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

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[Prognosis Review]

Prognosis of adults and children following a first unprovoked seizure

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ABSTRACT

Background

Epilepsy is clinically defined as two or more unprovoked epileptic seizures more than 24 hours apart. Given that, a diagnosis of epilepsy can be associated with significant morbidity and mortality, it is imperative that clinicians (and people with seizures and their relatives) have access to accurate and reliable prognostic estimates, to guide clinical practice on the risks of developing further unprovoked seizures (and by definition, a diagnosis of epilepsy) following single unprovoked epileptic seizure.

Objectives

1. To provide an accurate estimate of the proportion of individuals going on to have further unprovoked seizures at subsequent time points following a single unprovoked epileptic seizure (or cluster of epileptic seizures within a 24-hour period, or a first episode of status epilepticus), of any seizure type (overall prognosis).
2. To evaluate the mortality rate following a first unprovoked epileptic seizure.

Search methods

We searched the following databases on 19 September 2019 and again on 30 March 2021, with no language restrictions.

The Cochrane Register of Studies (CRS Web), MEDLINE Ovid (1946 to March 29, 2021), SCOPUS (1823 onwards), ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). CRS Web includes randomized or quasi-randomized, controlled trials from PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Specialized Registers of Cochrane Review Groups including Epilepsy. In MEDLINE (Ovid) the coverage end date always lags a few days behind the search date.

Selection criteria

We included studies, both retrospective and prospective, of all age groups (except those in the neonatal period (< 1 month of age)), of people with a single unprovoked seizure, followed up for a minimum of six months, with no upper limit of follow-up, with the study end point being seizure recurrence, death, or loss to follow-up. To be included, studies must have included at least 30 participants.

We excluded studies that involved people with seizures that occur as a result of an acute precipitant or provoking factor, or in close temporal proximity to an acute neurological insult, since these are not considered epileptic in aetiology (acute symptomatic seizures). We also excluded people with situational seizures, such as febrile convulsions.

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Data collection and analysis

Two review authors conducted the initial screening of titles and abstracts identified through the electronic searches, and removed non-relevant articles. We obtained the full-text articles of all remaining potentially relevant studies, or those whose relevance could not be determined from the abstract alone and two authors independently assessed for eligibility. All disagreements were resolved through discussion with no need to defer to a third review author.

We extracted data from included studies using a data extraction form based on the **ch**ecklist for critical **a**ppraisal and data extraction for systematic**r**eviews of prediction **m**odelling **s**tudies (CHARMS).

Two review authors then appraised the included studies, using a standardised approach based on the **qu**ality **i**n **p**rognostic **s**tudies (QUIPS) tool, which was adapted for overall prognosis (seizure recurrence).

We conducted a meta-analysis using Review Manager 2014, with a random-effects generic inverse variance meta-analysis model, which accounted for any between-study heterogeneity in the prognostic effect. We then summarised the meta-analysis by the pooled estimate (the average prognostic factor effect), its 95% confidence interval (CI), the estimates of I^2 and Tau^2 (heterogeneity), and a 95% prediction interval for the prognostic effect in a single population at three various time points, 6 months, 12 months and 24 months. Subgroup analysis was performed according to the ages of the cohorts included; studies involving all ages, studies that recruited adult only and those that were purely paediatric.

Main results

Fifty-eight studies (involving 54 cohorts), with a total of 12,160 participants (median 147, range 31 to 1443), met the inclusion criteria for the review. Of the 58 studies, 26 studies were paediatric studies, 16 were adult and the remaining 16 studies were a combination of paediatric and adult populations.

Most included studies had a cohort study design with two case-control studies and one nested case-control study. Thirty-two studies (29 cohorts) reported a prospective longitudinal design whilst 15 studies had a retrospective design whilst the remaining studies were randomised controlled trials.

Nine of the studies included presented mortality data following a first unprovoked seizure. For a mortality study to be included, a proportional mortality ratio (PMR) or a standardised mortality ratio (SMR) had to be given at a specific time point following a first unprovoked seizure.

To be included in the meta-analysis a study had to present clear seizure recurrence data at 6 months, 12 months or 24 months. Forty-six studies were included in the meta-analysis, of which 23 were paediatric, 13 were adult, and 10 were a combination of paediatric and adult populations.

A meta-analysis was performed at three time points; six months, one year and two years for all ages combined, paediatric and adult studies, respectively. We found an estimated overall seizure recurrence of all included studies at six months of 27% (95% CI 24% to 31%), 36% (95% CI 33% to 40%) at one year and 43% (95% CI 37% to 44%) at two years, with slightly lower estimates for adult subgroup analysis and slightly higher estimates for paediatric subgroup analysis. It was not possible to provide a summary estimate of the risk of seizure recurrence beyond these time points as most of the included studies were of short follow-up and too few studies presented recurrence rates at a single time point beyond two years. The evidence presented was found to be of moderate certainty.

Authors' conclusions

Despite the limitations of the data (moderate-certainty of evidence), mainly relating to clinical and methodological heterogeneity we have provided summary estimates for the likely risk of seizure recurrence at six months, one year and two years for both children and adults. This provides information that is likely to be useful for the clinician counselling patients (or their parents) on the probable risk of further seizures in the short-term whilst acknowledging the paucity of long-term recurrence data, particularly beyond 10 years.

PLAIN LANGUAGE SUMMARY

Predicting a second seizure after a single unprovoked seizure

Why was this review performed?

A single unprovoked seizure is fairly common, with estimates that up to 3% to 4% of the population will have one by age 85. This translates to approximately one in 25 people having an epileptic seizure during their lifetime. It is therefore of the utmost importance that accurate prognostic data are available so that clinicians can reliably counsel people on the risk of further seizures, and factors that predict the recurrence of seizures and therefore the development of epilepsy.

What is the aim of the review?

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The main objective of this review is to provide people presenting with a single seizure, their families, and the clinicians looking after them, with more accurate information relating to the risk of further unprovoked seizures and the development of epilepsy.

The additional objective of this review is to provide people presenting with a single seizure, their families, and the clinicians looking after them, with more accurate information relating to the risk of premature death following an unprovoked seizure.

Key messages

Despite some quite big differences in the design of the studies included in this review, we were able to provide information on the risk of having another seizure at 6 months, 12 months and 24 months.

What was studied in the review?

We searched for relevant studies that had a reliable design and that reported the number of people who had a second seizure after a first unprovoked seizure. We found 58 studies involving 12,160 people. Twenty-six studies involved children only, 16 were adult only and the remaining 16 studies were a combination of children and adults. People had to have been followed up for a minimum of six months and include a minimum number of 30 people.

What were the main results of the review?

We collected the reported second seizure rates at 6 months, 12 months and 24 months. We then combined the data at these three set time points and were able to compare the chances of having a second seizure according to how much time had passed after the first seizure. At six months the chances of having a second event was 27%, whilst it was 36% at one year and finally at two years it was 43%. The chances of having a second seizure are slightly higher in children compared to adults.

How up to date is this review?

The evidence is current to March 2021.

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SUMMARY OF FINDINGS

Summary of findings 1. Seizure recurrence and mortality at 6 months

Prognosis of adults and children following a first unprovoked seizure

Outcome: Seizure recurrence and mortality* at 6 months

Population	Anticipated Seizure recurrence (95% CI)	Number of studies (participants)	Overall certainty of the evidence (GRADE)
Mixed (adults and children)	27 per 100 people (24 to 31 per 100 people)	27 (7111)	⊕⊕⊕⊖ Moderate[a,b]
Adults	25 per 100 adults (19 to 30 per 100 adults)	7 (1914)	⊕⊕⊕⊖ Moderate[a,b]
Children	30 per 100 children (23 to 37 per 100 people)	14 (2232)	⊕⊕⊕⊖ Moderate[a,b]

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

a. Downgraded once due to heterogeneity
b. Although some study limitations were observed, the majority of studies were judged to be at low risk of bias; no downgrade made due to study limitations
* No specific mortality data at 6 months

Summary of findings 2. Seizure recurrence and mortality at 12 months

Prognosis of adults and children following a first unprovoked seizure

Outcome: Seizure recurrence and mortality* at 12 months

Population	Anticipated Seizure recurrence (95% CI)	Number of studies (participants)	Overall certainty of the evidence (GRADE)
Mixed (adults and children)	36 per 100 people (33 to 40 per 100 people)	34 (6843)	⊕⊕⊕⊖ Moderate[a,b]
Adults	35 per 100 adults (31 to 38 per 100 adults)	9 (2468)	⊕⊕⊕⊖ Moderate[a,b]
Children	38 per 100 children (31 to 44 per 100 people)	16 (2313)	⊕⊕⊕⊖ Moderate[a,b]

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GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

a. Downgraded once due to heterogeneity
b. Although some study limitations were observed, the majority of studies were judged to be at low risk of bias; no downgrade made due to study limitations
* No evidence of increased mortality (SMR) in idiopathic and cryptogenic seizures at 12 months (Loiseau 1999)

Summary of findings 3. Seizure recurrence and mortality at 24 months

Prognosis of adults and children following a first unprovoked seizure

Outcome: Seizure recurrence and mortality* at 24 months

Population	Anticipated Seizure recurrence (95% CI)	Number of studies (participants)	Overall certainty of the evidence (GRADE)
Mixed (adults and children)	43 per 100 people (39 to 47 per 100 people)	27 (6908)	⊕⊕⊕⊖ Moderate[a,b]
Adults	41 per 100 adults (37 to 44 per 100 adults)	9 (2043)	⊕⊕⊕⊖ Moderate[a,b]
Children	45 per 100 children (36 to 54 per 100 people)	12 (2172)	⊕⊕⊕⊖ Moderate[a,b]

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

a. Downgraded once due to heterogeneity
b. Although some study limitations were observed, the majority of studies were judged to be at low risk of bias; no downgrade made due to study limitations
* No specific mortality data at 24 months

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BACKGROUND

Epilepsy, clinically defined after two or more unprovoked epileptic seizures, is one of the most common neurological disorders worldwide, with significant psychosocial sequelae; it has an estimated incidence of 50 to 70 per 100,000 person years, and a prevalence of 5 to 10 per 1000 persons. It affects more than 50 million people world-wide (Neligan 2012; Ngugi 2011). Given that a diagnosis of epilepsy can be associated with significant morbidity and mortality (Loiseau 1999), it is imperative that clinicians (and people with seizures and their relatives) have access to accurate and reliable prognostic estimates and models, to guide clinical practice on the risks of developing further unprovoked seizures (and by definition, a diagnosis of epilepsy) following a single unprovoked seizure.

Description of the health condition and context

The condition under study is the occurrence of a single unprovoked epileptic seizure of any semiology (study of signs/symptoms), and the subsequent risk of seizure recurrence of any type, within a two-year period. Seizure semiology is defined according to the recent International League Against Epilepsy (ILAE) classification of seizures (Scheffer 2017). Epileptic seizures are synchronous and excessive discharges in the cerebral cortex, leading to a clinically discernable event. There are many seizure types, depending on the area of the cerebral cortex in which the discharges originate. Seizures can be broadly sub classified into focal onset or generalised seizures, depending on whether the epileptic focus originates in a localised area in one cerebral cortex, as in focal onset seizures, or from both hemispheres simultaneously, as in generalised seizures. Focal seizures can be subdivided into seizures with and without impairment of consciousness, depending on how localised and widespread the epileptic focus is. Seizures may take the form of short sensory, motor, or psychic symptoms, typically lasting 15 to 30 seconds and resolving without cognitive sequelae, or progress to an episode of impaired or complete loss of consciousness. All focal onset seizures have the potential to evolve from a state without impaired consciousness, to one with impaired consciousness, or complete loss of consciousness (focal to bilateral tonic-clonic seizure), as a result of the localised epileptic focus spreading to a more widespread area, or to the opposite cerebral hemisphere.

Focal seizures with impaired consciousness, which predominantly arise from the temporal or frontal lobes, are said to occur when the person is less responsive, or more commonly, completely unresponsive to external stimuli, with or without prominent motor symptoms. These seizures can be short (15 to 30 seconds in frontal seizures, often with hypermotor activity), or more prolonged (two to four minutes in temporal seizures, often with oral or manual symptoms), following which there may be a period of confusion that lasts several minutes, and amnesia for the episode. Generalised seizures, which can occur without warning, or evolve from a more focal seizure (focal to bilateral tonic-clonic seizure typically involve loss of tone (atonia) and posture, with bilateral convulsive movements (tonic-clonic movements) lasting several minutes, during which there may or may not be associated tongue-biting, or incontinence (urinary, or faecal, or both), or both). A typical generalised seizure lasts several minutes (normally less than five minutes), following which there is a prolonged period of drowsiness and confusion lasting minutes to hours, during which the person may sleep. People may have a headache or generalised muscle aching following a generalised seizure. Generalised seizures may have isolated features of a generalised tonic-clonic seizure, such as atonia (atonic seizures), a tonic phase (tonic seizures), or a clonic phase (clonic seizures). Other generalised seizure types include absence seizures (brief staring episodes without a significant component, lasting less than a minute, occurring in children), and myoclonus (brief involuntary contraction of a single muscle or group of muscles).

Description of the prognostic factors

The primary outcome of this review is overall prognosis (seizure recurrence and mortality) in people with a single unprovoked seizure. We will identify potential prognostic factors in relation to seizure recurrence in a separate review (Adan 2021). Prognostic factors in relation to mortality following a first unprovoked seizure will be briefly discussed if relevant.

Health Outcomes

Seizure recurrence and mortality following a first unprovoked seizure.

Why it is important to do this review

It is estimated that the cumulative incidence of a single unprovoked epileptic seizure in the general population is approximately 3% to 4% by the time one reaches 85 years of age (Hauser 1993). Consequently, almost one in 25 people will have an epileptic seizure during their lifetime, and it is imperative that accurate prognostic data are available so that clinicians can reliably counsel people on the risk of further seizures, and factors that predict the recurrence of seizures and the development of epilepsy. People who present with a single unprovoked seizure will be typically investigated with magnetic resonance imaging (MRI), and possibly an electroencephalogram (EEG), depending on age, which is justified on prognostic grounds. Nevertheless, it is unclear what additional risk an abnormal EEG or a specific abnormality on MRI confers. If the risk is sufficiently increased, this may justify commencing antiepileptic medication after a single seizure (rather than after two or more unprovoked seizures more than 24 hours apart, as is standard practise). People presenting with a single seizure, their families, and the clinicians looking after them, deserve more accurate prognostic estimates of the risk of further unprovoked seizures and the development of epilepsy.

OBJECTIVES

Primary objectives

To provide an accurate estimate of the proportion of individuals going on to have further unprovoked seizures and the development of epilepsy at any subsequent time point, following a single unprovoked seizure (or cluster of epileptic seizures within a 24-hour period, or a first episode of status epilepticus), of any seizure type (overall prognosis). In particular we will try to provide accurate estimates for seizure recurrence at specific time points, namely at 6 months, 12 months and at 24 months and beyond.

Secondary objectives

To evaluate the mortality rate following a first unprovoked epileptic seizure.

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Investigation of sources of heterogeneity between studies

We anticipate that there will be heterogeneity between studies, particularly in studies that have focused on adults compared to the paediatric population, and studies that have a combination of paediatric and adult populations.

METHODS

This review was conducted within the framework of the Cochrane Epilepsy Review Group, and reported in line with the PRISMA guidelines (Moher 2009). This methods section is based 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 (1 month to 16 years) and adults (> 16 years) with a previous unprovoked epileptic seizure of any semiology in observational cohort studies, case control and nest case-control studies and randomised controlled trials of first unprovoked seizures.

Intervention:not applicable in the context of an overall prognosis review.

Comparator: not applicable in the context of an overall prognosis review.

Outcome: the primary outcome is recurrence of a further unprovoked seizure of any semiology where a clear time point for seizure recurrence (for example at 6 or 12 months) is given. The secondary outcome is mortality following a first unprovoked seizure.

Timing :any seizure recurrence of any semiology more than 24 hours after the index seizure, in studies with a minimum of six months follow-up, with no upper time limit for inclusion.

Settings: hospital outpatients or the community.

Types of studies

We included mostly cohort studies, both retrospective and prospective, of all age groups (except those in the neonatal period (< 1 month of age)), of people with a single unprovoked seizure (of any semiology), followed up for a minimum of six months, with no upper limit of follow-up, with the study end point being (an unprovoked) seizure recurrence, death, or loss to follow-up. We also included randomised controlled trials of immediate and delayed treatment in first unprovoked seizure cohorts. In addition, we included rare case-control or nested case-control studies (typically in the context of specific aetiologies) where applicable. To be included, studies must have included at least 30 participants (West 2019).

Targeted population

Population and hospital cohorts of people older than one month, 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 occur 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, acute cerebrovascular accident), since these are not considered epileptic in aetiology (acute symptomatic seizures; (Kwan 2010)). We also excluded people with situational seizures, such as febrile convulsions, which occur in young children in the context of a high temperature.

Types of prognostic or predictive factor(s) or model(s)

Not applicable.

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 go on to have a further seizure where a seizure recurrence rate is given for a specific time period. Specifically we aimed to provide estimates for seizure recurrence at the clinically important time points of 6 months, 12 months, 24 months and beyond. We also present, where available, the risk of seizure recurrence following a first unprovoked seizure in specific populations such as people with dementia, people with a moderate to severe traumatic brain injury and people following a single episode of idiopathic status epilepticus (as opposed to a single self-terminating unprovoked seizure). This necessitated the inclusion of a number of case-control and nest case-control studies.

The secondary outcome is mortality following a first unprovoked seizure, again where a proportional mortality ratio (PMR) or standardised mortality ratio (SMR) at a specific time point (for example five years) is given.

Search methods for identification of studies

Electronic searches

We searched the following databases on 30 March 2021, with no language restrictions.

1. The Cochrane Register of Studies (CRS Web), using the strategy outlined in Appendix 1.
2. MEDLINE Ovid (1946 to March 29, 2021), using the strategy outlined in Appendix 2.
3. SCOPUS (1823 onwards), using the strategies outlined in Appendix 3.
4. ClinicalTrials.gov, using the strategy outlined in Appendix 4.
5. The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), using the strategy outlined in Appendix 5.

CRS Web includes randomized or quasi-randomized, controlled trials from PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Specialized Registers of Cochrane Review Groups including Epilepsy. In MEDLINE (Ovid) the coverage end date always lags a few days behind the search date.

To avoid unnecessary duplication of work, we used the same search for both this review and the prognostic factors review (Adan 2021).

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Searching other resources

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

Data collection

Selection of studies

Two review authors (AN, GA), conducted the initial screening of titles and abstracts identified through the electronic searches, and removed clearly irrelevant articles. We then obtained the full-text articles of all potentially relevant studies, or those whose relevance cannot be determined from the abstract, AN and GA independently assessed studies for eligibility. A pilot test of the inclusion criteria of the first 10 potential eligible studies was performed to ensure a similar approach by both review authors.

Where studies are reported in multiple publications or reports, we collated all relevant reports under a single study, so that the study, rather than the report, is the unit of interest in the review.

We outlined the study selection process in a PRISMA study flow diagram (Moher 2009).

