.4–3.9	< 0.002	Neurologic exam, EEG abnormality, seizure type, medication use, aetiology (idiopathic vs remote symptomatic)
	Abnormal EEG (idiopathic)	2.20	1.1–4.3	Not stated	
	Partial seizure (idiopathic)	1.60	1.2–3.2	Not stated	
	Abnormal neurologic exam (remote symptomatic)	1.40	0.8–2.3	Not stated	
	Abnormal EEG (remote symptomatic)	1.30	0.6–3.0	Not stated	
	Partial seizure (remote symptomatic)	1.80	1.1–3.0	Not stated	
	Anticonvulsant medication	0.90	0.6–1.4	Not stated	
Boonluksiri 2003	Male	0.83	0.473–1.459	0.305	Sex, seizure type, family history of febrile seizures, family history of epilepsy, EEG findings, developmental delay
	Partial seizure	0.981	0.423–2.276	0.439	
	Prior febrile seizures	1.197	0.595–2.406	0.714	
	Family history of febrile seizures	1.25	0.548–2.851	0.205	
	Family history of epilepsy	0.466	0.111–1.952	0.292	
	Epileptiform activity on EEG	1.512	0.677–3.376	0.485	
	Non-epileptiform EEG	1.097	0.237–5.088	0.485	
	Delayed development	1.699	0.493–5.861	0.799	
Bora 1995	Nocturnal seizure	2.10	1.0–4.3	0.028	Age, sex, family history, EEG pattern, time of seizure, ASM treatment
	Male	1.20	0.6–2.4	Not stated	
	Age 16–20	1.60	0.7–3.3	Not stated	
	Age 21–40	0.60	0.4–1.5	Not stated	
	Age > 40	1.20	0.4–1.3	Not stated	
	Abnormal EEG (various types)	0.6–1.5	Not stated	Not stated	
	Family history of seizures	1.20	0.4–3.6	Not stated	

Table 1. Summary of multivariable analyses reported by excluded studies (Continued)

	Anticonvulsant untreated	1.60	0.8–3.3	Not stated	
Haltiner 1997	Duration of coma ≥ 7 days	4.45 (≥ 5 seizures)	—	0.02	Glasgow Coma Scale, duration of coma, subdural haematoma, depressed skull fracture, neurosurgical intervention
	Duration of coma ≥ 7 days	7.67 (≥ 10 seizures)	—	0.05	
	Subdural haematoma	2.42 (≥ 5 seizures)	—	0.04	
	Subdural haematoma	2.55 (≥ 10 seizures)	—	0.09	
	Depressed skull fracture	1.99 (≥ 2 seizures)	—	0.04	
	Subdural haematoma	1.86 (≥ 2 seizures)	—	0.03	
	One or more non-reactive pupils	2.15 (≥ 5 seizures)	—	0.06	
Hopkins 1988	Initial seizure occurred mid-night–8:59am	1.5	Not stated	<0.004	Seizure timing, family history of seizures, age, EEG findings, CT findings
	Family history of seizures (any type)	1.34	Not stated	0.057	
	Age < 50 years	1.43	Not stated	Not stated	
Inaloo 2008	Sleep onset seizure	2.261	1.302–3.928	0.004	Seizure during sleep, abnormal EEG, abnormal imaging, history of perinatal problems
	Abnormal EEG	1.929	1.045–3.561	0.036	
	Abnormal brain imaging	2.808	1.084–7.273	0.033	
	Perinatal problems	4.959	1.203–20.441	0.027	
	Age < 1	1			
	Age 1–3 years	0.855	0.389–3.122	0.855	
	Age 3–10 years	0.404	0.552–4.362	0.404	
	Age > 10 years	0.844	0.370–3.378	0.844	
	Male	1.575	0.904–2.746	0.109	
	Partial seizures	1			
	Generalised seizure	0.824	0.310–2.193	0.698	
	Partial with secondary generalised seizure	0.933	0.199–4.371	0.93	
	> 1 seizures in 24h	1.759	0.950–3.258	0.072	

Table 1. Summary of multivariable analyses reported by excluded studies (Continued)