Data extraction and management

We extracted data from included studies using a data extraction form based on the **ch**ecklist for critical **a**ppraisal and data extraction for systematic**r**eviews of prediction **m**odelling **s**tudies (CHARMS; (Moons 2014)); a pilot test was carried out on several studies and appropriate edits made thereafter. Two review authors (AN, GA) extracted data and a third review author (SJN) checked the data. We resolved disagreements through discussion, or if required, consultation with a fourth review author (AGM).

List of data extracted:

- Date of first seizure and any subsequent seizures
- Age
- Gender
- Seizure semiology – focal onset, generalise, impairment of consciousness

We contacted trial authors for missing data and gave them 30 days to respond, after which time, only published data were included for the purposes of this review.

Assessment of risk of bias in included studies

Two review authors (AN and GA) appraised the included studies for bias, using a standardised approach based on the **qu**ality **i**n **p**rognostic **s**tudies (QUIPS) tool, which was adapted for the overall prognosis (seizure recurrence; Hayden 2013, Appendix 6). In the case of discrepancies, AN and AG discussed and reached a consensus view. In particular there is no specific bias tool available for an overall prognosis review (nor indeed for data extraction, as the CHARMS extraction form and the QUIPS tool are specifically designed for prognostic factors, although one for overall prognosis reviews is in preparation for the former (personal communication from the Cochrane Prognostic Methods Group (PMG). Consequently, a pilot test of the use of the QUIPS tool on the first 10 eligible studies was carried out and appropriate modifications to the QUIPS tool. These modifications were discussed and approved by SJN (who is a member of the Cochrane PMG).

Our approach assessed the risk of bias of all prognostic studies (in addition to any missing or unclear information) for six domains of bias; study participation (selection bias), study attrition, prognostic factor measurement, outcome measurement, adjustment and statistical analysis, and reporting. We judged each domain at high, unclear, or low risk of bias, using the modified version of the QUIPS tool.

We also judged overall risk of bias, by defining studies with a low risk of bias as those in which we rated most of the six domains at low risk of bias.

Measures of association or predictive performance measures to be extracted

Not applicable.

Dealing with missing data

We included studies that give an overall prognosis (seizure recurrence rate) even if there are missing or incomplete data on some participants, as long as a clear seizure recurrence ratio at a specific time point of follow-up was given.

Where required, we calculated or estimated seizure recurrence ratios on any data reported (e.g. 2 x 2 frequency tables, graphs, and figures, such as Kaplan-Meier curves, using indirect estimation measures as described by Parmar 1998 and Tierney 2007). Specifically we calculated seizures recurrence ratios at 6 months, 12 months and 24 months if possible.

Assessment of heterogeneity

We anticipated that clinical and statistical heterogeneity will be present between studies, due to the wide 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 cutoff points), and the outcome measurement.

We synthesised associations within clinically relevant subgroups (for example we synthesised studies of adult and paediatric cohorts separately). To assess statistical heterogeneity across studies included in each synthesis, we inspected forest plots, and quantified heterogeneity statistically using the I^2 statistic and Tau^2 (the estimate of between-study variance; (Snell 2016)).

Assessment of reporting deficiencies

Where data required for the review were not reported in a study, we contacted corresponding authors and if no reply was received within 30 days, the study was excluded.

Data synthesis

Data synthesis and meta-analysis approaches

We anticipated that relevant data for this review would be presented in a range of formats, and levels of detail. Therefore, wherever possible, we transformed the data to a common format

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for synthesis; we examined the impact of any assumptions made when transforming data in a sensitivity analysis (e.g. if data were converted from one effect measure to another, or estimated from graphical figures).

We conducted the meta-analyses using Review Manager 2014, with a random-effects generic inverse variance meta-analysis model, which accounts for any between-study heterogeneity in the prognostic effect. We then summarised the meta-analysis by the pooled estimate (the average prognostic factor effect), its 95% confidence interval (CI), the estimates of I^2 and Tau^2 (heterogeneity), and a 95% prediction interval for the prognostic effect in a single population (Riley 2011); we calculated this in STATA version 15 (Stata).

In the case it was not appropriate to combine results using a meta-analysis (due to excess clinical heterogeneity or lack of appropriate data presented), we presented the results qualitatively, considering the strength and consistency of results using the following schema:

- strong evidence of effect: consistent findings (defined as greater than 75% of studies showing the same direction of effect) in multiple low risk of bias studies;
- moderate evidence of effect: consistent findings in multiple high risk of bias, or one study with low risk of bias;
- limited evidence of effect: one study available;
- conflicting evidence of effect: inconsistent findings across studies;
- no effect: no association between participant expectations and the outcome of interest.

Subgroup analysis and investigation of heterogeneity

We conducted separate meta-analyses based on studies including adults and children (age group as defined within the individual study), in the expectation that the overall prognosis would differ in paediatric compared to adult populations. With regard to age, overall prognosis summary data have been presented separately, given that epidemiological and prognosis studies in epilepsy tend to study children and adults separately, with different overall prognosis and prognostic factors.

Sensitivity analysis

Not applicable.

Conclusions and summary of findings

We used an approach modified from the GRADE framework to assess the overall certainty of evidence regarding the association of each prognostic factor with each outcome (Guyatt 2011; Hayden 2014; Huguet 2013; Iorio 2015).

We rated the overall strength of evidence as high, moderate, low, or very low considering the phase of the prognostic study and internal validity, size and precision of effect, heterogeneity, generalisability, and potential reporting bias.

RESULTS

Description of studies

Results of the search

The search generated 1310 records and review of the relevant bibliographies did not identify any further studies; 1100 studies were screened after 210 duplicates were removed. We obtained 138 full text papers (Figure 1) including several reviews for bibliographic checks and background material. We excluded 80 studies with reasons (Table 1). We included 58 studies in the qualitative analysis and 46 studies were included in the meta-analysis.

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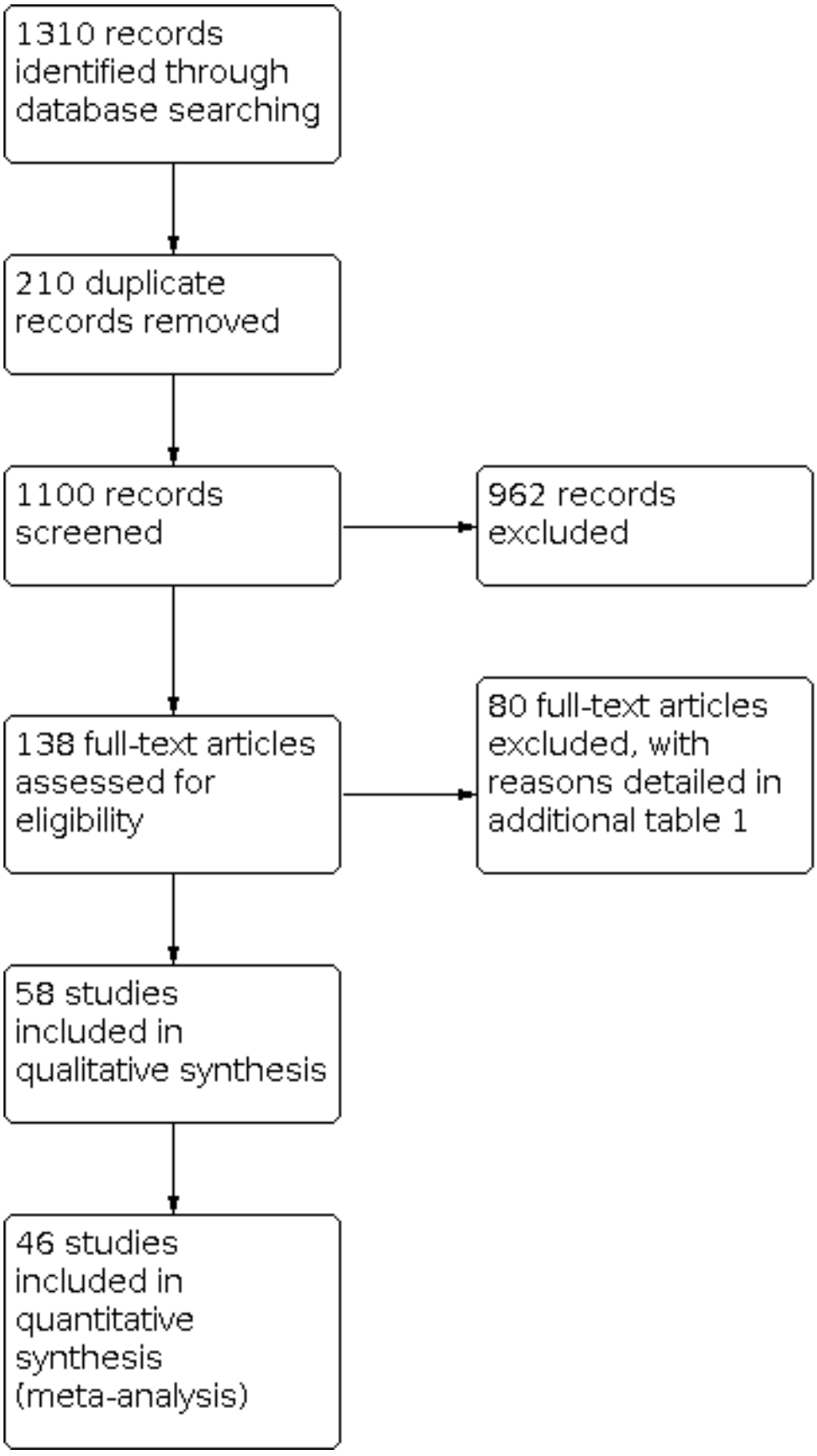
Figure 1. Study flow diagram.



Included studies

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Studies are described in detail in the Characteristics of included studies table. To be included, a study had to present the seizure recurrence rate after a first unprovoked seizure at a specific time point rather than as a proportion of the total who had a seizure recurrence. For studies which reported seizure recurrence in several publications of seizure recurrence at different time points (for example the National General Practice Study of Epilepsy (NGPSE) and the FIRST study) only the publications including recurrence at the 6-month, 12-month and 24-month time points (Hart 1990; Musicco 1997), as well as the final recurrence data (Leone 2006; Bell 2016), as well as the final mortality data if presented separately (Leone 2011).

Fifty-eight studies (involving 54 cohorts), with a total of 12,160 participants (median 147 range 31 to 1443), met the inclusion criteria for the review (Al-Momani 2020; Annegers 1986; Arthur 2008; Assarzadegan 2015; Austin 2002; Baldin 2017; Bell 2016; Benn 2009; Beretta 2017; Bessiso 2001; Blom 1978; Boonluksiri 2003; Bora 1995; Boulloche 1989; Camfield 1989; Camfield 1985; Chan 2012; Chandra 1992; Chen 2016; Daoud 2004; Das 2000; Elwes 1985; Geut 2017; Gilad 1996; Haltiner 1997; Hart 1990; Hauser 1990; Hesdorffer 2009; Hopkins 1988; Huang 2008; Hui 2001; Inaloo 2008; Jagtap 2013; Jason 2018; Kanemura 2015; Kawkabani 2004; Kho 2006; Klotz 2021; Lawn 2015; Leone 2006; Leone 2011; Lin 2014; Llevadias 2004; Logroscino 2008; Loiseau 1999; de Rezende Machado 2021; Mahamud 2020; Marson 2005; Mizrogi 2015; Musicco 1997; Schreiner 2003; Scotoni 2004; Shinnar 2000; Shinnar 2005; Van Donselaar 1991; Winckler 2004; Zhang 2014; Zhang 2017).

Of the 58 studies 26 studies were paediatric studies (Al-Momani 2020; Arthur 2008; Austin 2002; Bessiso 2001; Blom 1978; Boulloche 1989; Boonluksiri 2003; Camfield 1989; Camfield 1985; Chan 2012; Daoud 2004; Inaloo 2008; Jagtap 2013; Jason 2018; Kanemura 2015; Klotz 2021; Lin 2014; Llevadias 2004; de Rezende Machado 2021; Mizrogi 2015; Scotoni 2004; Shinnar 2000; Shinnar 2005; Winckler 2004; Zhang 2014; Zhang 2017); 16 were adult (Assarzadegan 2015; Bora 1995; Baldin 2017; Chandra 1992; Van Donselaar 1991; Gilad 1996; Haltiner 1997; Hopkins 1988; Huang 2008; Hui 2001; Kawkabani 2004; Kho 2006; Lawn 2015; Logroscino 2008; Mahamud 2020; Schreiner 2003), and the remaining 16 studies were a combination of paediatric and adult populations (Annegers 1986; Bell 2016; Benn 2009; Beretta 2017; Chen 2016; Das 2000; Elwes 1985; Geut 2017; Hart 1990; Hauser 1990; Hesdorffer 2009; Leone 2006; Leone 2011; Loiseau 1999; Marson 2005;Musicco 1997).

Most included studies had a cohort study design with two case-control studies (Hesdorffer 2009; Mahamud 2020) and one nested case-control study (Chan 2012). Thirty-two studies (29 cohorts) reported a prospective longitudinal design (Arthur 2008; Austin 2002; Baldin 2017; Bell 2016; Bessiso 2001; Blom 1978; Boonluksiri 2003; Bora 1995; Boulloche 1989; Chen 2016; Daoud 2004; Das 2000; Van Donselaar 1991; Hart 1990; Hauser 1990; Hopkins 1988; Huang 2008; Jagtap 2013; Inaloo 2008; Kanemura 2015; Kawkabani 2004; Kho 2006; Klotz 2021; Lawn 2015; Loiseau 1999; Mizrogi 2015; Schreiner 2003; Scotoni 2004; Shinnar 2000; Shinnar 2005; Winckler 2004; Zhang 2014), whilst fifteen studies had a retrospective design (Annegers 1986; Benn 2009; Beretta 2017; Camfield 1985; Elwes 1985; Geut 2017; Hesdorffer 2009; Hui 2001; Jason 2018; Al-Momani 2020; de Rezende Machado 2021; Llevadias 2004; Logroscino 2008; Zhang 2017), one of which was a multicentre study (Beretta 2017).

The remaining studies were randomised control trials, foremost amongst them in terms of cohort size and duration being the FIRST study (Musicco 1997; Leone 2006; Leone 2011) comparing immediate versus delayed treatment following a first generalised tonic seizure and the MESS study (Marson 2005) compared immediate versus delayed treatment following a first seizure of any semiology although those presenting with absence or myoclonic jerks were small in numbers (<1%). The remaining randomised control trials compared treatment with carbamazepine or placebo in children following a first seizure (focal or generalised seizure) (Camfield 1985) or carbamazepine or placebo following a first generalised tonic-clonic seizure in adults (Gilad 1996). Two studies compared treatment with sodium valproate or placebo following a first focal seizure (aware or unaware) or generalised tonic-clonic seizure (Chandra 1992), or following a first generalised tonic-clonic seizure (Assarzadegan 2015) in adults. The final randomised controlled trial (Lin 2014) compared children with a first unprovoked seizure (seizure type not specified) with epileptiform discharges on an EEG were randomised to treatment with listening to Mozart's Sonata for Two Pianos in D major, K.448 (Mozart K.448), with the treatment group listening to the first movement of Mozart K.448 for eight minutes once daily before bedtime for at least six months. Recurrence rates at 12 and 24 months were compared between the treatment and the control groups and changes in the frequency of epileptiform discharges on follow-up EEGs was also compared between the two groups.

Nine of the studies included presented mortality data following a first unprovoked seizure. For a mortality study to be included a proportional mortality ratio (PMR), or a standardised mortality ratio (SMR) had to be given at a specific time point following a first unprovoked seizure. One-year mortality associated with a first unprovoked seizure was the sole focus of the one prospective study (Loiseau 1999) ,whilst mortality data were either presented separately for several cohort studies (Shinnar 2005; Leone 2011), or in conjunction with other prognostic data such as in the NGPSE cohort (Hart 1990; Bell 2016), and in a prospective Swiss cohort study after six months (Kawkabani 2004). One study of 10-year mortality following a single unprovoked epileptic seizure compared to an episode of idiopathic status epilepticus (Logroscino 2008). One case-control study compared short- (30-day case fatality) and long-term mortality (10-year mortality) comparing an acute symptomatic seizure (defined as occurring within seven days of an acute insult (Beghi 2010)), or a first unprovoked seizure occurring more than seven days after the acute insult in people with a cerebrovascular accident (CVA), a traumatic brain injury (TBI) or a central nervous system (CNS) infection (Hesdorffer 2009). The recurrence rate of a new (or second) unprovoked seizure was also calculated. The final mortality study followed a cohort of patients with a first unprovoked seizure or a new diagnosis of epilepsy in a defined geographical area (Northern Manhattan, New York) over a four-year period (Benn 2009).

Seizure types included

Almost all studies excluded acute symptomatic or provoked seizures, and where such seizures were included in a study, for inclusion these data had to be presented separately (Hesdorffer 2009; Bell 2016), or had to be extracted from the data presented in the analysis (Loiseau 1999; Kho 2006).

Most studies excluded those who presented with typical absence seizures, myoclonic jerks or infantile spasms, given the fact that any presentation with such seizures is unlikely to have been the first presentation and the very high probability of seizure recurrence,

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although these were specifically included in a small number of studies (Austin 2002; Blom 1978; Llevadias 2004; Marson 2005).

Several studies only included people with a single generalised tonic-clonic seizure (Assarzadegan 2015; Bora 1995; Boulloche 1989; Das 2000; Elwes 1985; the FIRST Study (Musicco 1997; Leone 2006; Leone 2011); Gilad 1996), while several studies specifically excluded cases of status epilepticus (typically defined as a seizure or a series of seizures without an intervening period of recovery lasting more than 30 minutes) (Chan 2012; Van Donselaar 1991; Gilad 1996; Hui 2001; Kanemura 2015; Mizrogi 2015), although many studies did not make any specific mention of status epilepticus and did not record any cases.

Treatment

Excluding the six randomised controlled studies involving anti-seizure medications, 23 studies (22 cohorts) presented recurrence on a combination of treated and untreated patients, which in the majority of cases it was not possible to separate these groups out and therefore recurrence data for all studies are presented as a combination of the two. In18 studies (Al-Momani 2020; Boonluksiri 2003; Chen 2016; Daoud 2004;Van Donselaar 1991; Elwes 1985; Geut 2017; Hui 2001; Boulloche 1989; Kanemura 2015; Klotz 2021; Lin 2014; Mizrogi 2015; Schreiner 2003; Scotoni 2004; Winckler 2004; Zhang 2014; Zhang 2017), treatment with anti-seizure medication was a specified exclusion criteria, whilst in two studies (Arthur 2008; Baldin 2017), no specific mention of treatment was made nor presented in the results.

Specific populations

Three studies presented the risk of a second unprovoked seizure (more than seven days after an acute insult if specified) in specific subpopulations and the results are therefore presented separately. The risk of a second unprovoked seizure in a cohort of patients with TBI and a first unprovoked seizure (Haltiner 1997). The second study examined the short- and long-term mortality (and risk of a further unprovoked seizure) was calculated for those with a CVA, TBI and CNS infection (Hesdorffer 2009). The third study examined the risk of developing epilepsy following a first unprovoked seizure at five years in a cohort of patients with dementia (Mahamud 2020).