	Febrile seizures	0.441	0.189–1.030	0.058	
	Family history of afebrile seizure	1.987	0.993–3.976	0.052	
	Treatment received	0.965	0.461–2.018	0.924	
	Past history of provoked seizure	0.693	0.198–2.420	0.566	
Kho 2006	Remote symptomatic aetiology	2.17	1.39–3.38	< 0.001	Aetiology, seizure type, age at first seizure, sex, family history of epilepsy
	Unprovoked aetiology	1.79	1.18–2.72	0.006	
	Remote symptomatic aetiology	2.17	1.39–3.38	0.0006	
	Epileptogenic lesion on imaging	1.87	1.24–2.83	0.003	
Lawn 2015	Remote symptomatic aetiology	1.42	1.16–1.75	0.0001	Aetiology (remote symptomatic vs idiopathic), seizure type, presence of epileptiform EEG abnormalities, presence of epileptogenic lesion on neuroimaging, seizure from sleep
	Simple partial seizures	2.26	1.20–4.25	0.01	
	Epileptiform abnormality on EEG	1.49	1.10–1.71	0.005	
Musicco 1997	Treatment after first seizure	0.5	0.30–0.60	Not stated	Age, treatment after first seizure, EEG findings, aetiology, seizure type, acute treatment
	Age < 16	0.80	0.63–1.01	Not stated	
	Age > 60	0.67	0.42–1.05	Not stated	
Paliwal 2015	Abnormal MRI	9.38	3.09–28.44	0.003	EEG abnormality, MRI abnormality, clinical seizure characteristics
	Abnormal EEG	4.09	1.61–10.36	0.003	
Woo 2021	Age 11–15 years	5.781	2.249–14.858	0.001	Age group, seizure duration, Todd's palsy, Cr > 1.2 mg/dL, blood pH, glucose level
	Age 16–18 years	6.223	1.965–19.711	0.002	
	Seizure duration 1–5 min	3.043	1.483–6.245	0.002	
	Seizure duration 6–10 min	5.629	1.844–17.186	0.002	
	Seizure duration >10 min	8.882	2.187–36.083	0.002	
	Ph < 7.2	8.308	1.519–45.447	0.015	
	Glucose > 144 mg/dL	6.408	1.195–34.370	0.030	
Woo 2022	Age 2–5 years	2.611	1.263–5.398	0.010	Age group, seizure count, seizure duration, Todd's paralysis, diarrhoea, lethargy, dehydrated tongue, Cr > 1.21 mg/dL, glucose level, and lactate level
	Age 11–15 years	3.138	1.469–6.702	0.003	
	Age 16–18 years	4.292	1.677–10.982	0.002	

Table 1. Summary of multivariable analyses reported by excluded studies (Continued)

	Seizure count ≥ 2	2.378	1.324–4.272	0.004	
	Seizure duration >10 min	4.869	1.579–15.017	0.006	
	Lethargy	2.341	1.134–4.831	0.021	
	Lactate > 2.27 mg/dL	4.205	2.585–6.839	<0.001	
Zhang 2017	Age 12–24 months	0.876	0.518–1.484	0.623	Age, cause of seizure, seizure during sleep, type of seizure, EEG pattern, imaging findings, developmental quotient
	Age 24–36 months	0.498	0.285–0.869	0.014	
	Cause of disease	1.624	1.020–2.587	0.041	
	Seizure during sleep	2.779	1.757–4.397	0.001	
	Status epilepticus	1.37	0.835–2.249	1.370	
	Type of seizure	1.502	0.894–2.524	0.705	
	Abnormal background EEG	1.192	0.540–2.631	Not stated	
	Epileptic discharge EEG	3.269	2.049–5.217	0.664	
	Imaging examination	1.431	0.904–2.264	<0.001	
	Average development	1.273	0.580–2.793	0.547	
	Below average development	1.163	0.528–2.562	0.709	
	Borderline intellectual functioning	1.64	0.716–3.760	0.242	
	Deficiency	0.941	0.240–3.687	0.931	

ASM: anti-seizure medication; **Cr:** creatinine; **CT:** computed tomography; **EEG:** electroencephalogram; **HR:** hazard ratio; **MRI:** magnetic resonance imaging; **OR:** odds ratio; **RR:** risk ratio

APPENDICES

Appendix 1. CRS Web search strategy

1. ((first or single or initial) ADJ4 seizure*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET
2. (unprovoked or untreated):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET
3. #1 AND #2
4. ((first or single or unprovoked) adj3 seizure*):TI AND CENTRAL:TARGET
5. #3 OR #4
6. MESH DESCRIPTOR Diagnosis EXPLODE ALL AND CENTRAL:TARGET
7. MESH DESCRIPTOR Risk Factors EXPLODE ALL AND CENTRAL:TARGET
8. MESH DESCRIPTOR Recurrence EXPLODE ALL AND CENTRAL:TARGET

9. MESH DESCRIPTOR Mortality EXPLODE ALL AND CENTRAL:TARGET
10. (diagnos* or prognos* or risk or recur* or recurrence* or relaps* or remission* or mortalit*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET
11. #6 OR #7 OR #8 OR #9 OR #10
12. MESH DESCRIPTOR Epilepsy EXPLODE ALL AND CENTRAL:TARGET
13. (epilep*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET
14. MESH DESCRIPTOR Seizures AND CENTRAL:TARGET
15. #12 OR #13 OR #14
16. #11 AND #15
17. MESH DESCRIPTOR Epilepsy EXPLODE ALL WITH QUALIFIER DI AND CENTRAL:TARGET
18. MESH DESCRIPTOR Seizures WITH QUALIFIER DI AND CENTRAL:TARGET
19. #16 OR #17 OR #18
20. (Validat* OR Rule*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET
21. (Predict*):TI AND CENTRAL:TARGET
22. (Predict* AND (Outcome* or Risk* or Model*)):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET
23. ((History or Variable* or Criteria or Scor* or Characteristic* or Finding* or Factor*) and (Predict* or Model* or Decision* or Identif* or Prognos*)):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET
24. (Decision*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET
25. (Model* or Clinical*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET
26. MESH DESCRIPTOR Logistic Models AND CENTRAL:TARGET
27. #25 OR #26
28. #24 AND #27
29. (Prognostic and (History or Variable* or Criteria or Scor* or Characteristic* or Finding* or Factor* or Model*)):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET
30. #20 OR #21 OR #22 OR #23 OR #28 OR #29
31. (Predict* OR Scor* OR Observ*):TI,AB AND CENTRAL:TARGET
32. MESH DESCRIPTOR Predictive Value of Tests AND CENTRAL:TARGET
33. MESH DESCRIPTOR Observer Variation AND CENTRAL:TARGET
34. #31 OR #32 OR #33
35. (Stratification OR Discrimination OR Discriminate OR "c-statistic" OR "c statistic" OR "Area under the curve" OR AUC OR Calibration OR Indices OR Algorithm OR Multivariable):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET
36. MESH DESCRIPTOR ROC Curve AND CENTRAL:TARGET
37. #35 OR #36
38. #30 OR #34 OR #37
39. #19 OR #38
40. #5 AND #39
41. (cancer* or glioma* or glioblast* or neoplasm* or tumor* or tumour* or stroke):TI AND CENTRAL:TARGET

42. ((eclamp* or alcohol withdraw* or febril*) NOT "non-febril*");TI AND CENTRAL:TARGET

43. #41 OR #42

44. #40 NOT #43

Appendix 2. MEDLINE Ovid (from 1946)

This includes the search filters recommended by the Cochrane Prognosis Methods Group ([Geersing 2012](#)):

1. ((first or single or initial) adj4 seizure?).mp.

2. (unprovoked or untreated).mp.

3. 1 and 2

4. ((first or single or unprovoked) adj3 seizure?).ti.

5. 3 or 4

6. exp Diagnosis/ or exp risk factors/ or exp RECURRENCE/ or exp Mortality/

7. (diagnos\$ or prognos\$ or risk or recur? or recurrence? or relaps\$ or remission\$ or mortalit\$).mp.

8. 6 or 7

9. exp Epilepsy/ or epilep*.mp. or seizures/ [seizures deliberately not exploded]

10. 8 and 9

11. exp Epilepsy/di or seizures/di [seizures deliberately not exploded]

12. 10 or 11

13. Validat\$.mp. or Predict\$.ti. or Rule\$.mp. or (Predict\$ and (Outcome\$ or Risk\$ or Model\$)).mp. or ((History or Variable\$ or Criteria or Scor\$ or Characteristic\$ or Finding\$ or Factor\$) and (Predict\$ or Model\$ or Decision\$ or Identif\$ or Prognos\$)).mp. or (Decision\$.mp. and ((Model\$ or Clinical\$).mp. or Logistic Models/)) or (Prognostic and (History or Variable\$ or Criteria or Scor\$ or Characteristic\$ or Finding\$ or Factor\$ or Model\$)).mp.