Meta-analysis

To be included in the meta-analysis a study had to present clear seizure recurrence data at 6 months, 12 months or 24 months. 46 studies were included in the meta-analysis, of which 23 were paediatric (Al-Momani 2020; Arthur 2008; Austin 2002; Bessiso 2001; Boonluksiri 2003; Boulloche 1989; Camfield 1985; Camfield 1989; Daoud 2004; Jagtap 2013; Jason 2018; Inaloo 2008; Jason 2018; Klotz 2021; Lin 2014; Llevadias 2004; de Rezende Machado 2021; Mizrogi 2015; Scotoni 2004; Shinnar 2000; Winckler 2004; Zhang 2014; Zhang 2017), 13 were adult (Assarzadegan 2015; Baldin 2017; Bora 1995; Chandra 1992; Van Donselaar 1991; Gilad 1996; Hopkins 1988; Hui 2001; Huang 2008; Kawkabani 2004; Kho 2006; Lawn 2015; Schreiner 2003), and 10 were a combination of paediatric and adult populations (Annegers 1986; Beretta 2017; Chen 2016; Das 2000; Elwes 1985; Geut 2017; Hart 1990; Hauser 1990; Marson 2005; Musicco 1997).

The data at the three time points six months, one year and two years were presented separately for all ages combined, paediatric and adults.

Six months - Paediatric (Arthur 2008; Bessiso 2001; Boonluksiri 2003; Boulloche 1989; Camfield 1985; Daoud 2004; Jason 2018; Inaloo 2008; Lin 2014; Mizrogi 2015; Scotoni 2004; Shinnar 2000; Zhang 2014; Zhang 2017); Adult – (Assarzadegan 2015; Bora 1995; Van Donselaar 1991; Hopkins 1988; Kawkabani 2004; Lawn 2015; Schreiner 2003); Paediatric and Adult combined - (Annegers 1986; Chen 2016; Elwes 1985; Hart 1990; Marson 2005; Musicco 1997).

One year – Paediatric (Al-Momani 2020; Boonluksiri 2003; Boulloche 1989; Camfield 1985; Camfield 1989; Daoud 2004; Inaloo 2008; Jagtap 2013; Klotz 2021; Llevadias 2004; de Rezende Machado 2021; Mizrogi 2015; Scotoni 2004; Shinnar 2000; Zhang 2014; Zhang 2017); Adult – (Bora 1995; Chandra 1992; Van Donselaar 1991; Gilad 1996; Hopkins 1988; Hui 2001; Kho 2006; Lawn 2015; Schreiner 2003); Paediatric and Adult combined – (Annegers 1986; Beretta 2017 Chen 2016; Das 2000; Elwes 1985; Geut 2017; Hart 1990; Hauser 1990; Musicco 1997).

Two-years – Paediatric (Austin 2002; Camfield 1985; Daoud 2004; Inaloo 2008; Jason 2018; Lin 2014; Mizrogi 2015; Scotoni 2004; Shinnar 2000; Winckler 2004; Zhang 2014; Zhang 2017); Adult (Baldin 2017; Bora 1995; Van Donselaar 1991; Gilad 1996; Hopkins 1988; Huang 2008; Hui 2001; Lawn 2015; Schreiner 2003); Paediatric and Adult combined (Beretta 2017; Chen 2016; Elwes 1985; Hart 1990; Marson 2005; Musicco 1997).

Follow-up beyond two years

Twenty-five studies reported seizure recurrence of >2 years, of which 11 were paediatric, with a maximum reported follow-up period of 10 years (Shinnar 2000); six were adult with the longest follow-up period being 10 years (Lawn 2015); and eight were a combination of paediatric and adult populations, with the longest follow-up reported being that in the NGPSE (>20 years Bell 2016). Of these, eight out of the paediatric studies, five of the six adult studies and all of the eight combined paediatric and adult studies were also included in the meta-analysis.

Excluded studies

We excluded 80 studies from the review for the following main reasons (see Characteristics of excluded studies table: Table 1): 12 studies and their corresponding full texts were unable to be accessed (Binelli 1988; Gupta 1993; Jafari 2020, Koelfen 1991; Kollár 2006; Masato 1999; Murthy 2020; Rozsavolgyi 2007; Tanabe 2005; Thoon 2006; Weber 1987; Zhang 2016); 21 studies included duplicate datasets that were included elsewhere in this review (Benn 2008; Bonnett 2010; Bonnett 2014; Cremo 1993; First Seizure Trial Group 1993; Hauser 1982; Jallon 2007; Kim 2006; Kita 1992; Lawn 2013; Lindsten 2001a; Lindsten 2001b; Olafsson 1998; Ramos Lizana 2009; Scotoni 1999; Shinnar 1990; Shinnar 1993; Shinnar 1996; Stroink 1998; van Donselaar 1992; Winckler 1997); two studies had an insufficient follow-up duration (Alesefir 2020; McIntosh 2021); three studies had an insufficient number of participants (Drenthen 2021; Kotov 2020; Koutroumanidis 2018); 17 studies had an ineligible population (Brown 2015; Chen 2018; Fonseca 2018; Haapaniemi 2014; Hesdorffer 1996; Lindsten 2000; Lühdorf 1986; Mahamud 2018; Mahler 2015; Matsushita 1993; Pathan 2014; Potchen 2014; Poudel 2016; Pujar 2018; Qadri 2017; Ramos Lizana 2000; Takami 2015); 21 studies had seizure recurrence rates which were not clearly stated (Langenbruch 2019; Bensken 2020; Douw 2010; Fisch 2016; Hesdorffer 2007; Jallon 2001; Jha 2004; Keret 2020; Khan 2020; Kim 2016; Kim 2020; Kramer 1997; Llaurado 2020; Maia 2017; McManus 2021; Olivé-Gadea 2019; Paliwal 2015; Saemundsen 2008; Sathirapanya 2020; Specchio

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2019; van Donselaar 1997) , and four studies described recurrence time points which were not clearly stated (Falip-Centellas 2002; Martinović 1997; Najafi 2008; Pereira 2014).

Ongoing studies

We found no ongoing studies.

Risk of Bias

A risk of bias assessment was performed on the 46 studies included in the meta-analysis, but not for the mortality studies, nor for studies with a follow-up time period >2 years. Figure 2 shows the risk of bias for each cohort, whilst Figure 3 shows assessments for each domain across studies. We were able to assess each study in all available domains. Overall all, studies were felt to have at least one domain with moderate or unclear risk of bias. Lawn 2015 was felt to be the study with the lowest risk of bias.

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Figure 2.

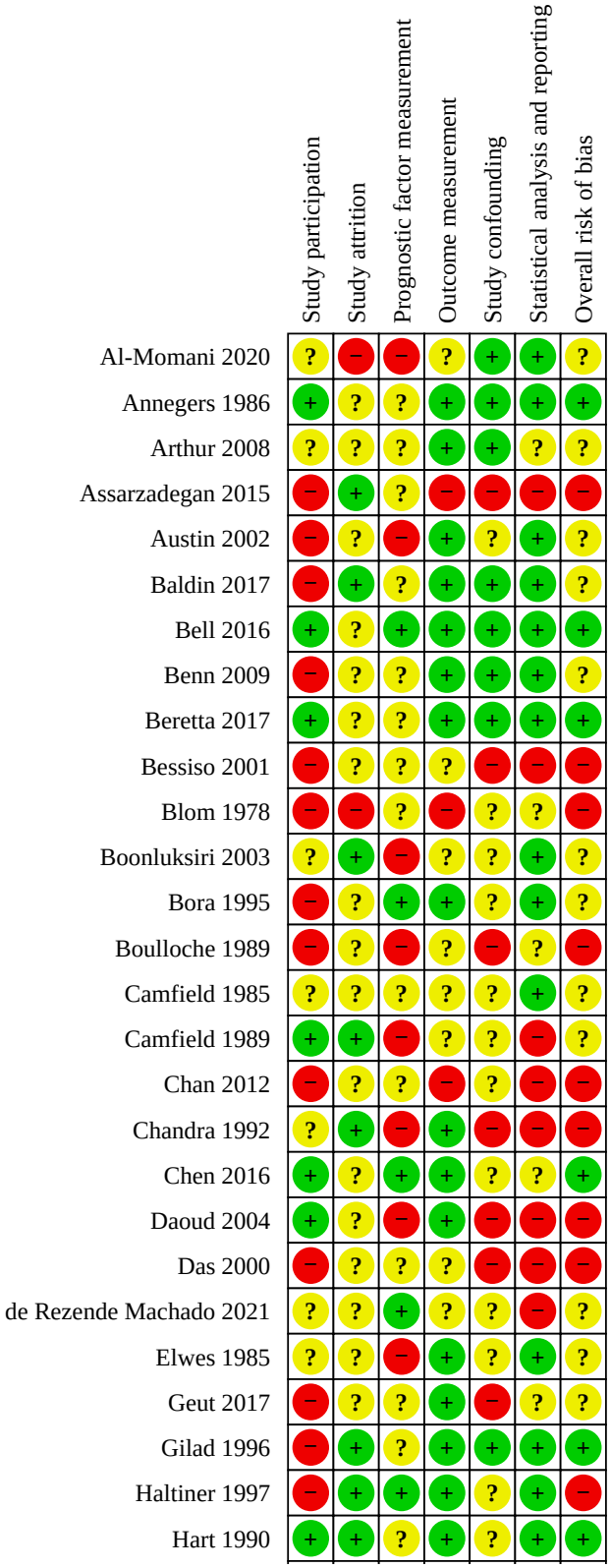

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Figure 2. (Continued)

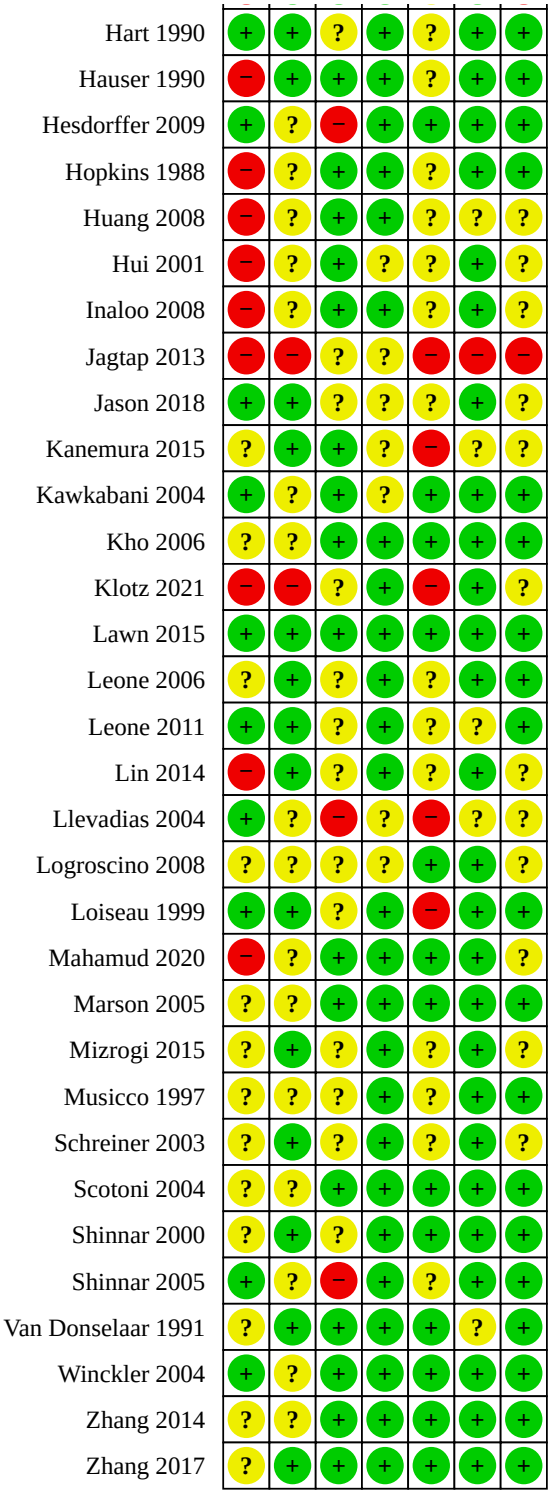

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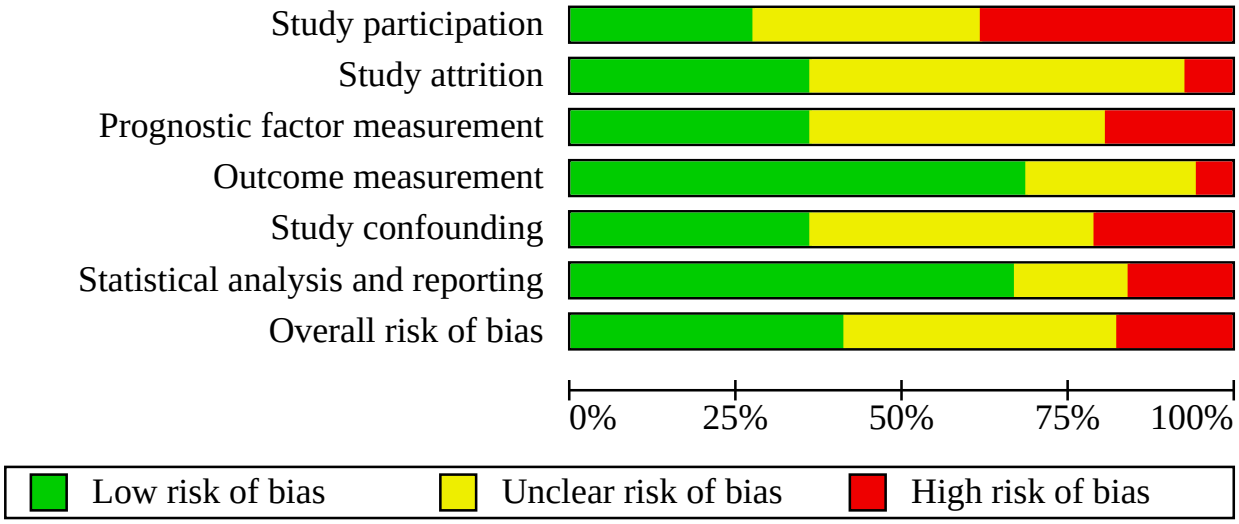
Figure 3.



Results

Seizure recurrence at six months

Seizure recurrence at six months following a first unprovoked seizure is shown in Figure 4. The overall estimated recurrence rate at six months for all studies (All studies: 27 studies, 7111 participants) was 27% (95% confidence interval (CI) 24% to 31%) with overall study heterogeneity (I^2 = 93%). The estimated seizure recurrence rate for adults (7 studies, 1914 participants) was 25% (95% CI 19% to 30%, I^2 = 88%), whilst the estimated recurrence rate for children (14 studies, 2232 participants) was slighter higher at 30% (95% CI 23% to 37%), again with very high study heterogeneity (I^2 = 95%).

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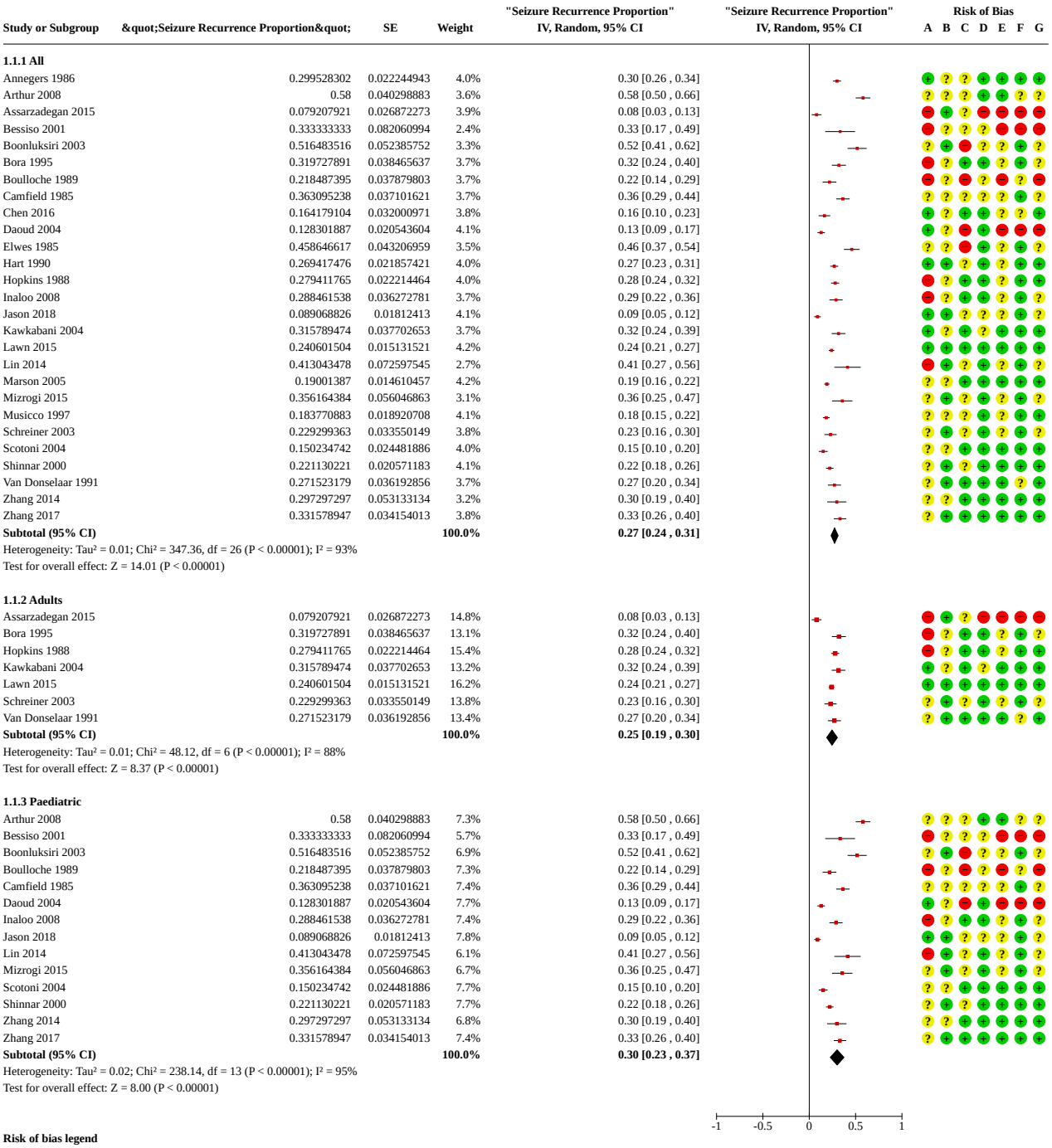
Figure 4.



We judged the certainty of the evidence to be moderate. We downgraded the certainty of evidence due to high levels of statistical heterogeneity between studies (Summary of findings 1).

Seizure recurrence at on year

The forest plot for seizure recurrence at one year is shown in Figure 5. Overall estimated seizure recurrence at one year for all studies (34 studies, 6843 participants) was 36% (95% CI 33% to 40%) with very high study heterogeneity (I^2 = 89%). As shown for seizure recurrence at six months, the estimated seizure recurrence rate for adults (9

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studies, 2468 participants) was lower than for all studies at 35% (95% CI 31% to 38%), but with lower study heterogeneity (I^2 = 64%), whilst the estimated seizure recurrence rate for children (16 studies, 2313 participants) was higher at 38% (95% CI 31% to 44%) with very high study heterogeneity (I^2 = 90%).

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Figure 5.