14. Predict\$.ti,ab. or Predictive value of tests/ or Scor\$.ti,ab. or Observ\$.ti,ab. or observer variation/

15. "Stratification".mp. or roc curve/ or "Discrimination".mp. or "Discriminate".mp. or "c-statistic".mp. or "c statistic".mp. or "Area under the curve".mp. or "AUC".mp. or "Calibration".mp. or "Indices".mp. or "Algorithm".mp. or "Multivariable".mp.

16. 13 or 14 or 15

17. 12 or 16

18. 5 and 17

19. exp *Neoplasms/ or exp *Stroke/

20. (cancer\$ or glioma\$ or glioblast\$ or neoplasm\$ or tumor\$ or tumour\$ or stroke).ti.

21. exp *Pre-Eclampsia/ or exp *Eclampsia/

22. exp *alcohol withdrawal seizures/ or exp *seizures, febrile/

23. ((eclamp\$ or alcohol withdraw\$ or febril\$) not non-febril\$).ti.

24. or/19-23

25. 18 not 24

26. exp animals/ not humans.sh.

27. 25 not 26

28. (case adj (report? or study or studies)).ti.

29. 27 not 28

30. remove duplicates from 29

Appendix 3. SCOPUS search strategies

Subject search

```
(((((TITLE-ABS-KEY(((first OR single OR initial) PRE/4 seizure) AND TITLE-ABS-KEY(unprovoked OR untreated)) OR (TITLE(((first OR single OR unprovoked) PRE/3 seizure))) AND (((TITLE-ABS-KEY(diagnos* OR prognos* OR risk OR recur OR recurrence OR relaps* OR remission OR mortalit*) AND ((TITLE-ABS-KEY(epilep* OR "infantile spasm" OR "ring chromosome 20" OR "R20" OR "myoclonic encephalopathy" OR "pyridoxine dependency") OR (TITLE-ABS-KEY(syndrome) W/2 (aicardi OR angelman OR doose OR dravet OR janz OR jeavons OR "landau kleffner" OR "lennox gastaut" OR ohtahara OR panayiotopoulos OR rasmussen OR rett OR "sturge weber" OR tassinari OR "unverricht lundborg" OR west)) OR TITLE(seizure OR convuls*) OR (TITLE-ABS-KEY(lafora*) W/4 (disease OR epilep*) AND NOT (TITLE(dog OR canine) OR INDEXTERMS(dog OR canine)))) AND NOT (TITLE(*eclampsia) OR INDEXTERMS(*eclampsia))) OR ((TITLE-ABS-KEY(Validat* OR Rule*) OR TITLE(Predict*)) OR (TITLE-ABS-KEY(Predict* AND (Outcome* OR Risk* OR Model*))) OR ((TITLE-ABS-KEY(History OR Variable* OR Criteria OR Scor* OR Characteristic* OR Finding* OR Factor*)) AND (TITLE-ABS-KEY(Predict* OR Model* OR Decision* OR Identif* OR Prognos*))) OR (TITLE-ABS-KEY(Decision* AND (Model* OR Clinical* OR "Logistic Model*"))) OR (TITLE-ABS-KEY(Prognostic AND (History OR Variable* OR Criteria OR Scor* OR Characteristic* OR Finding* OR Factor* OR Model*))) OR (TITLE-ABS(Predict* OR Scor* OR Observ*) OR TITLE-ABS-KEY("Predictive value of tests" OR "observer variation")) OR (TITLE-ABS-KEY(Stratification OR "roc curve" OR Discrimination OR Discriminate OR "c-statistic" OR "c statistic" OR "Area under the curve" OR AUC OR Calibration OR Indices OR Algorithm OR Multivariable)))) AND NOT (TITLE(animal* OR mouse OR mice OR rat OR dog OR canine) AND NOT TITLE(human* OR patient OR child* OR infant* OR adolescen* OR adult OR elderly OR man OR men OR male OR wom?n OR female))) AND ((TITLE-ABS((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR "cross over" OR cluster OR "head to head") W/4 (analy* OR investigat* OR method OR procedure OR study OR studies OR trial))) OR ((( TITLE-ABS(("before and after" OR cohort OR comparative OR "cross section*" OR "follow up" OR longitudinal OR multicenter OR observation* OR prospective OR quasicontrol* OR "quasi control*" OR quasiexperiment* OR "quasi experiment*" OR quasirandom* OR "quasi random*" OR "record linkage" OR retrospective OR "time series") W/4 (analy* OR investigat* OR method OR procedure OR study OR studies OR trial))) OR (TITLE-ABS(case* W/3 (comparison* OR control* OR series))) OR (TITLE-ABS((clinical OR epidemiologic OR evaluation OR validation) PRE/3 (study OR studies OR trial))) OR (ABS("time points" W/3 (over OR multiple OR three OR four OR five OR six OR seven OR eight OR nine OR ten OR eleven OR twelve OR month OR hour OR day OR "more than")))) OR (ABS(control W/3 (area OR cohort OR compare* OR condition OR design OR group OR intervention OR participant OR study))) OR (TITLE-ABS("control year" OR "experimental year" OR "control period" OR "experimental period")) OR (TITLE-ABS((strategy OR strategies) W/2 (improv* OR education*))) OR (TITLE-ABS-KEY((single OR doubl* OR tripl* OR treb*) PRE/3 (blind* OR mask*))) OR (TITLE-ABS-KEY("4 arm" OR "four arm")))) AND NOT (TITLE(case PRE/0 (report OR study OR studies))) AND NOT (TITLE(cancer* OR glioma* OR glioblast* OR neoplasm* OR tumor* OR tumour* OR stroke OR eclamp* OR "alcohol withdraw*" OR febril*) AND NOT TITLE("non-febril*"))
```

Citation search

Documents that cite

PMID(26780937 OR 18184149 OR 2864487 OR 1978114 OR 26215392 OR 26222507 OR 24055222 OR 10528934 OR 23181965 OR 25676481 OR 24691297 OR 8692621 OR 27680779)
LIMIT-TO(DOCTYPE, "ar") OR LIMIT-TO(DOCTYPE, "cp") AND (EXCLUDE(EXACTKEYWORD, "Animals") OR EXCLUDE(EXACTKEYWORD, "Nonhuman") OR EXCLUDE(EXACTKEYWORD, "Case Report"))
[DOCTYPE, "ar" = Article, DOCTYPE, "cp" = Conference paper]

Cited documents

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Appendix 4. ClinicalTrials.gov search strategy

prognosis OR recurrence OR relapse OR remission OR mortality | (first OR single OR initial OR unprovoked OR untreated) AND (epilepsy OR epileptic OR seizure)

Appendix 5. WHO ICTRP search strategy

(prognosis OR recurrence OR relapse OR remission OR mortality) AND ((first OR single OR initial OR unprovoked OR untreated) AND (epilepsy OR epileptic OR seizure))

Appendix 6. Assessing bias

We used a modified version of the quality assessment strategy recommended by Hayden and colleagues to assess the quality of included studies (Hayden 2013). This assessment covered six domains of potential bias: study participation, study attrition, prognostic factors measurement, outcome measurement (seizure recurrence, death), study confounding, statistical analysis, and reporting. Our approach assessed the risk of bias by considering responses to the prompting items for all reported prognostic factors together (in addition to any missing or unclear information).

The issues to consider for judging the overall rating of risk of bias for each domain are listed below. We provided study methods and comments, in addition to a rating of reporting within the review.

Bias: study participation

Goal: To judge the risk of selection bias (likelihood that the relationship between prognostic factors (PF) and outcome is different for participants and eligible non-participants)

Issues to consider for judging overall rating of risk of bias

Source of target population	<p>The source population, or population of interest, is adequately described, including who the target population is (e.g. all people with a single unprovoked seizure, or people with a specific type of seizure, focal onset or generalised, or a single seizure occurring after a specific aetiology e.g. post-traumatic seizure), when (time period of study), where (tertiary care epilepsy clinic, First Seizure Clinic, general neurology or paediatric clinic, Accident and Emergency, primary care, community), and how (description of recruitment strategy – referrals from Accident and Emergency, primary care).</p> <p>Comprehensive description would include demographic (age, sex, date of seizure), relevant co-morbidities and history (history of childhood febrile seizures, previous head injury, previous cerebrovascular accident, dementia), seizure type (focal, generalised, undefined), and whether any treatment (anti-epileptic medication) was initiated, and for how long.</p>
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(Continued)