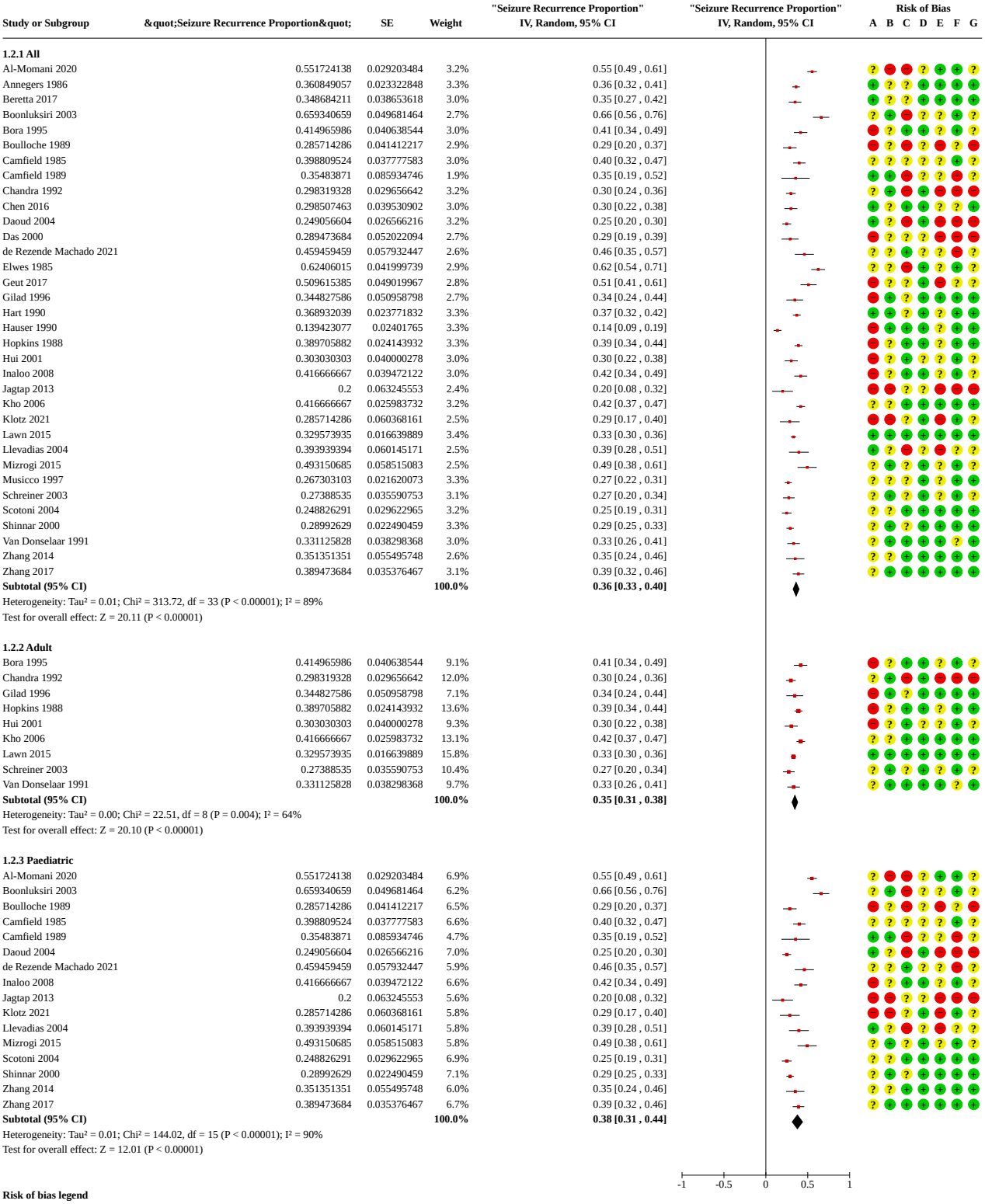

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Figure 5. (Continued)

(C) Prognostic factor measurement
(D) Outcome measurement
(E) Study confounding
(F) Statistical analysis and reporting
(G) Overall risk of bias

We judged the certainty of the evidence to be moderate; we downgraded the certainty of evidence due to high levels of statistical heterogeneity between studies (Summary of findings 2).

Seizure recurrence at two years

The forest plot for seizure recurrence at two years is shown in Figure 6. Overall estimated seizure recurrence at two years for all studies (27 studies, 6908 participants) was 43% (95% CI 39% to 47%) with very high study heterogeneity (I^2 = 92%). As shown for seizure recurrence at six months and at one year, the estimated seizure recurrence rate at two years was lower for adults (9 studies, 2043 participants) than for all studies at 41% (95% CI 37% to 44%) with lower estimated study heterogeneity (I^2 = 58%), whilst the estimated seizure recurrence rate for children (12 studies, 2172 participants) was higher at 45% (95% CI 36% to 54%), with very high study heterogeneity (I^2 = 95%).

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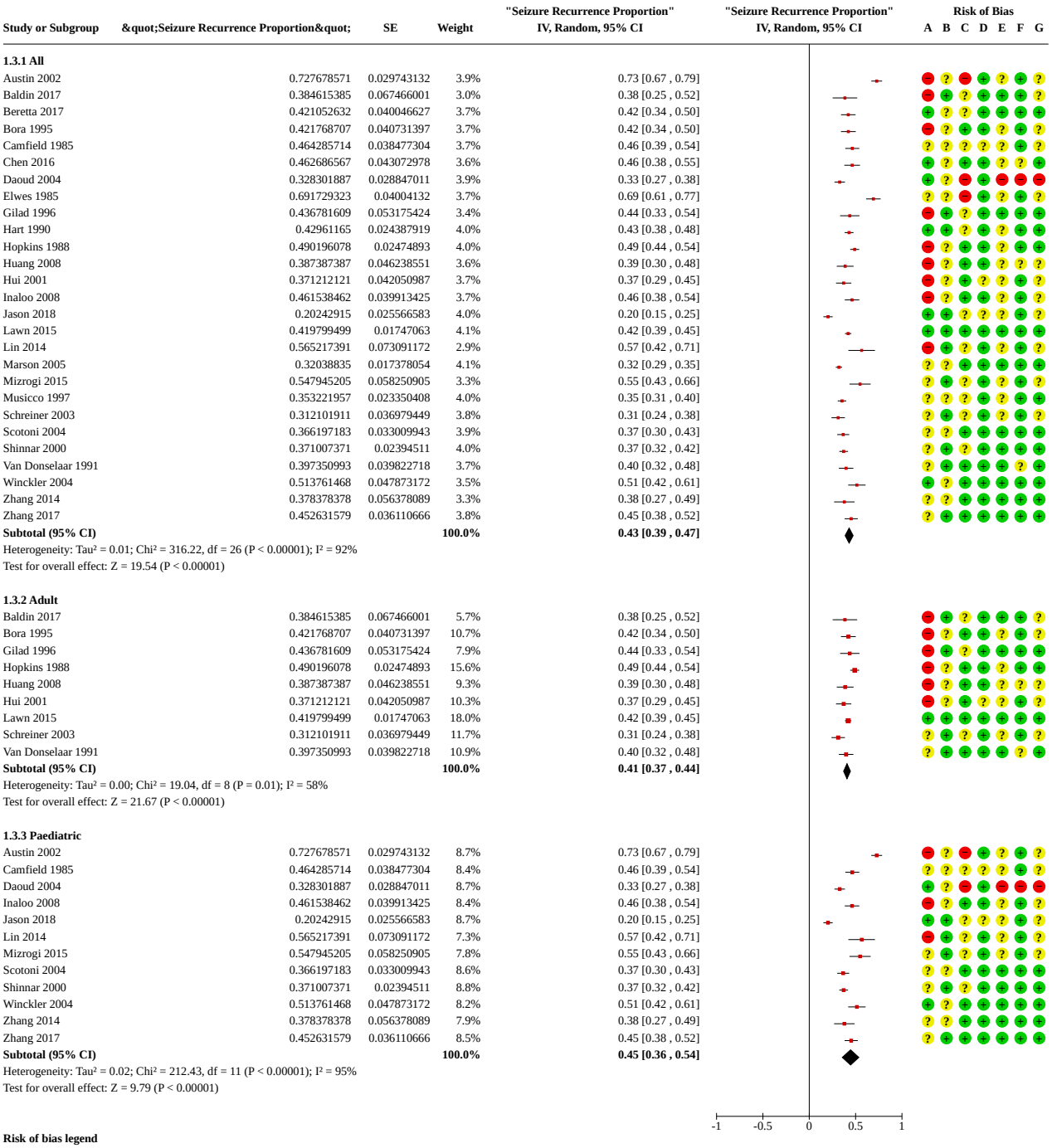
Figure 6.



We judged the certainty of the evidence to be moderate; we downgraded the certainty of evidence due to high levels of statistical heterogeneity between studies (Summary of findings 3).

We assessed publication bias for all three meta-analyses by visually assessing funnel plots of ten randomly selected studies, with no significant evidence of publication bias.

Mortality following a first unprovoked seizure

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Results relating to mortality following a first unprovoked seizure were reported in nine studies including 2373 participants (Bell 2016; Benn 2009; Hesdorffer 2009; Kawkabani 2004; Leone 2006; Leone 2011; Logroscino 2008; Loiseau 1999; Shinnar 2005). Meta-analysis of mortality results could not be conducted due to variability in the reporting of results. A summary of study SMRs at different time points, where given, are detailed in Table 2.

In the prospective cohort study by Loiseau, one-year mortality was calculated for 505 people with a first unprovoked seizure. Overall, the standardised mortality ratio (SMR) was 4.1 (95% CI 2.5 to 6.2). Mortality was related to underlying seizure aetiology with no deaths reported with an idiopathic seizure (SMR 0), an SMR of 1.6 (95% CI 0.4 to 4.1) for those with a cryptogenic seizure and an SMR of 19.8 (95% CI 14.0 to27.3) for those with a remote symptomatic seizure or a seizure in a progressive condition. (Loiseau 1999).

In the prospective cohort study by Shinnar of 407 children following a first unprovoked seizure followed up for a mean of 14.2 years, nine children died. Four deaths were considered to be unrelated to the seizure, all four children did not have any further seizures and were not on anti-seizure medication. In contrast, the other five children who died all had refractory epilepsy on multiple medications and four of the deaths were considered to possibly be SUDEP (sudden unexpected death in epilepsy) related. It was concluded that initiating treatment after the first seizure would not have altered mortality in any of the five cases (Shinnar 2005).

Delaying treatment after a first generalised tonic-clonic seizure was also not found to mortality in a long-term follow-up analysis of 419 patients in the FIRST study. Patients were followed up for a median 19.2 years (0.2 to 21.5 years), during which time 40 people (9.6%) died, 19 (8.9%) in the immediate treatment group and 21 (10.3%) in the delayed treatment group. The probability of survival at all time points was comparable in the immediate versus the delayed treatment groups (one year (100%), five years 97% (95% CI 95% to 99%) versus 98% (95% CI 95% to 100%)), 10 years, 94% (95% CI 91% to 97%) versus 97% (95% CI 94% to 99%) and 20 years (91% (95% CI 87% to 95%) versus 89% (95% CI 85% to 94%)) (P = 0.7). In multivariate analysis, the only significant predictor of higher mortality (HR (hazard ratio) 3.4 (95% CI 2.5 to 4.3)) was a remote symptomatic aetiology, with mortality being highest in those failing to achieve a five-year seizure remission (Leone 2011).

In the NGPSE (Hart 1990; Bell 2016), 302 people with a single unprovoked seizure were followed up for a median of 17 years (10.0 to 24.1) years during which 109 (36%) died. The SMR was 2.65 (95% CI 2.23 to 3.15) in those with a single seizure at presentation, with the SMR being highest if the first seizure was in childhood (<18 years: SMR 5.34 (95% CI 3.32 to 8.59))compared to those with the first seizure later in life (≥18 years: SMR 1.89 (95% CI 1.75 to 2.25)). In the 146 people with a single seizure who went into early remission (defined as no recorded seizures after the first year of follow-up) and had more than two years follow-up, the SMR was 1.86 (95% CI 1.40 to 2.46), whilst in 112 people who ever had a single notified seizure and greater than one-year follow-up the SMR was 1.57 (SMR 95% CI 1.15 to 2.13) (Bell 2016).

In a retrospective study of reported seizures in Northern Manhattan over a three-year period, 123 people were identified with a single seizure with a case fatality of 14.6% (18/123) observed, with the majority of deaths being attributable to malignant neoplasms. Cardiovascular disease and pneumonia and influenza (Benn 2009).

One prospective study compared the 10-year mortality following a first unprovoked seizure with that following a first of idiopathic episode of status epilepticus. Two-hundred and ninety-one people with a first unprovoked seizure were identified compared to 16 with status epilepticus. At 10 years, there were five deaths (31.2%) in the status epilepticus compared to 27 (9.3%) in the seizure group. Kaplan-Meier analysis estimated the cumulative mortality at 10 years was to be 32.3% and 11.8%, respectively. The SMR for status epilepticus at 10 years compared to the general population was 2.6 (95% CI 0.8 to 5.3) compared to an SMR of 1.2 (95% 0.8 to 1.6) for those with a first unprovoked seizure and an SMR of 1.3 (95% CI 0.9 to1.8) for a first unprovoked seizure of any type (307). Amongst those aged > 65 years, status epilepticus was associated with a higher risk of mortality (SMR 3.18 (95% CI 1.01 to 6.60)), but not a first unprovoked seizure of short duration (SMR 0.73 (95% CI 0.39 to 1.18)). In those who did not develop epilepsy (184/307 (59.9%)) the cumulative risk of mortality was comparable in the status epilepticus (20%) and seizure group (13.7%) (P = 0.5). In those who had further unprovoked seizures (127/307 (40.0%)), the cumulative risk of mortality at 10 years was 60% in the status epilepticus group and 9.6% in the seizure group. After adjusting for age and sex, the presence of status epilepticus was associated with an increased risk of death amongst those who developed epilepsy, there was no increased risk conferred in those who did not have a seizure recurrence (Logroscino 2008).

The final study assessed the mortality associated with three aetiologies (CVA, TBI and CNS Infections), comparing those with an acute symptomatic seizure to those with an unprovoked seizure for each aetiology with the 30-day and 10-year mortality for each group calculated. A first acute symptomatic seizure was associated with a significantly higher risk of 30-day mortality (21.4% (95% CI 16.9% to 26.9%)) compared to a first unprovoked seizure (3.4% (95% CI 1.4% to 7.9%) P < 0.001). Those with an acute symptomatic seizure had a rate ratio (RR) of 6.9 times more likely to die within 30 days compared to those with an unprovoked seizure (95% CI 2.8 to 17.3). The 30-day mortality for those with an unprovoked seizure with stroke was 5.0% (95% CI 2.1% to 11.5%), whilst there were none observed at 30 days after a first unprovoked seizure in the TBI and CNS Infections groups. Amongst 30-day survivors the 10-year mortality was comparable for those with acute symptomatic and unprovoked seizures (RR 1.0 (95% CI 0.7 to 1.5). Specifically, the 10-year mortality for those with an unprovoked seizure and stroke was 71.6% (95% CI 61.0 to 81.4)), and an unprovoked seizure and TBI was 28.1% (95% CI 15.6% to 47.4%). There were no observed deaths at 10 years in those with an unprovoked seizure and CNS infection (Hesdorffer 2009).

Seizure recurrence in specific populations

In a cohort of 63 participants with a moderate to severe traumatic brain injury, who had a late post-traumatic seizure (>7 days following the head injury), the risk of a further unprovoked seizure was 47% at one month, 69% at six months, 82% at one year and approximately 86% at two years (Haltiner 1997).

The risk of a further unprovoked seizure at 10 years was calculated at 71.5% (95% CI 59.7% to 81.9%) for those with stroke, 46.6% (95% CI 30.4% to 66.3%) for those with a TBI, and 63.5% (95% CI 21.2% to 98.6%) for those with a CNS infection (Hesdorffer 2009).

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In those with a single episode of idiopathic status epilepticus, 5 out of 16 (31.3%) developed epilepsy at 10-year follow-up (Logroscino 2008).

Individuals with a first unprovoked seizure and dementia were identified using the Swedish Dementia Register and were matched by age and gender to controls with a first unprovoked seizure without dementia. The five-year risk of developing subsequent epilepsy after a first unprovoked seizure was 32% (95% CI 27% to 37%) for those with dementia and 31% (95% CI 25% to 38%) in controls. The five-year risk of epilepsy was 48% (95% CI 37% to 59%) for those aged 70 years and below and 26% (95% CI 21% to 30%) for those aged 70 years and above. The five-year risk of developing subsequent epilepsy, calculated by dementia subtype, was highest amongst those with early onset Alzheimer's (50% (95% CI 33.3% to 66.7%)), followed by Frontotemporal dementia (39% (95% CI 11.2% to 66.8%)), unclassified dementia (35.3% (95% CI 23.0% to 47.6%)), mixed type dementia (34.1% (95% CI 23.1% to 45.1%)), and vascular dementia (26.4% (95% CI 17.6% to 35.2%)). The lowest risk of subsequent epilepsy was seen in those with Lewy body dementia (8.5% (95% CI 0.0% to 19.9%)) and Parkinson's disease with dementia (10.0% (95% CI 0.0% to 23.1%) (Mahamud 2020).

Seizure recurrence beyond two years

Twenty-five studies (24 cohorts; 6774 participants) reported seizure recurrence rate beyond two years, with the majority reporting seizure recurrence rates for five years or less (summarised in Table 3), with only three studies (1252 participants) reporting recurrence rates at 10 years or more (Lawn 2015; Bell 2016; Beretta 2017).

In the NGPSE in the 302 people with a single unprovoked seizure at presentation, the probability of remaining seizure-free at five years from the first seizure was 43% (95% CI 37% to 49%), 39% (95% 33% to 44%) at 10-years from the first seizure, 38% (95% CI 33% to 44%) at 15-years, 38% (95% CI 33% to 44%), at 20-years and 36%(95% CI 30% to 42%) at 25-years. In those who presented with a single seizure and remained seizure-free for the first five years (n = 113), the probability of remaining seizure-free at 10-years was 90%(95% CI 82% to 94%) 89%(95% CI 81% to 93%), at 15-years, 89%(95% CI 81% to 93%), at 20 years 83%(95% CI 72% to 90%) at 25-years. For those who presented with a single seizure and remained seizure-free for the first 10 years (n = 94), the probability of remaining seizure-free at 15 years was 99%(95% CI 92% to 99.8%), 99%(95% CI 92% to 99.8%) at 20-years and 92% (95% CI 80% to97%) (Bell 2016).

In a multicentre retrospective cohort study, 1006 patients with newly diagnosed epilepsy were followed up over a median 16 years (10 to 57 years), comparing seizure recurrence in 854 (84.9%) people diagnosed with epilepsy using the traditional definition of epilepsy (TD) (defined as two or more unprovoked seizures more than 24 hours apart) and 152 people (15.1%) were diagnosed with epilepsy using the new definition (ND) (one unprovoked (or reflex) seizure and an estimated probability of seizure recurrence occurring over the next 10 years or diagnosis of an epileptic syndrome (Fisher 2014)). 92% of those with the ND of epilepsy were started on treatment within one month of the first unprovoked seizure (comparable to those with the TD). The probability of occurrence of a second unprovoked seizure was 34.2% at one year, 42.1% at two years, 66.5% at five years, 83.6% at 10 years, and 89.1% at 15 years, consistent with the ND with a probability of > 60% seizure recurrence at 10 years (Beretta 2017).

Certainty of the evidence (GRADE)

The evidence presented was of moderate certainty. Most studies showed reasonably consistent results, although there was heterogeneity it appeared to be driven by a few studies which showed quite extreme results compared to the others. This heterogeneity was the main driving factor to downgrade the certainty of the evidence by one level. This moderate level of certainty applied across all three time points, (6 m, 12 m and 24 m) and for adults, children and all studies. The evidence was not downgraded further as it was thought that the heterogeneity did not impact on the overall results too much.

DISCUSSION

Summary of main findings

Seizure recurrence

When counselling people with a first unprovoked seizure as to their risk of a further unprovoked seizure, clinicians are faced with a lack of clarity in the evidence with significant variation in the estimates provided. The primary aim of this review was to provide more precision as to the risk of seizure recurrence at specific time points. We included 46 studies in the meta-analysis, out of 58 included studies in the review, with an estimated seizure recurrence at six months of 27% (95% CI 24% to 31%), 36% (95% CI 33% to 40%) at one year and 43% (95% CI 37% to 44%) with slightly lower estimates for adults and slightly higher estimates for children. It was impossible to provide a summary estimate of the risk of seizure recurrence beyond these time points. Most of the included studies had a short follow-up, and few studies presented recurrence rates at a single time point beyond two years. Few studies had a follow-up period beyond 10 years, and only one, the NGPSE (Bell 2016) provided recurrence risks beyond 20 years. The early (and small) randomised controlled trials (RCTs) of short follow-up duration suggested an apparent reduction in seizure recurrence in immediate versus delayed treatment. This initial benefit is lost with longer follow-up with near-identical rates of three year- and five-year remission achieved in those in whom treatment was initiated or delayed after a first unprovoked seizure, as demonstrated by the MESS (Marson 2005) FIRST (Musico 1997 [https://revman.cochrane.org/#/584919020710582866/dashboard/htmlView/current?revertEnabled=false&versionWithProductionChanges=false#STD-Musico-1997]) studies.

Mortality following a single unprovoked seizure

Similarly, this study tries to clarify the associated mortality with a first unprovoked seizure. Overall, the data seem to support the consensus that the underlying aetiology mainly drives the underlying risk of mortality with a first unprovoked seizure. Those with a remote symptomatic aetiology and failure to achieve seizure remission are the most important predictors of mortality. In particular, those with an idiopathic or cryptogenic first seizure did not appear to be at a higher risk of premature mortality than the general population. Delaying treatment following a first unprovoked seizure did not increase the risk of early death. In summary, the primary driver of mortality following a first unprovoked seizure appears to be the underlying aetiology, but nevertheless this is with the caveat that we did not undertake any formal assessment of prognostic factors for mortality in this review.

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Comparison with other studies or reviews

Given the clinical importance of the risk of seizure recurrence following a first unprovoked seizure, there have been surprisingly few studies, other than narrative reviews covering clinical aspects of first seizures such as (Jiménez-Villegas 2021), addressing this question. Those systematic reviews (and meta-analysis), where these have been done, has been in children. In an early systematic review and meta-analysis, the risk of seizure recurrence in 16 studies was given as 51% overall (to last follow-up) with a reported recurrence rate range of 23% to 71%. At or near two years seizure recurrence rate was estimated to be 36% and 47% in prospective and retrospective studies, respectively (Berg 1991). A more recent meta-analysis again in children from six studies in 815 neurologically and developmentally normal children (aged 1 month to 17.5 years) gave an estimated seizure recurrence rate within three years of 45% (95% CI 37% to 60%) (Garcia 2017), which is broadly in line with our results. For adults, we found no systematic reviews/meta-analyses to guide clinical practice.

In terms of mortality we only identified one early mortality review based on a small number of studies, with the authors concluding that mortality is largely driven by underlying aetiology, is higher in children and highest in the first year following the seizure. In contrast, it was concluded that a single idiopathic unprovoked seizure was probably not associated with increased mortality (Beghi 2005).

Overall completeness and applicability

The primary aim of this review was to provide clarification as to the risk of seizure recurrence following a first unprovoked seizure in children and adults. In providing seizure recurrence estimates at 6 months, 12 months, 24 months as well as providing a narrative overview of seizure recurrence beyond two years, is of practical clinical utility. In particular, having accurate estimates for seizure recurrence at si6 and 12 months, is important as this is the time period that patients with a first seizure are typically excluded from driving in most countries. This is also the typical duration of follow-up that is offered to patients in a First Seizure clinic. Having a seizure recurrence estimate at two years is similarly of clinical importance as this is the time point that patients with seizures are considered in seizure remission. It was our intention to provide clear separate seizure recurrence estimates following a first unprovoked seizure for people treated and not treated with anti-seizure medications, but this was not possible. In many cases it was not possible to separate those treated and not treated with patients typically grouped together. This was a feature of most studies other than the RCTS such as the Mess (Marson 2005) and the FIRST study (Leone 2006; Musicco 1997). Indeed, the recent ILAE definition of epilepsy, where someone can be diagnosed with epilepsy following a single seizure with a clear epileptic syndromic diagnosis on EEG further complicates the picture (Fisher 2014). This is reflected in the most recent large cohort studies from Australia (Lawn 2015) and Italy (Beretta 2017), where a large number of people started on anti-seizure medication (ASMs) following a first unprovoked seizure. This has implications for future research.

Potential biases in the review process

One of the major issues of the review process relates to the fact that this is an overall prognosis review whilst the available tools for data extraction (CHARMS) and assessment of study bias (QUIPS and PROBAST) are specifically designed for prognostic factors studies (CHARMS and QUIPS) and prognostic models studies (PROBAST). This necessitated modification of these tools to allow their adaption potentially introducing bias as well as a sub-optimal assessment of bias. In discussion with the Cochrane Prognostic Methods Group, it is hoped that an extraction tool and bias assessment tool specific for overall prognosis reviews will be developed in time.

Certainty of the evidence

The limitations of the findings of this review are inherent in the evidence. There was significant heterogeneity between the included studies, with the result that any summary statistics need to be interpreted with caution. Repeat sensitivity analysis following exclusion of studies considered at the highest risk of bias did not significantly change the observed heterogeneity. This is something that we will try to explore further in the prognostic factors review (Adan 2021). This is particularly the case with the paediatric studies (with the I^2 scores consistently >90%), where there was significant variation in how the specific age group was defined, ranging from one month to three years in one study to one month to 19 years in another. Secondly, we had initially intended to present the risk of seizure recurrence separately for those treated and not treated. This was not possible as most studies contained a combination of treated and untreated individuals. Accordingly, it was necessary to provide recurrence rates for the combined groups even when recurrence rates for the two groups were presented separately, as in the MESS study. Combining treated and untreated people in a single cohort will undoubtedly become more widespread given the new ILAE definition of epilepsy. A diagnosis of epilepsy following a first unprovoked seizure can be if the risk of seizure recurrence is estimated to be > 60% at ten years (Fisher 2014), as discussed above.

Implications and recommendations for future research

There is a clear need to standardise definitions in terms of age as to what constitutes the different age groups in prognostic studies. It is also apparent that further studies of first seizure cohorts need to clearly differentiate between people who are treated and not treated to allow for the separate prognosis for the two groups to be delineated. Moreover, there is a need for longer prospective cohort studies to give a clearer consensus on seizure recurrence rates beyond two years. Finally, tools for data extraction and assessment of bias need to be developed for overall prognosis studies in the future.

AUTHORS' CONCLUSIONS

With moderate certainty and despite the limitations of the data, we find that providing summary estimates for the risk of seizure at six months, one year and two years for both children and adults provides useful information for the clinician counselling patients (or their parents) on the risk of further seizures in the short term whilst acknowledging the paucity of long-term recurrence data, particularly beyond 10 years.

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West 2019

West S, Nevitt SJ, Cotton J, Gandhi S, Weston J, Sudan A, et al. Surgery for epilepsy. *Cochrane Database of Systematic Reviews* 2019, Issue 6. Art. No: CD010541. [DOI: 10.1002/14651858.CD010541.pub3]

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Neligan 2021

Neligan A, Adan G, Nevitt SJ, Pullen A, Sander JW, Marson AG. Prognosis of adults and children following a first unprovoked seizure. *Cochrane Database of Systematic Reviews* 2021, Issue 1. Art. No: CD013847. [DOI: 10.1002/14651858.CD013847]

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Al-Momani 2020

Study characteristics	
Notes	Retrospective cohort, paediatric study: 1mth-16 yrs, excluded: Previous febrile seizures, absences, myoclonus, participant number: 290

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
Study confounding	Yes	Univariate and multivariate analysis conducted
Statistical analysis and reporting	Yes	Appropriate statistical methods applied include modelling of data
Overall risk of bias	Unclear	Moderate

Annegers 1986

Study characteristics	
Notes	Retrospective Registry, paediatric and adult, exclusion criteria: absences, myoclonus and infantile spasms. ASMs given to 60.6% of participants. Participant number: 424.

Item	Authors' judgement	Support for judgement
Study participation	Yes	Clear inclusion/exclusion criteria with large numbers of participants
Study attrition	Unclear	Moderate drop off rate over the follow-up period
Prognostic factor measurement	Unclear	Limited prognostic factors are considered in the study

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Annegers 1986 *(Continued)*

Outcome measurement	Yes	Clear and well-defined outcomes with clear time points in the data reporting
Study confounding	Yes	Multiple corrections for confounding factors made
Statistical analysis and reporting	Yes	Appropriate employment of the statistical methods of the time of publication include modelling
Overall risk of bias	Yes	Low

Arthur 2008

Study characteristics	
Notes	Prospective cohort, paediatric: 6-14 yrs, Absences, myoclonus, infantile spasms excluded, no mention of ASM administration, participant number: 140

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Exclusion of children with absence and other none motor seizures
Study attrition	Unclear	No clear mention of study dropout or loss to follow-up provided
Prognostic factor measurement	Unclear	A reasonable number of prognostic factors have been extracted for the purposes of the study
Outcome measurement	Yes	clear time points and outcomes defined in the study
Study confounding	Yes	Adjusted for missing data.
Statistical analysis and reporting	Unclear	Apropiate use of statistical methods to analyse and present results
Overall risk of bias	Unclear	Moderate

Assarzadegan 2015

Study characteristics	
Notes	Prospective RCT, GTCS only included, no specific mention of status epilepticus but no cases recorded, unclear age of included participants, partial treatment of participants with ASMs, participant number: 101

Item	Authors' judgement	Support for judgement
Study participation	No	Unclear age criteria
Study attrition	Yes	Low dropout rate and loss to follow-up reported

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Assarzadegan 2015 *(Continued)*

Prognostic factor measurement	Unclear	Compares treated and untreated participants
Outcome measurement	No	Follow-up only at 6 months
Study confounding	No	No adjustment attempted
Statistical analysis and reporting	No	No adjustment
Overall risk of bias	No	High risk

Austin 2002

Study characteristics	
Notes	Prospective cohort, paediatric cohort: 4-14 yrs. All seizures included in study - focal aware seizures and absences. ASMs given. 225 participants.

Item	Authors' judgement	Support for judgement
Study participation	No	Prospective multicentre study, clear selection criteria - bias as not representative ages 4-14 for a paediatric cohort and no justification given for age... also children with febrile seizures excluded
Study attrition	Unclear	Unclear dropout rate
Prognostic factor measurement	No	Not relevant to seizure recurrence but prognostic factors are not the primary end point of the study
Outcome measurement	Yes	Adequately reported outcomes at multiple time points
Study confounding	Unclear	Children included in the study compared with healthy siblings
Statistical analysis and reporting	Yes	Appropriate methods applied
Overall risk of bias	Unclear	Moderate

Baldin 2017

Study characteristics	
Notes	Prospective cohort. Adult cohort, No mention of ASMs or seizure types. 52 participants.

Item	Authors' judgement	Support for judgement

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Baldin 2017 *(Continued)*

Study participation	No	Ascertainment methods different for each recruiting site. Poor response rate of 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
Study confounding	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	Prospective cohort. All age cohort. 302 participants but missing data in 22 participants (324-22).

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
Study confounding	Yes	Multiple adjustments
Statistical analysis and reporting	Yes	Appropiate analysis applied to the data
Overall risk of bias	Yes	Low

Benn 2009

Study characteristics	
Notes	Retrospective Registry. Paediatric and Adult cohort. 123 participants.

Item	Authors' judgement	Support for judgement

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Benn 2009 *(Continued)*

Study participation	No	Unable to clearly differentiate between acute symptomatic and unprovoked, retrospective registry
Study attrition	Unclear	No mention of missing data or any participants have been lost to follow-up
Prognostic factor measurement	Unclear	No prognostic factors measured
Outcome measurement	Yes	Well-defined outcome and consistent amongst all participants
Study confounding	Yes	Adjusted according to cause and race/demographic
Statistical analysis and reporting	Yes	Appropriate analysis
Overall risk of bias	Unclear	Moderate

Beretta 2017

Study characteristics	
Notes	Multicentre retrospective cohort study. All ages in cohort. Focal aware, unaware and generalised seizures all included. ASMs given to most participants - 92.8%. 152 participants.

Item	**Authors' judgement**	**Support for judgement**
Study participation	Yes	Very well-defined recruitment criteria
Study attrition	Unclear	Unclear if missing data recorded or complete data sets for all patients
Prognostic factor measurement	Unclear	Prognostic factors not applicable
Outcome measurement	Yes	Clearly defined and reported
Study confounding	Yes	Multiple adjustments made in analysis
Statistical analysis and reporting	Yes	Data appropriately and comprehensively reported in study
Overall risk of bias	Yes	Low

Bessiso 2001

Study characteristics	
Notes	Prospective cohort. Paediatric cohort - 2mths-12 yrs. Absences, myoclonus and infantile spasms all excluded. ASMs given to some participants (5/33 15.1%). 33 participants.

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Bessiso 2001 *(Continued)*

Item	Authors' judgement	Support for judgement
Study participation	No	Small sample size despite limited exclusion criteria, some are treated
Study attrition	Unclear	Limited follow-up data presented - no mention of follow-up
Prognostic factor measurement	Unclear	Conflates imaging data - MRI and CT otherwise reasonable
Outcome measurement	Unclear	Poorly reported but 6 month outcomes presented
Study confounding	No	No adjustment for key variables - some patients treated (5/31) after first seizure
Statistical analysis and reporting	No	Limited detail of statistical methodology used and justification
Overall risk of bias	No	High

Blom 1978

Study characteristics	
Notes	Prospective cohort. Paediatric cohort: <16 yrs. ASMs given to some participants. All seizures including focal aware seizures and absences. 71 participants.

Item	Authors' judgement	Support for judgement
Study participation	No	Unclear inclusion criteria
Study attrition	No	No clear reason for loss of follow-up given
Prognostic factor measurement	Unclear	Limited prognostic factors taken into account
Outcome measurement	No	Unclear outcome reporting
Study confounding	Unclear	Descriptive study only
Statistical analysis and reporting	Unclear	Descriptive study only
Overall risk of bias	No	High

Boonluksiri 2003

Study characteristics	
Notes	Prospective cohort. Paediatric cohort: 2mths - 15 yrs. Status epilepticus included.Absences, myoclonus, infantile spasms excluded. No ASMs given. 91 participants.

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Boonluksiri 2003 *(Continued)*

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Unclear how participants are identified
Study attrition	Yes	No apparent loss to follow-up
Prognostic factor measurement	No	No brain imaging for cohort, CT scan only in a proportion
Outcome measurement	Unclear	Defines what a seizure recurrence but relatively short follow up period (9.9months per participant)
Study confounding	Unclear	Performs a multivariate analysis but not completely accounting for most factors
Statistical analysis and reporting	Yes	Appropriate statistical methodology applied and presentation of data
Overall risk of bias	Unclear	Moderate

Bora 1995

Study characteristics	
Notes	Prospective cohort. Adult cohort > 16 years. GTCS only. ASMs given (42.2%). No specific mention of status epilepticus but no cases recorded. 147 participants.

Item	Authors' judgement	Support for judgement
Study participation	No	Risk of bias introduced as only those with generalised tonic clonic seizures and normal imaging on CT were included
Study attrition	Unclear	Minimal loss to follow-up
Prognostic factor measurement	Yes	Very comprehensive
Outcome measurement	Yes	Well outlined and documented
Study confounding	Unclear	Attempts to control for some factors
Statistical analysis and reporting	Yes	Well-described methodology with multiple Kaplan Meier curves
Overall risk of bias	Unclear	Moderate

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Boulloche 1989

Study characteristics	
Notes	Prospective cohort, single-centre paediatric cohort 2-16yrs. GTCS only included. 73(61%) prescribed ASMs. 119 participants.

Item	Authors' judgement	Support for judgement
Study participation	No	Only generalised seizures included and also excluded those who had focal abnormalities on EEG
Study attrition	Unclear	Unclear re loss to follow-up
Prognostic factor measurement	No	All abnormal imaging has been excluded from the study
Outcome measurement	Unclear	Reasonable description of outcomes
Study confounding	No	61% of sample had ASMs started
Statistical analysis and reporting	Unclear	Dated statistical methods employed
Overall risk of bias	No	High

Camfield 1985

Study characteristics	
Notes	Retrospective Registry. Paediatric cohort: 1mth - 16 yrs. No specific mention of status epilepticus but no cases recorded. ASMs given to 68.5%. Exclusion criteria: absences, myoclonus and infantile spasms. Focal aware, unaware and generalised seizures all included. 168 participants.

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Works on the assumption that all children after a first seizure would get an EEG
Study attrition	Unclear	80% response rate for postal survey
Prognostic factor measurement	Unclear	Limited prognostic factors considered
Outcome measurement	Unclear	Not clear how seizure recurrence defined
Study confounding	Unclear	Partial treatment of cohort
Statistical analysis and reporting	Yes	Appropriately analysed and reported
Overall risk of bias	Unclear	Moderate

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Camfield 1989

Study characteristics	
Notes	Prospective RCT. Paediatric cohort: 1mth - 16 yrs Absences, myoclonus and infantile spasms excluded. 31 participants.

Item	Authors' judgement	Support for judgement
Study participation	Yes	Very clearly defined study population
Study attrition	Yes	No issues with drop out of study
Prognostic factor measurement	No	Only prognostic factor considered is treatment
Outcome measurement	Unclear	Unclear definition of recurrence and how it is established
Study confounding	Unclear	Some attempts made to ensure factors were controlled for
Statistical analysis and reporting	No	Small study numbers so only simple comparative stats performed
Overall risk of bias	Unclear	Moderate

Chan 2012

Study characteristics	
Notes	Nested case control study. Retrospective cohort. Paediatric cohort: 1mth -15 yrs. Status epilepticus excluded. ASMs given but numbers unclear from study. 54 participants.

Item	Authors' judgement	Support for judgement
Study participation	No	Over 50% uncontactable - large proportion of eligible patients not recruited
Study attrition	Unclear	Unclear dropout rate or follow-up
Prognostic factor measurement	Unclear	Reasonable spread of prognostic factors collected
Outcome measurement	No	Unclear outcomes that are being measured in the study
Study confounding	Unclear	Multivariate analysis attempted to control for confounding factors
Statistical analysis and reporting	No	Data are not transparent and easily interpretable
Overall risk of bias	No	High

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Chandra 1992

Study characteristics	
Notes	Prospective double-blind RCT. Adult cohort > 16 years. Focal aware, unaware and generalised seizures. 228 participants.