Method used to identify population	Recruitment methodology is adequately described (direct referrals from primary care, Accident and Emergency), or is identified directly from the community (method of case ascertainment is clearly described).
Recruitment period	Place of recruitment (setting – e.g. First Seizure Clinic, and geographic location) are adequately described.
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described, and define a discrete group with a single unprovoked seizure. In particular, people with provoked (acute symptomatic) seizures are specifically excluded, as people referred with a single seizure and have had a recurrence by the time of initial review in clinic are excluded, or people are included as a seizure relapse, with an accurate timeframe established.
Adequate study participation	The baseline characteristics of the individuals enrolled are adequately described. This would include age, sex, date of seizure, seizure type, and any identified risk factors for epilepsy or comorbidities.
Summary study participation: The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome (low, moderate, or high risk of bias).	

Bias: study attrition

Goal: *To judge the risk of attrition bias (likelihood that relationship between PF and outcome are different for completing and non-completing participants)*

Issues to consider for judging overall risk of bias

Proportion of baseline sample available for analysis	Response rate (i.e. proportion of people in a cohort on whom we have complete follow-up seizure recurrence/mortality data) is adequate.
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who were lost to follow-up are adequately described.
Reasons and potential impact of subjects lost to follow-up	Potential individual reasons for loss to follow-up are provided.
Outcome and prognostic factor information on those lost to follow-up	Baseline demographic characteristics and potential risk factors for seizure recurrence are adequately described in those lost to follow-up.

Summary study attrition:

Loss to follow-up (from baseline sample to study population analysed) is not associated with key characteristics (i.e. the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome (low, moderate, high risk of bias).

Bias: prognostic (PF measurement)

Goal: *To assess the risk of measurement bias of prognostic factors related to seizure recurrence*

Issues to consider for judging overall risk of bias

(Continued)

Definition of the PF	Potential PFs, such as specific electroencephalogram (EEG) findings and specific neuroimaging findings, are clearly and consistently defined.
Valid and reliable measurement of PF	Method of documentation of seizure recurrence is consistent for all individuals, i.e. use of seizure diaries, confirmed eyewitness accounts with accurate dates, and accurate seizure classification to avoid misclassification bias. Clear details of electroencephalogram (EEG) or neuroimaging methods provided, and classification of seizure type made using appropriate methods (e.g. using International League Against Epilepsy (ILAE) classifications (e.g. Berg 2010 or earlier versions)).
Method and setting of PF measurement	The method of establishing seizure recurrence (e.g. seizure diary, eyewitness account) is consistent for all participants.
Proportion of data on PF available for analysis	Adequate proportion of the cohort has complete data on potential PF (adequate to be judged, based on context of the study).
Method used for missing data	If used, appropriate methods of imputation are used for missing individual PFs.

Summary prognostic factor measurement:

PFs are adequately measured in study participants to sufficiently limit potential bias (low, moderate, high risk of bias).

Bias: outcome measurement

Goal: To assess the risk of bias related to seizure outcome (differential measurement of seizure outcome related to the baseline level of PF)

Issues to consider for judging overall risk of bias

Definition of the outcome	A clear definition of what constitutes a seizure recurrence is provided, including clear documentation of the time period between the index seizure and seizure recurrence, as well as clear documentation of seizure semiology.
Valid and reliable measurement of outcome	The method of establishing seizure recurrence (outcome measurement) used is adequately valid and reliable, to limit misclassification bias. In particular, that sufficient clinical details are available regarding all potential seizures after the index seizure, to avoid misclassification of other differentials (syncope, non-epileptic attacks, provoked (acute symptomatic) seizures).
Method and setting of outcome measurement	The method and setting of seizure recurrence is the same for all study participants.

Summary outcome measurement: outcome is adequately measured in study participants to sufficiently limit potential bias (low, moderate, high risk of bias).