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Single centre, adult patients with a low number of eligible patients declined with a reasonable number recruited despite being a single centre.
Study attrition	Yes	Only 6 out of 234 declined or dropped out of the study
Prognostic factor measurement	No	Only looking at one variable - the impact of treatment vs no treatment.
Outcome measurement	Yes	Careful consideration of outcome and well detailed in the paper
Study confounding	No	No adjustment undertaken
Statistical analysis and reporting	No	Raw data on recurrence presented only, no modelling performed.
Overall risk of bias	No	Simple descriptive study, no statistical analysis performed.

Chen 2016

Study characteristics	
Notes	Prospective cohort. Ages of participant: 3-77yrs. No ASMs Absences, myoclonus and unspecified seizures excluded. SE included. 134 participants.

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
Study confounding	Unclear	Unclear if controlled for variables that could effect outcomes
Statistical analysis and reporting	Unclear	Univariate analysis undertaken only, no multivariate analysis performed

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Chen 2016 *(Continued)*

Overall risk of bias	Yes	Low

Daoud 2004

Study characteristics	
Notes	Prospective cohort. Paediatric cohort: 3mths-14 yrs. SE included. No ASMs. Absences, myoclonus, infantile spasms excluded. 265 participants.

Item	Authors' judgement	Support for judgement
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 eg EEG and brain imaging due to cost limitations
Outcome measurement	Yes	Detailed reporting of recurrence at several time points that are well described
Study confounding	No	No adjustments undertaken
Statistical analysis and reporting	No	Univariate analysis only no multivariate analysis performed
Overall risk of bias	No	High

Das 2000

Study characteristics	
Notes	Prospective RCT. Age of cohort: 0-50yrs. ASMs given (45%). GTCS only included. 76 participants.

Item	Authors' judgement	Support for judgement
Study participation	No	Excludes those with febrile seizures in past also excludes childhood absence, unclear if recruitment consecutive
Study attrition	Unclear	Unclear dropout/retention rate in study
Prognostic factor measurement	Unclear	Some basic prognostic factors reported eg EEG findings
Outcome measurement	Unclear	Outcomes not clearly defined
Study confounding	No	No clear attempts employed for adjustments

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Das 2000 *(Continued)*

Statistical analysis and reporting	No	Basic statistical methods described
Overall risk of bias	No	High

de Rezende Machado 2021

Study characteristics	
Notes	Retrospective cohort. Paediatric cohort: 1mth -14yrs. ASMs given. No specific mention of SE but no cases recorded. Focal and generalised seizures included. 74 participants.

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	Recrrence rates presented but not very clearly defined with time points
Study confounding	Unclear	unclear that adjustments undertaken
Statistical analysis and reporting	No	No univariate or multivariate modelling undertaken and no survival curves presented
Overall risk of bias	Unclear	Moderate

Elwes 1985

Study characteristics	
Notes	Retrospective cohort. All ages. GTCS only included. No ASMs. 133 participants.

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Restricted to those with generalised tonic clonic seizures unclear if patients are representative
Study attrition	Unclear	Reasonable follow-up but no mention of dropout rates
Prognostic factor measurement	No	Limited description and measurement of relevant prognostic factors
Outcome measurement	Yes	Well described and presented

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Elwes 1985 *(Continued)*

Study confounding	Unclear	No mention of adjustments
Statistical analysis and reporting	Yes	Appropiate use of stats and presentation of data
Overall risk of bias	Unclear	Moderate

Geut 2017

Study characteristics	
Notes	Retrospective cohort. Paediatric cohort >6 yrs. Normal EEG, focal and generalised seizures make up inclusion criteria. No specific mention of SE but no cases recorded. No ASMs. 104 participants.

Item	Authors' judgement	Support for judgement
Study participation	No	Only convulsive seizures, only those with an EEG, which was normal - retrospective review, unclear if all patients were consecutive
Study attrition	Unclear	Retrospective study
Prognostic factor measurement	Unclear	Rudimentary description of prognostic factors eg MRI normal/abnormal - EEG changes are more specific in description
Outcome measurement	Yes	Well-described outcome in text
Study confounding	No	No adjustments made
Statistical analysis and reporting	Unclear	Limited stats techniques applied
Overall risk of bias	Unclear	Moderate

Gilad 1996

Study characteristics	
Notes	Prospective RCT. Adult cohort: 18-50 years. Treatment with CBZ for some participants. GTCS only included. SE excluded. 87 participants.

Item	Authors' judgement	Support for judgement
Study participation	No	Narrow age range for inclusion, had to present to hospital within 24 hours of seizure, only convulsive seizures included
Study attrition	Yes	Four patients out od 91 dropped out

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Gilad 1996 *(Continued)*

Prognostic factor measurement	Unclear	Limited prognostic factor measurement - mainly focused on recurrence
Outcome measurement	Yes	Well defined and represented
Study confounding	Yes	Adjustments attempted for a number of factors
Statistical analysis and reporting	Yes	Appropriate methods employed and described
Overall risk of bias	Yes	L

Haltiner 1997

Study characteristics	
Notes	Nested prospective cohort study. Adult cohort >16 yrs. 63/404 who had one late posttraumatic seizure. ASMs given. 63 participants.

Item	Authors' judgement	Support for judgement
Study participation	No	Very specific cohort of patients that is not generally representative of the wider population who will have an unprovoked seizure given nature of the study
Study attrition	Yes	Eight participants died, and 5 were lost to follow-up
Prognostic factor measurement	Yes	Extensive prognostic factors
Outcome measurement	Yes	Very well reported
Study confounding	Unclear	Unclear adjustment but also crossover between treated and untreated
Statistical analysis and reporting	Yes	Appropiate statistical methods applied with graphical representation in form of survival curves etc
Overall risk of bias	No	High

Hart 1990

Study characteristics	
Notes	Prospective cohort. All ages. ASMs given to 15%. 412 participants.

Item	Authors' judgement	Support for judgement
Study participation	Yes	Well-described cohort

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Hart 1990 *(Continued)*

Study attrition	Yes	low rates of loss to follow-up
Prognostic factor measurement	Unclear	Reasonable list of aetiologies given
Outcome measurement	Yes	Clear outcomes and definitions of end points
Study confounding	Unclear	Confounders mentioned but no clear adjustments made
Statistical analysis and reporting	Yes	Appropiate statistical analysis with kaplein meyer curves calculated
Overall risk of bias	Yes	Low

Hauser 1990

Study characteristics	
Notes	Prospective cohort. All ages included. Focal and generalised seizures. SE included. ASMs given (80%). 208 participants.

Item	Authors' judgement	Support for judgement
Study participation	No	Very narrow inclusion criteria - recruitment had to be within 24 hours
Study attrition	Yes	20 partixipants out of 208 withdrew from the study
Prognostic factor measurement	Yes	Well described
Outcome measurement	Yes	Well represented
Study confounding	Unclear	Some attempt to adjust made
Statistical analysis and reporting	Yes	Appropiate methods used
Overall risk of bias	Yes	Low

Hesdorffer 2009

Study characteristics	
Notes	Retrospective Registry. Case-control study. Acute vs unprovoked seizures in Stroke, TBI and CNS Infections. Stoke (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. SE (25.7%) included. All ages <1->65. 148 participants.

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Hesdorffer 2009 *(Continued)*

Item	Authors' judgement	Support for judgement
Study participation	Yes	Representative of wider population
Study attrition	Unclear	Case-control database study
Prognostic factor measurement	No	Rudimentary in selection of factors
Outcome measurement	Yes	well described and defined outcomes with time points clearly set out
Study confounding	Yes	Multiple adjustments made
Statistical analysis and reporting	Yes	Well described and represented
Overall risk of bias	Yes	Low

Hopkins 1988

Study characteristics	
Notes	Retrospective Registry. Prospective cohort. Adult cohort >16 yrs. Follow-up in single centre. Unclear if retrospective or prospective. ASMs given. No specific mention of SE but no cases recorded. 408 participants.

Item	Authors' judgement	Support for judgement
Study participation	No	Unclear inclusion criteria with bias involved
Study attrition	Unclear	No mention of dropout rate
Prognostic factor measurement	Yes	Good description of factors
Outcome measurement	Yes	Well-described outcomes
Study confounding	Unclear	Adjustments only for age and sex, unclear if others made
Statistical analysis and reporting	Yes	Appropiate statistical methods applied and reported
Overall risk of bias	Yes	Llow

Huang 2008

Study characteristics	
Notes	Prospective cohort. Single centre. Focal and generalised seizures, myoclonus. 22 (19.8%) SE. ASMs given. 111 participants.

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Huang 2008 *(Continued)*

Item	Authors' judgement	Support for judgement
Study participation	No	Specific cohort of patients, only those with hyperglycaemia - unclear if febrile seizures also were excluded
Study attrition	Unclear	No mention of dropout from study
Prognostic factor measurement	Yes	Comprehensive reporting of factors
Outcome measurement	Yes	Given recurrence rates in table format and in text
Study confounding	Unclear	Attempts made e.g. comparison between hyperglycaemic cohort and none DH
Statistical analysis and reporting	Unclear	Univariate analysis performed no multivariate modelling
Overall risk of bias	Unclear	Moderate

Hui 2001

Study characteristics	
Notes	Retrospective cohort. Single centre. Participants >14 years. GTCS only. Absences, myoconus, infantile spasms excluded.SE excluded. No ASMs. 132 participants.

Item	Authors' judgement	Support for judgement
Study participation	No	Multiple exclusion criteria makes it a none representative cohort
Study attrition	Unclear	Retrospective so unclear
Prognostic factor measurement	Yes	Multiple prognostic factors
Outcome measurement	Unclear	seizure recurrence until 4 years
Study confounding	Unclear	Some adjustment undertaken
Statistical analysis and reporting	Yes	Appropiate stats - univariate and multivariate, survival curves included
Overall risk of bias	Unclear	Moderate

Inaloo 2008

Study characteristics

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Inaloo 2008 *(Continued)*

Notes	Prospective cohort. Paediatric cohort: 1mth - 18yrs. Absences, myoconus, infantile spasms excluded. Focal and generalised seizures included. No specific mention of SE but no cases recorded. 156 participants.

Item	Authors' judgement	Support for judgement
Study participation	No	Excluded a number of presentations e.g. myoclonus and absence, also unclear if cases are consecutive
Study attrition	Unclear	No mention
Prognostic factor measurement	Yes	Lots of prognostic factors reported and displayed appropriately
Outcome measurement	Yes	Well documented
Study confounding	Unclear	Unclear if adjustments have been made
Statistical analysis and reporting	Yes	Uni- and multivariate analysis
Overall risk of bias	Unclear	Moderate

Jagtap 2013

Study characteristics	
Notes	Prospective cohort. Paediatric cohort: 1mth - 12yrs. Single centre. ASMs given (15 (37.5%)). 20% SE. Focal aware, unaware and generalised seizures. 40 participants.

Item	Authors' judgement	Support for judgement
Study participation	No	Unclear selection criteria, no inclusion or exclusion criteria
Study attrition	No	No mention of dropout despite short follow-up
Prognostic factor measurement	Unclear	Some factors measured but limited
Outcome measurement	Unclear	Seizure recurrence rates mention in text but 12 mths only
Study confounding	No	No adjustments, mixed treated and untreated
Statistical analysis and reporting	No	Descriptive stats only used
Overall risk of bias	No	High

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Jason 2018

Study characteristics	
Notes	Retrospective Registry. Paediatric cohort: 1mth-18 yrs. ASMs given. All seizures including focal aware seizures are included. 247 participants.

Item	Authors' judgement	Support for judgement
Study participation	Yes	Representative of a paediatric population
Study attrition	Yes	16/750 were lost before 2 years of follow-up
Prognostic factor measurement	Unclear	Not the relevant factors to seizure recurrence - more catered to neurodevelopmental abnormality
Outcome measurement	Unclear	Recurrence of seizure is not the main objective of paper
Study confounding	Unclear	Adjustments made
Statistical analysis and reporting	Yes	Extensive statistical methods explained
Overall risk of bias	Unclear	Moderate

Kanemura 2015

Study characteristics	
Notes	Prospective cohort, Paediatric cohort: 1mth-15yrs. Single centre. No ASMs. SE excluded. 87 participants.

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 4 years given
Study confounding	No	No adjustments
Statistical analysis and reporting	Unclear	No survival curves
Overall risk of bias	Unclear	Moderate

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Kawkabani 2004

Study characteristics	
Notes	Prospective cohort, adult cohort, Focal and generalised seizures. SE included. ASMs given. 58 participants.

Item	Authors' judgement	Support for judgement
Study participation	Yes	Very extensive criteria for study
Study attrition	Unclear	14% lost to follow-up at 6 months
Prognostic factor measurement	Yes	Lots of prognostic factors listed for inclusion
Outcome measurement	Unclear	Recurrence data only until 6 months
Study confounding	Yes	Adjustments performed
Statistical analysis and reporting	Yes	Multivariate and univariate analysis performed
Overall risk of bias	Yes	low

Kho 2006

Study characteristics	
Notes	prospective cohort, adult cohort. SE excluded. ASMs given. Provoked seizures included (497-137=360). Focal and generalised seizures. 360 participants.

Item	Authors' judgement	Support for judgement
Study participation	Unclear	inclusion/exclusion criteria well set out but unclear re: how exactly patients recruited, includes provoked and unprovoked
Study attrition	Unclear	No mention of dropouts
Prognostic factor measurement	Yes	Extensive reporting
Outcome measurement	Yes	Clear outcome given and survival curves clearly documented
Study confounding	Yes	Appropiate adjustments performed
Statistical analysis and reporting	Yes	Comprehensive analysis
Overall risk of bias	Yes	Low

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Klotz 2021

Study characteristics	
Notes	Prospective cohort. Paediatric cohort: age 0.2 -17.4. Focal and generalised seizures included. 56 participants.

Item	Authors' judgement	Support for judgement
Study participation	No	Very selective inclusion criteria - at least 10 minutes of good quality EEG with sample rate >1000 within the first 72 hours after seizure had to be available.
Study attrition	No	High drop out rate
Prognostic factor measurement	Unclear	Very specific measurement of EEG factors
Outcome measurement	Yes	Well described
Study confounding	No	No adjustment
Statistical analysis and reporting	Yes	Comprehensive
Overall risk of bias	Unclear	Moderate

Lawn 2015

Study characteristics	
Notes	Prospective cohort. Adult cohort. 21% treated with ASM. All seizures types included. SE not specifically mentioned. 798 participants.

Item	Authors' judgement	Support for judgement
Study participation	Yes	Very well described and clear inclusion/exclusion criteria
Study attrition	Yes	Forty- eight patients (6%) had <1 year of follow-up of whom 22 patients died within the first year.
Prognostic factor measurement	Yes	Lots of prognostic factors presented
Outcome measurement	Yes	Clear presentation of outcome
Study confounding	Yes	Controlled for variety of factors
Statistical analysis and reporting	Yes	Univariate and multivariate analysis, survival curves clearly presented
Overall risk of bias	Yes	Low

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Leone 2006

Study characteristics	
Notes	Prospective RCT. Paediatric and Adult cohort. GTCS only. 419 participants.

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Prospective RCT - clear inclusion/exclusion, some patients randomised to treatment which introduces bias
Study attrition	Yes	Low dropout rate and loss to follow-up
Prognostic factor measurement	Unclear	Ample prognostic factors measured
Outcome measurement	Yes	Cear outcomes and time points
Study confounding	Unclear	Some adjustment attempted for confounding factors
Statistical analysis and reporting	Yes	Appropriate analysis made for the age of paper
Overall risk of bias	Yes	Low

Leone 2011

Study characteristics	
Notes	Prospective RCT. Paediatric and Adult cohort. GTCS only (primary or secondary). Median follow-up 19.7 yrs. 419 participants.

Item	Authors' judgement	Support for judgement
Study participation	Yes	Well-defined inclusion/exclusion criteria
Study attrition	Yes	Low dropout rate in follow-up
Prognostic factor measurement	Unclear	Moderate reporting of prognostic factors
Outcome measurement	Yes	Clear measurement of outcomes
Study confounding	Unclear	Attempts for confounding adjustments
Statistical analysis and reporting	Unclear	appropriate use of statistical methodology
Overall risk of bias	Yes	Low

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Lin 2014

Study characteristics	
Notes	Paediatric RCT. Paediatric cohort, <18 years. Seizure types not specified. No ASMs. Had to have epileptifrom discharges on an EEG post first unprovoked seizure to be included. 46 participants.

Item	Authors' judgement	Support for judgement
Study participation	No	IIncludes only those children with epileptiform discharges on EEG
Study attrition	Yes	Two patients only lost to follow-up out of 48
Prognostic factor measurement	Unclear	Some factors measured but not exhaustive
Outcome measurement	Yes	Seizure recurrence by 24 months - quite clear
Study confounding	Unclear	Unclear if controlled for different factors
Statistical analysis and reporting	Yes	Reasonable in approach
Overall risk of bias	Unclear	Moderate

Llevadias 2004

Study characteristics	
Notes	Retrospective cohort. Paediatric cohort: 8mths -17 yrs. ASM started in 50.1%. Included absence seizures and myoclonus. SE included. 66 participants.

Item	Authors' judgement	Support for judgement
Study participation	Yes	Well described
Study attrition	Unclear	No mention of dropout
Prognostic factor measurement	No	Very limited included factors
Outcome measurement	Unclear	Reasonably clear outcome
Study confounding	No	No adjustments, especially for those treated and untreated
Statistical analysis and reporting	Unclear	Limited statistical analysis
Overall risk of bias	Unclear	Moderate

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Logroscino 2008

Study characteristics	
Notes	Retrospective cohort. Paediatric and Adult cohort. Mortality at 10 years of FUS and SE. 307 participants.

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Unclear as this study sample is not entirely representative of the general population
Study attrition	Unclear	No mention
Prognostic factor measurement	Unclear	In the context of recurrence not many factors but in the context of mortality relevant factors presented
Outcome measurement	Unclear	Not entirely clear with the recurrence data but the mortality data, the primary outcome of the study was displayed here without any issues
Study confounding	Yes	Adjusted for confounding
Statistical analysis and reporting	Yes	Very clear statistical analysis and presentation
Overall risk of bias	Unclear	Moderate

Loiseau 1999

Study characteristics	
Notes	Prospective cohort. Paediatric and Adult cohort: 2.5-94 years. Included provoked seizures (289) (804-289 =515). 515 participants.

Item	Authors' judgement	Support for judgement
Study participation	Yes	Large numbers, consecutive cases well-defined inclusion/exclusion criteria
Study attrition	Yes	Low loss to follow up - 3.9%
Prognostic factor measurement	Unclear	Aetiology of seizure really the main and only prognostic factor collected
Outcome measurement	Yes	Clear outcomes and time points clearly stated
Study confounding	No	No clear adjustment performed
Statistical analysis and reporting	Yes	Appropiate statistical methods applied to the dataset
Overall risk of bias	Yes	Low

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Mahamud 2020

Study characteristics	
Notes	Retrospective case control. Adult cohort. SE included. Acute/remote symptomatic excluded. 1131 participants.

Item	Authors' judgement	Support for judgement
Study participation	No	Specific sub population - not generallisable to the general population.
Study attrition	Unclear	Case-control - not applicable.
Prognostic factor measurement	Yes	Extensive prognostic factors
Outcome measurement	Yes	Very clear and well represented
Study confounding	Yes	Lots of adjustments
Statistical analysis and reporting	Yes	Well presented
Overall risk of bias	Unclear	Moderate

Marson 2005

Study characteristics	
Notes	Multicentre RCT. Paediatric and Adult. ASM given and recurrences reported separately. 1443 participants.

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Only patients where there was equipose re: starting treatment was 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
Study confounding	Yes	Multiple adjustments made
Statistical analysis and reporting	Yes	Excellent stats reporting
Overall risk of bias	Yes	Low

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Mizrogi 2015

Study characteristics	
Notes	Prospective cohort. Paediatric cohort. Focal and generalised seizures. Absence, myoclonus excluded. SE excluded. No ASMs. 73 participants.

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
Study confounding	Unclear	Unclear if adjustments have been made
Statistical analysis and reporting	Yes	Good and appropriate
Overall risk of bias	Unclear	Good and appropriate

Musicco 1997

Study characteristics	
Notes	Prospective RCT. Paediatric and Adult cohort (>2yrs). GTCS only (primary or secondary). ASMs partially given - 215/419 - treated 204/419 - untreated. 419 participants.

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Well-described patient population
Study attrition	Unclear	No mention of dropout rates clearly in the manuscript
Prognostic factor measurement	Unclear	Comprehensive list of factors but age of study precludes routine neuroimaging
Outcome measurement	Yes	Clear endpoints of study and outcomes reported
Study confounding	Unclear	By nature of study - some patients had been treated with ASM
Statistical analysis and reporting	Yes	Appropiate statistical methods utilised and survival curves utilised
Overall risk of bias	Yes	Low

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Schreiner 2003

Study characteristics	
Notes	Prospective cohort. Adult cohort >16 years. All seizure types including SE included. Absences and myoconus excluded. No ASMs given. 157 participants.

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Adult patients 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
Study confounding	Unclear	Unclear adjustments made
Statistical analysis and reporting	Yes	Survival curves and multivariate/univariate analysis performed
Overall risk of bias	Unclear	Moderate

Scotoni 2004

Study characteristics	
Notes	Prospective cohort. Paediatric cohort - 1mth -17 yrs. No ASMs. Absence seizures, myoclonus, infantile spasms. SE (6%) included. Focal and generalised seizures included. 213 participants.

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Clear criteria but exclude absence and myoclonus which will introduce some bias
Study attrition	Unclear	16% of participants had less than 6 months of follow-up
Prognostic factor measurement	Yes	Extensive
Outcome measurement	Yes	Well reported
Study confounding	Yes	Plenty of adjustments
Statistical analysis and reporting	Yes	Appropriate survival curves, uni and multivariate analyses

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Scotoni 2004 *(Continued)*

Overall risk of bias	Yes	Low

Shinnar 2000

Study characteristics	
Notes	Prospective cohort. Paediatric cohort: 1mth -19 yrs. No ASMs. All seizures included. No specific mention of SE. 407 participants.

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Imaging is variable across the cohort despite EEG being uniformly provided
Study attrition	Yes	Incredibly low despite the long follow-up
Prognostic factor measurement	Unclear	Not extensive in the reporting and definition of factors
Outcome measurement	Yes	Very well set out and incredibly clear
Study confounding	Yes	Adjustments made for various confounders
Statistical analysis and reporting	Yes	Appropriate statistical analysis of data performed and presented clearly
Overall risk of bias	Yes	Low

Shinnar 2005

Study characteristics	
Notes	Prospective cohort. Paediatric cohort, predominantly a mortality study. 407 participants.

Item	Authors' judgement	Support for judgement
Study participation	Yes	Clear inclusion/exclusion criteria
Study attrition	Unclear	No clear mention of study dropout rate
Prognostic factor measurement	No	Limited prognostic factors described
Outcome measurement	Yes	Clear outcome measurement with time points
Study confounding	Unclear	No mentioning of adjustments undertaken
Statistical analysis and reporting	Yes	Aappropiate presentation and analysis of data

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Shinnar 2005 *(Continued)*

Overall risk of bias	Yes	Low

Van Donselaar 1991

Study characteristics	
Notes	Prospective cohort. Adult cohort, >15 yrs. Focal and generalised seizures included. SE excluded. No ASMs. 151 participants.

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Some patients unduly excluded e.g. those presenting with status or prolonged seizures.
Study attrition	Yes	Two patients lost to follow-up out of a total of 151 participants
Prognostic factor measurement	Yes	Well-described and defined factors
Outcome measurement	Yes	Clear outcome reporting and measurement
Study confounding	Yes	Adjustment for a number of factors performed
Statistical analysis and reporting	Unclear	No multivariate analysis performed, all univariate
Overall risk of bias	Yes	Low

Winckler 2004

Study characteristics	
Notes	Prospective cohort, Paediatric cohort: 1mth - 16 yrs. All seizures. No specific mention of SE. No ASMs. 109 participants.

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
Study confounding	Yes	Multiple adjustments

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Winckler 2004 *(Continued)*

Statistical analysis and reporting	Yes	Well-reported methods
Overall risk of bias	Yes	Low

Zhang 2014

Study characteristics	
Notes	prospective cohort, Paediatric: 1mth -3yrs. Three groups of children with a FS, GI, non-GI illness and FUS. Epileptic spasms excluded, otherwise all seizure types included. 5.4% SE. No ASMs. 74 participants.

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Dififcult to generalise because very young cohort with mild infection
Study attrition	Unclear	Moderate attrition rate - 31 did not have valid follow-up out of 287
Prognostic factor measurement	Yes	Very comprehensive
Outcome measurement	Yes	Very comprehensive
Study confounding	Yes	Multiple adjustment
Statistical analysis and reporting	Yes	Excellent statistical analysis
Overall risk of bias	Yes	Low

Zhang 2017

Study characteristics	
Notes	Retrospective cohort, Paediatric cohort: 1mth - 3 yrs. All seizures and SE included.No ASMs. 190 participants.

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Unclear how cases were identified and included, only children under 3
Study attrition	Yes	Loss of follow-up rate of 6%
Prognostic factor measurement	Yes	Very comprehensive
Outcome measurement	Yes	Well-documented

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Zhang 2017 *(Continued)*

Study confounding	Yes	Multiple controls employed and adjustment attempted
Statistical analysis and reporting	Yes	Appropiate and survival curves clearly included, univariate and multivariate analysis
Overall risk of bias	Yes	Low

ASM: anti-seizure medication; CBZ: carbamazepine;**CNS:** central nervous system; **CT:** computerised tomography; **DH:** diabetic hyperglycaemia;**EEG**: electroencephalogram; **FUS:** first unprovoked seizure; **GI**: gastrointestinal infection; **GTCS:** generalized tonic-clonic seizures; **MRI:** magnetic resonance imaging; **mth:** month; **SE:** status epilepticus; **TBI:** traumatic brain injury;**US:** unprovoked seizure; **yrs:** years.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alesefir 2020	Insufficient follow-up duration
Benn 2008	Duplicate dataset
Bensken 2020	Insufficient data on seizure recurrence rates
Binelli 1988	Full text not available for review
Bonnett 2010	Duplicate dataset
Bonnett 2014	Duplicate dataset
Brown 2015	Participants do not fulfil study inclusion criteria
Chen 2018	participants do not fulfil study inclusion criteria
Cremo 1993	Duplicate dataset
Douw 2010	Unclear recurrence rates
Drenthen 2021	Insufficient participant numbers
Falip-Centellas 2002	Unclear recurrence time points
First Seizure Trial Group 1993	Duplicate dataset
Fisch 2016	Unclear recurrence rates
Fonseca 2018	Participants do not fulfil study inclusion criteria
Gupta 1993	Full text not available for review
Haapaniemi 2014	Participants do not fulfil study inclusion criteria
Hauser 1982	Duplicate dataset
Hesdorffer 1996	Participants do not fulfil study inclusion criteria
Hesdorffer 2007	Unclear recurrence rates

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Study	Reason for exclusion
Jafari 2020	Unable to access fullfil text
Jallon 2001	Unclear recurrence rates
Jallon 2007	Duplicate dataset
Jha 2004	Unclear recurrence rates
Keret 2020	Unclear seizure recurrence rates
Khan 2020	Unclear seizure recurrence rates
Kim 2006	Duplicate dataset
Kim 2016	unclear recurrence rates
Kim 2020	Unclear seizure recurrence rates
Kita 1992	Duplicate dataset
Koelfen 1991	Full text not available for review
Kollár 2006	Full text not available for review
Kotov 2020	Insufficient participant numbers
Koutroumanidis 2018	Insufficient number of participants
Kramer 1997	Unclear seizure recurrence rates
Langenbruch 2019	No seizure recurrence rates reported
Lawn 2013	Duplicate dataset
Lindsten 2000	Participants do not fulfil study inclusion criteria
Lindsten 2001a	Duplicate dataset
Lindsten 2001b	Duplicate dataset
Llaurado 2020	Unclear seizure recurrence rates
Lühdorf 1986	Participants do not fulfil study inclusion criteria
Mahamud 2018	Participants do not fulfil study inclusion criteria
Mahler 2015	Participants do not fulfil study inclusion criteria
Maia 2017	Unclear recurrence rates
Martinović 1997	Unclear recurrence time points
Masato 1999	Full text not available
Matsushita 1993	Participants do not fulfil study inclusion criteria

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Study	Reason for exclusion
McIntosh 2021	Insufficient follow-up duration
McManus 2021	Unclear seizure recurrence rates
Murthy 2020	Full text not available for review
Najafi 2008	Unclear recurrence time points
Olafsson 1998	duplicate dataset
Olivé-Gadea 2019	Unclear seizure recurrence rates
Paliwal 2015	Unclear recurrence rates
Pathan 2014	Participants do not fulfil study inclusion criteria
Pereira 2014	Unclear recurrence time points
Potchen 2014	Participants do not fulfil study inclusion criteria
Poudel 2016	Participants do not fulfil study inclusion criteria
Pujar 2018	Participants do not fulfil study inclusion criteria
Qadri 2017	Participants do not fulfil study inclusion criteria
Ramos Lizana 2000	Participants do not fulfil study inclusion criteria
Ramos Lizana 2009	Duplicate dataset
Rozsavolgyi 2007	Full text not available for review
Saemundsen 2008	Unclear recurrence rates
Sathirapanya 2020	Unclear seizure recurrence rates
Scotoni 1999	Duplicate dataset
Shinnar 1990	Duplicate dataset
Shinnar 1993	Duplicate dataset
Shinnar 1996	duplicate dataset
Specchio 2019	Unclear seizure recurrence rates
Stroink 1998	Duplicate dataset
Takami 2015	Participants do not fulfil study inclusion criteria
Tanabe 2005	Full text not available for review
Thoon 2006	Full text not available for review
van Donselaar 1992	Duplicate dataset

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Study	Reason for exclusion
van Donselaar 1997	Unclear recurrence rates
Weber 1987	Full text not available for review
Winckler 1997	Duplicate dataset
Zhang 2016	Full text not available for review

DATA AND ANALYSES

Comparison 1. Seizure Recurrence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Seizure Recurrence at 6 Months	27		"Seizure Recurrence Proportion" (IV, Random, 95% CI)	Subtotals only
1.1.1 All	27		"Seizure Recurrence Proportion" (IV, Random, 95% CI)	0.27 [0.24, 0.31]
1.1.2 Adults	7		"Seizure Recurrence Proportion" (IV, Random, 95% CI)	0.25 [0.19, 0.30]
1.1.3 Paediatric	14		"Seizure Recurrence Proportion" (IV, Random, 95% CI)	0.30 [0.23, 0.37]
1.2 Seizure Recurrence at 12 Months	34		"Seizure Recurrence Proportion" (IV, Random, 95% CI)	Subtotals only
1.2.1 All	34		"Seizure Recurrence Proportion" (IV, Random, 95% CI)	0.36 [0.33, 0.40]
1.2.2 Adult	9		"Seizure Recurrence Proportion" (IV, Random, 95% CI)	0.35 [0.31, 0.38]
1.2.3 Paediatric	16		"Seizure Recurrence Proportion" (IV, Random, 95% CI)	0.38 [0.31, 0.44]
1.3 Seizure Recurrence at 24 Months	27		"Seizure Recurrence Proportion" (IV, Random, 95% CI)	Subtotals only
1.3.1 All	27		"Seizure Recurrence Proportion" (IV, Random, 95% CI)	0.43 [0.39, 0.47]
1.3.2 Adult	9		"Seizure Recurrence Proportion" (IV, Random, 95% CI)	0.41 [0.37, 0.44]
1.3.3 Paediatric	12		"Seizure Recurrence Proportion" (IV, Random, 95% CI)	0.45 [0.36, 0.54]

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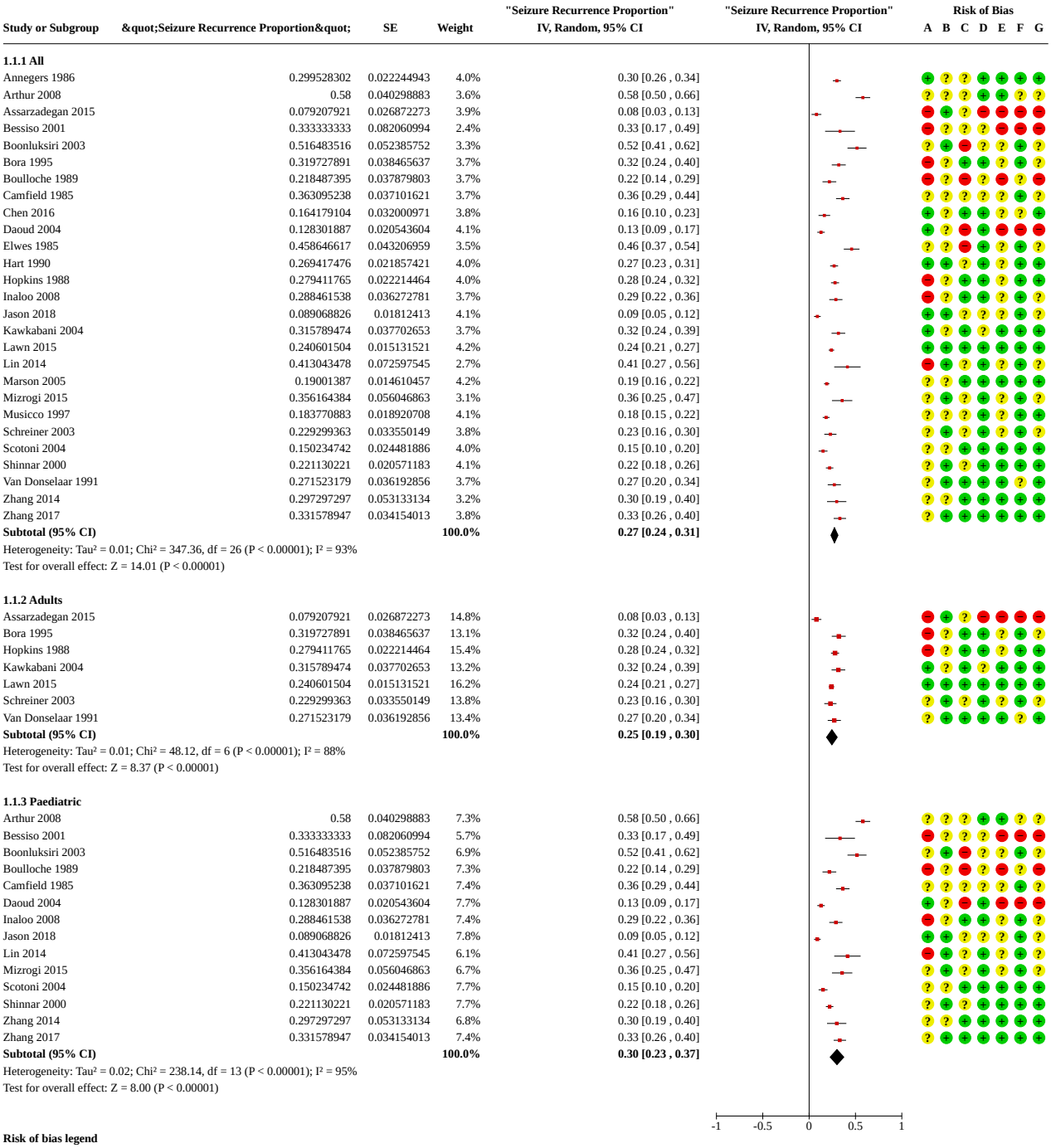
Analysis 1.1. Comparison 1: Seizure Recurrence, Outcome 1: Seizure Recurrence at 6 Months