Bias: study confounding

Goal: To judge the risk of bias due to confounding – i.e. the effect of a PF is distorted by another factor related to the PF and the risk of seizure recurrence or mortality

Issues to consider for judging overall risk of bias

Important confounders measured	All important potential confounders related to the risk of seizure recurrence, such as significant sleep deprivation, anti-seizure medication (ASM) treatment initiated, and premature mortality fol-
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(Continued)

	lowing a single seizure (such as important medical comorbidities, like ischaemic heart disease and diabetes mellitus) are measured.
Definition of the confounding factor	Clear definitions of important confounding factors measured are provided (e.g. what constitutes significant sleep deprivation in the context of seizure recurrence).
Valid and reliable measurement of confounders	Measurement of all important confounders is adequately valid and reliable (e.g. confirmed documentation in previous medical records, clear EEG parameters for classification for non-diagnostic features).
Method and setting of confounding measurements	The method and setting of confounding measurements and recording are the same for all study participants.
Method used for missing confounding factor data	Appropriate methods are used if imputation is used for missing confounding factor data.
Appropriate accounting for confounding	Important potential confounders are accounted for in study design (i.e. matching for key variables – age, sex, seizure semiology).
Summary study confounding: important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PFs and the outcome (low, moderate, high risk of bias).	

Bias: statistical analysis and reporting

Goal: to judge the risk of bias related to the statistical analysis and presentation of results

Issues to consider for judging overall rating of bias	
Presentation of analytical strategy	There is sufficient presentation of data to assess the appropriateness of the analysis used.
Model developmental strategy	The strategy for prognostic model building is appropriate, and the statistical model used is appropriate for the study design.
Reporting of results	There is no manifest selective reporting of results.
Summary statistical analysis and reporting: the statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results, and selective reporting is unlikely (low, moderate, high risk of bias).	

HISTORY

Protocol first published: Issue 1, 2021

CONTRIBUTIONS OF AUTHORS

GA: Conceptualisation; Methodology; Formal analysis; Data curation; Writing – original draft; Writing – review & editing.

AN: Conceptualisation; Methodology; Formal analysis; Data curation; Writing – original draft; Writing – review & editing.

LB: Methodology; Formal analysis; Validation; Writing – review & editing.

SJN: Methodology; Formal analysis; Validation; Writing – review & editing.

TM: Conceptualisation; Writing – review & editing.

JWS: Conceptualisation; Writing – review & editing.

All authors contributed to revising and approving the final manuscript.

We adhered to [Cochrane Commercial Sponsorship policy](#) (2014) (clause 8), whereby authors of primary studies did not extract data from their own studies. Specifically, the authors involved in data extraction and analysis were clearly indicated in the Methods section for the two studies where this clause applied ([Bell 2016](#); [Bonnett 2010](#)).

DECLARATIONS OF INTEREST

AN: an author of one of the included studies ([Bell 2016](#)); all data relating to the study have been independently extracted and analysed by two other independent review authors. Associate editor for BMC Neurology.

GA: no relevant interests to disclose.

SJN: received consulting fees as an independent contractor from Saluda Medical Americas, Inc; received grant from National Institute of Health Research. She was Statistical Editor of the Cochrane Epilepsy Group; however, not involved in the editorial process of this review.

LB: an author of one of the included studies ([Bonnett 2010](#)); all data relating to the study have been independently extracted and analysed by two other independent review authors.

JWS: an author of one of the included studies ([Bell 2016](#)); all data relating to the study have been independently extracted and analysed by two other independent review authors. Trustee of SUDEP Action; received consulting fees as an independent contractor from Angelini Pharma and UCB Pharma. On the Lancet's International Advisory Board as an independent contractor.

AGM: an author of one of the included studies ([Bonnett 2010](#)); all data relating to the study have been independently extracted and analysed by two other independent review authors. Received non-personal grant/contract from UCB Pharma. Consultant for Angelini Pharma and Jazz Pharmaceuticals. He was the Co-ordinating Editor of the Cochrane Epilepsy Group; however, he was not involved in the editorial process for this review.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Insufficient data were available to conduct separate meta-analyses based on distinct subgroups, such as prospectively and retrospectively designed studies, studies including adults and children (age group as defined in the individual study), and studies considering different seizure types.

A sensitivity analysis was not required as no data transformation was part of the review process.

We included randomised controlled trials that provided relevant univariable prognostic data, thus contributing valuable evidence given the paucity of data.