Study or Subgroup	"Seizure Recurrence Proportion"	SE	Weight	"Seizure Recurrence Proportion" IV, Random, 95% CI	"Seizure Recurrence Proportion" IV, Random, 95% CI	Risk of Bias A B C D E F G
1.1.1 All						
Annegers 1986	0.299528302	0.022244943	4.0%	0.30 [0.26 , 0.34]		+ ? ? + + + +
Arthur 2008	0.58	0.040298883	3.6%	0.58 [0.50 , 0.66]		? ? ? + + ? ?
Assarzadegan 2015	0.079207921	0.026872273	3.9%	0.08 [0.03 , 0.13]		− + ? − − − −
Bessiso 2001	0.333333333	0.082060994	2.4%	0.33 [0.17 , 0.49]		− ? ? ? − − −
Boonluksiri 2003	0.516483516	0.052385752	3.3%	0.52 [0.41 , 0.62]		? + − ? ? + ?
Bora 1995	0.319727891	0.038465637	3.7%	0.32 [0.24 , 0.40]		− ? + + ? + ?
Boulloche 1989	0.218487395	0.037879803	3.7%	0.22 [0.14 , 0.29]		− ? − ? − ? −
Camfield 1985	0.363095238	0.037101621	3.7%	0.36 [0.29 , 0.44]		? ? ? ? ? + ?
Chen 2016	0.164179104	0.032000971	3.8%	0.16 [0.10 , 0.23]		+ ? + + ? ? +
Daoud 2004	0.128301887	0.020543604	4.1%	0.13 [0.09 , 0.17]		+ ? − + − − −
Elwes 1985	0.458646617	0.043206959	3.5%	0.46 [0.37 , 0.54]		? ? − + ? + ?
Hart 1990	0.269417476	0.021857421	4.0%	0.27 [0.23 , 0.31]		+ + ? + ? + +
Hopkins 1988	0.279411765	0.022214464	4.0%	0.28 [0.24 , 0.32]		− ? + + ? + +
Inaloo 2008	0.288461538	0.036272781	3.7%	0.29 [0.22 , 0.36]		− ? + + ? + ?
Jason 2018	0.089068826	0.01812413	4.1%	0.09 [0.05 , 0.12]		+ + ? ? ? + ?
Kawkabani 2004	0.315789474	0.037702653	3.7%	0.32 [0.24 , 0.39]		+ ? + ? + + +
Lawn 2015	0.240601504	0.015131521	4.2%	0.24 [0.21 , 0.27]		+ + + + + + +
Lin 2014	0.413043478	0.072597545	2.7%	0.41 [0.27 , 0.56]		− + ? + ? + ?
Marson 2005	0.19001387	0.014610457	4.2%	0.19 [0.16 , 0.22]		? ? + + + + +
Mizrogi 2015	0.356164384	0.056046863	3.1%	0.36 [0.25 , 0.47]		? + ? + ? + ?
Musicco 1997	0.183770883	0.018920708	4.1%	0.18 [0.15 , 0.22]		? ? ? + ? + +
Schreiner 2003	0.229299363	0.033550149	3.8%	0.23 [0.16 , 0.30]		? + ? + ? + ?
Scotoni 2004	0.150234742	0.024481886	4.0%	0.15 [0.10 , 0.20]		? ? + + + + +
Shinnar 2000	0.221130221	0.020571183	4.1%	0.22 [0.18 , 0.26]		? + ? + + + +
Van Donselaar 1991	0.271523179	0.036192856	3.7%	0.27 [0.20 , 0.34]		? + + + + ? +
Zhang 2014	0.297297297	0.053133134	3.2%	0.30 [0.19 , 0.40]		? ? + + + + +
Zhang 2017	0.331578947	0.034154013	3.8%	0.33 [0.26 , 0.40]		? + + + + + +
Subtotal (95% CI)			**100.0%**	**0.27 [0.24 , 0.31]**		
Heterogeneity: Tau² = 0.01; Chi² = 347.36, df = 26 (P < 0.00001); I² = 93%						
Test for overall effect: Z = 14.01 (P < 0.00001)						
1.1.2 Adults						
Assarzadegan 2015	0.079207921	0.026872273	14.8%	0.08 [0.03 , 0.13]		− + ? − − − −
Bora 1995	0.319727891	0.038465637	13.1%	0.32 [0.24 , 0.40]		− ? + + ? + ?
Hopkins 1988	0.279411765	0.022214464	15.4%	0.28 [0.24 , 0.32]		− ? + + ? + +
Kawkabani 2004	0.315789474	0.037702653	13.2%	0.32 [0.24 , 0.39]		+ ? + ? + + +
Lawn 2015	0.240601504	0.015131521	16.2%	0.24 [0.21 , 0.27]		+ + + + + + +
Schreiner 2003	0.229299363	0.033550149	13.8%	0.23 [0.16 , 0.30]		? + ? + ? + ?
Van Donselaar 1991	0.271523179	0.036192856	13.4%	0.27 [0.20 , 0.34]		? + + + + ? +
Subtotal (95% CI)			**100.0%**	**0.25 [0.19 , 0.30]**		
Heterogeneity: Tau² = 0.01; Chi² = 48.12, df = 6 (P < 0.00001); I² = 88%						
Test for overall effect: Z = 8.37 (P < 0.00001)						
1.1.3 Paediatric						
Arthur 2008	0.58	0.040298883	7.3%	0.58 [0.50 , 0.66]		? ? ? + + ? ?
Bessiso 2001	0.333333333	0.082060994	5.7%	0.33 [0.17 , 0.49]		− ? ? ? − − −
Boonluksiri 2003	0.516483516	0.052385752	6.9%	0.52 [0.41 , 0.62]		? + − ? ? + ?
Boulloche 1989	0.218487395	0.037879803	7.3%	0.22 [0.14 , 0.29]		− ? − ? − ? −
Camfield 1985	0.363095238	0.037101621	7.4%	0.36 [0.29 , 0.44]		? ? ? ? ? + ?
Daoud 2004	0.128301887	0.020543604	7.7%	0.13 [0.09 , 0.17]		+ ? − + − − −
Inaloo 2008	0.288461538	0.036272781	7.4%	0.29 [0.22 , 0.36]		− ? + + ? + ?
Jason 2018	0.089068826	0.01812413	7.8%	0.09 [0.05 , 0.12]		+ + ? ? ? + ?
Lin 2014	0.413043478	0.072597545	6.1%	0.41 [0.27 , 0.56]		− + ? + ? + ?
Mizrogi 2015	0.356164384	0.056046863	6.7%	0.36 [0.25 , 0.47]		? + ? + ? + ?
Scotoni 2004	0.150234742	0.024481886	7.7%	0.15 [0.10 , 0.20]		? ? + + + + +
Shinnar 2000	0.221130221	0.020571183	7.7%	0.22 [0.18 , 0.26]		? + ? + + + +
Zhang 2014	0.297297297	0.053133134	6.8%	0.30 [0.19 , 0.40]		? ? + + + + +
Zhang 2017	0.331578947	0.034154013	7.4%	0.33 [0.26 , 0.40]		? + + + + + +
Subtotal (95% CI)			**100.0%**	**0.30 [0.23 , 0.37]**		
Heterogeneity: Tau² = 0.02; Chi² = 238.14, df = 13 (P < 0.00001); I² = 95%						
Test for overall effect: Z = 8.00 (P < 0.00001)						

Risk of bias legend
(A) Study participation
(B) Study attrition
(C) Prognostic factor measurement
(D) Outcome measurement
(E) Study confounding
(F) Statistical analysis and reporting
(G) Overall risk of bias

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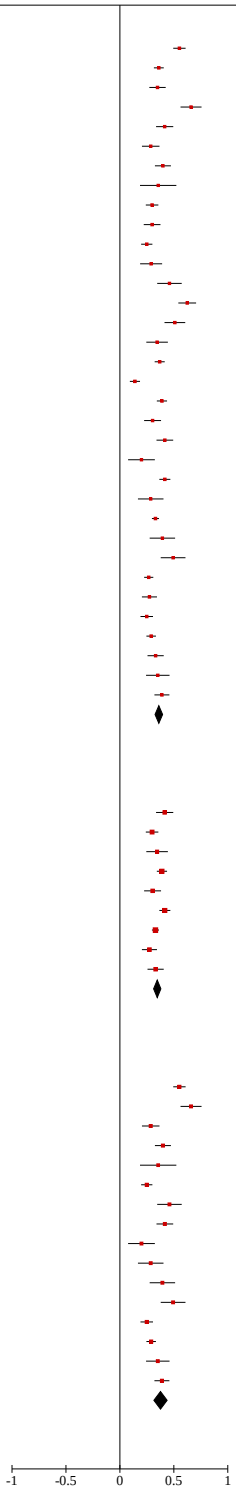
Analysis 1.2. Comparison 1: Seizure Recurrence, Outcome 2: Seizure Recurrence at 12 Months

Study or Subgroup	"Seizure Recurrence Proportion"	SE	Weight	"Seizure Recurrence Proportion" IV, Random, 95% CI	"Seizure Recurrence Proportion" IV, Random, 95% CI	Risk of Bias A B C D E F G
1.2.1 All						
Al-Momani 2020	0.551724138	0.029203484	3.2%	0.55 [0.49 , 0.61]		? - - ? + + ?
Annegers 1986	0.360849057	0.023322848	3.3%	0.36 [0.32 , 0.41]		+ ? ? + + + +
Beretta 2017	0.348684211	0.038653618	3.0%	0.35 [0.27 , 0.42]		+ ? ? + + + +
Boonluksiri 2003	0.659340659	0.049681464	2.7%	0.66 [0.56 , 0.76]		? + - ? ? + ?
Bora 1995	0.414965986	0.040638544	3.0%	0.41 [0.34 , 0.49]		- ? + + ? + ?
Boulloche 1989	0.285714286	0.041412217	2.9%	0.29 [0.20 , 0.37]		- ? - ? - ? -
Camfield 1985	0.398809524	0.037777583	3.0%	0.40 [0.32 , 0.47]		? ? ? ? ? + ?
Camfield 1989	0.35483871	0.085934746	1.9%	0.35 [0.19 , 0.52]		+ + - ? ? - ?
Chandra 1992	0.298319328	0.029656642	3.2%	0.30 [0.24 , 0.36]		? + - + - - -
Chen 2016	0.298507463	0.039530902	3.0%	0.30 [0.22 , 0.38]		+ ? + + ? ? +
Daoud 2004	0.249056604	0.026566216	3.2%	0.25 [0.20 , 0.30]		+ ? - + - - -
Das 2000	0.289473684	0.052022094	2.7%	0.29 [0.19 , 0.39]		- ? ? ? - - -
de Rezende Machado 2021	0.459459459	0.057932447	2.6%	0.46 [0.35 , 0.57]		? ? + ? ? - ?
Elwes 1985	0.62406015	0.041999739	2.9%	0.62 [0.54 , 0.71]		? ? - + ? + ?
Geut 2017	0.509615385	0.049019967	2.8%	0.51 [0.41 , 0.61]		- ? ? + - ? ?
Gilad 1996	0.344827586	0.050958798	2.7%	0.34 [0.24 , 0.44]		- + ? + + + +
Hart 1990	0.368932039	0.023771832	3.3%	0.37 [0.32 , 0.42]		+ + ? + ? + +
Hauser 1990	0.139423077	0.02401765	3.3%	0.14 [0.09 , 0.19]		- + + + ? + +
Hopkins 1988	0.389705882	0.024143932	3.3%	0.39 [0.34 , 0.44]		- ? + + ? + +
Hui 2001	0.303030303	0.040000278	3.0%	0.30 [0.22 , 0.38]		- ? + ? ? + ?
Inaloo 2008	0.416666667	0.039472122	3.0%	0.42 [0.34 , 0.49]		- ? + + ? + ?
Jagtap 2013	0.2	0.063245553	2.4%	0.20 [0.08 , 0.32]		- - ? ? - - -
Kho 2006	0.416666667	0.025983732	3.2%	0.42 [0.37 , 0.47]		? ? + + + + +
Klotz 2021	0.285714286	0.060368161	2.5%	0.29 [0.17 , 0.40]		- - ? + - + ?
Lawn 2015	0.329573935	0.016639889	3.4%	0.33 [0.30 , 0.36]		+ + + + + + +
Llevadias 2004	0.393939394	0.060145171	2.5%	0.39 [0.28 , 0.51]		+ ? - ? - ? ?
Mizrogi 2015	0.493150685	0.058515083	2.5%	0.49 [0.38 , 0.61]		? + ? + ? + ?
Musicco 1997	0.267303103	0.021620073	3.3%	0.27 [0.22 , 0.31]		? ? ? + ? + +
Schreiner 2003	0.27388535	0.035590753	3.1%	0.27 [0.20 , 0.34]		? + ? + ? + ?
Scotoni 2004	0.248826291	0.029622965	3.2%	0.25 [0.19 , 0.31]		? ? + + + + +
Shinnar 2000	0.28992629	0.022490459	3.3%	0.29 [0.25 , 0.33]		? + ? + + + +
Van Donselaar 1991	0.331125828	0.038298368	3.0%	0.33 [0.26 , 0.41]		? + + + + ? +
Zhang 2014	0.351351351	0.055495748	2.6%	0.35 [0.24 , 0.46]		? ? + + + + +
Zhang 2017	0.389473684	0.035376467	3.1%	0.39 [0.32 , 0.46]		? + + + + + +
Subtotal (95% CI)			**100.0%**	**0.36 [0.33 , 0.40]**		
Heterogeneity: Tau² = 0.01; Chi² = 313.72, df = 33 (P < 0.00001); I² = 89%						
Test for overall effect: Z = 20.11 (P < 0.00001)						
1.2.2 Adult						
Bora 1995	0.414965986	0.040638544	9.1%	0.41 [0.34 , 0.49]		- ? + + ? + ?
Chandra 1992	0.298319328	0.029656642	12.0%	0.30 [0.24 , 0.36]		? + - + - - -
Gilad 1996	0.344827586	0.050958798	7.1%	0.34 [0.24 , 0.44]		- + ? + + + +
Hopkins 1988	0.389705882	0.024143932	13.6%	0.39 [0.34 , 0.44]		- ? + + ? + +
Hui 2001	0.303030303	0.040000278	9.3%	0.30 [0.22 , 0.38]		- ? + ? ? + ?
Kho 2006	0.416666667	0.025983732	13.1%	0.42 [0.37 , 0.47]		? ? + + + + +
Lawn 2015	0.329573935	0.016639889	15.8%	0.33 [0.30 , 0.36]		+ + + + + + +
Schreiner 2003	0.27388535	0.035590753	10.4%	0.27 [0.20 , 0.34]		? + ? + ? + ?
Van Donselaar 1991	0.331125828	0.038298368	9.7%	0.33 [0.26 , 0.41]		? + + + + ? +
Subtotal (95% CI)			**100.0%**	**0.35 [0.31 , 0.38]**		
Heterogeneity: Tau² = 0.00; Chi² = 22.51, df = 8 (P = 0.004); I² = 64%						
Test for overall effect: Z = 20.10 (P < 0.00001)						
1.2.3 Paediatric						
Al-Momani 2020	0.551724138	0.029203484	6.9%	0.55 [0.49 , 0.61]		? - - ? + + ?
Boonluksiri 2003	0.659340659	0.049681464	6.2%	0.66 [0.56 , 0.76]		? + - ? ? + ?
Boulloche 1989	0.285714286	0.041412217	6.5%	0.29 [0.20 , 0.37]		- ? - ? - ? -
Camfield 1985	0.398809524	0.037777583	6.6%	0.40 [0.32 , 0.47]		? ? ? ? ? + ?
Camfield 1989	0.35483871	0.085934746	4.7%	0.35 [0.19 , 0.52]		+ + - ? ? - ?
Daoud 2004	0.249056604	0.026566216	7.0%	0.25 [0.20 , 0.30]		+ ? - + - - -
de Rezende Machado 2021	0.459459459	0.057932447	5.9%	0.46 [0.35 , 0.57]		? ? + ? ? - ?
Inaloo 2008	0.416666667	0.039472122	6.6%	0.42 [0.34 , 0.49]		- ? + + ? + ?
Jagtap 2013	0.2	0.063245553	5.6%	0.20 [0.08 , 0.32]		- - ? ? - - -
Klotz 2021	0.285714286	0.060368161	5.8%	0.29 [0.17 , 0.40]		- - ? + - + ?
Llevadias 2004	0.393939394	0.060145171	5.8%	0.39 [0.28 , 0.51]		+ ? - ? - ? ?
Mizrogi 2015	0.493150685	0.058515083	5.8%	0.49 [0.38 , 0.61]		? + ? + ? + ?
Scotoni 2004	0.248826291	0.029622965	6.9%	0.25 [0.19 , 0.31]		? ? + + + + +
Shinnar 2000	0.28992629	0.022490459	7.1%	0.29 [0.25 , 0.33]		? + ? + + + +
Zhang 2014	0.351351351	0.055495748	6.0%	0.35 [0.24 , 0.46]		? ? + + + + +
Zhang 2017	0.389473684	0.035376467	6.7%	0.39 [0.32 , 0.46]		? + + + + + +
Subtotal (95% CI)			**100.0%**	**0.38 [0.31 , 0.44]**		
Heterogeneity: Tau² = 0.01; Chi² = 144.02, df = 15 (P < 0.00001); I² = 90%						
Test for overall effect: Z = 12.01 (P < 0.00001)						



Risk of bias legend
(A) Study participation
(B) Study attrition
(C) Prognostic factor measurement
(D) Outcome measurement
(E) Study confounding

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Analysis 1.2. (Continued)

(C) Prognostic factor measurement
(D) Outcome measurement
(E) Study confounding
(F) Statistical analysis and reporting
(G) Overall risk of bias

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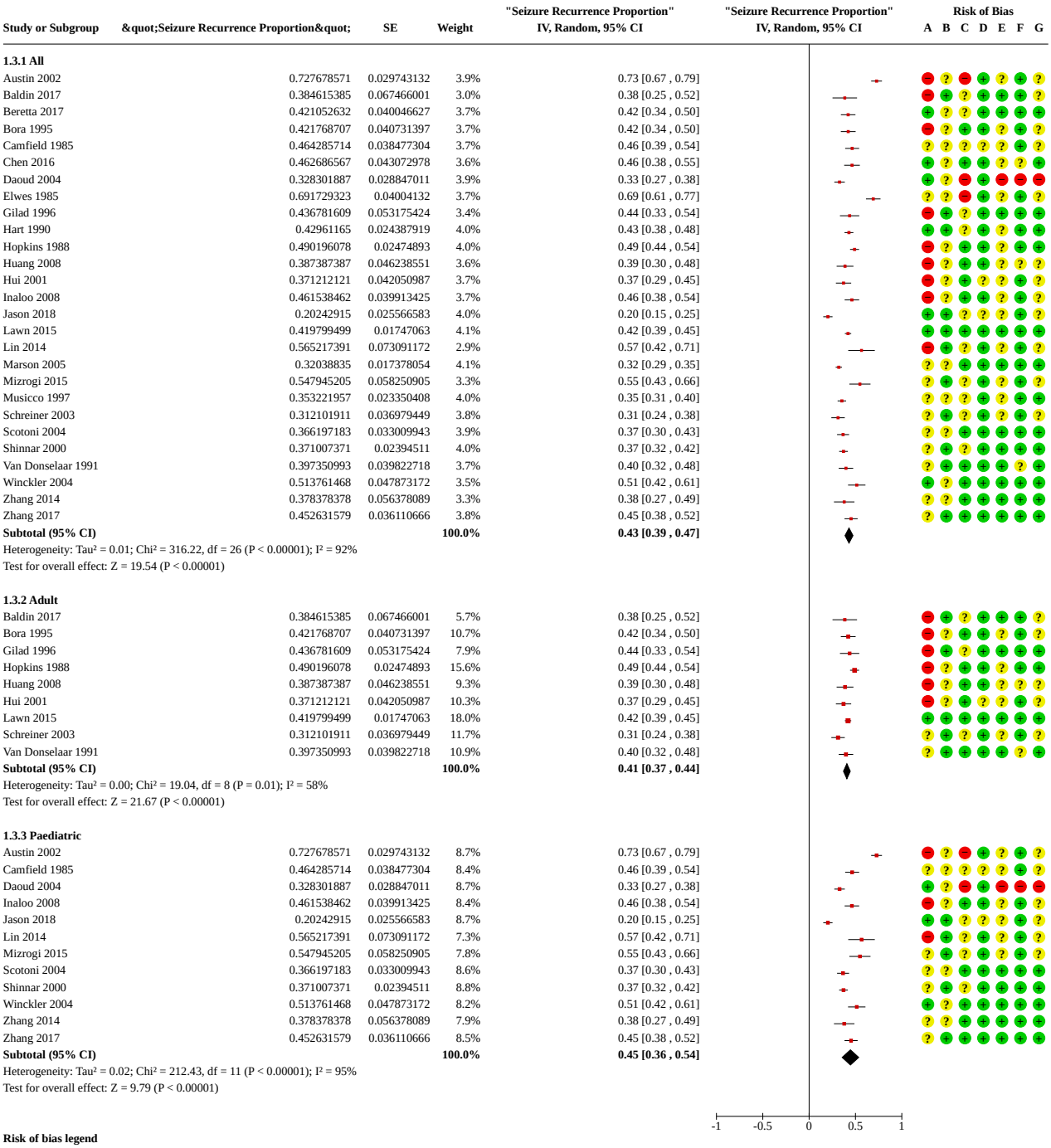
Analysis 1.3. Comparison 1: Seizure Recurrence, Outcome 3: Seizure Recurrence at 24 Months



Study or Subgroup	"Seizure Recurrence Proportion"	SE	Weight	"Seizure Recurrence Proportion" IV, Random, 95% CI	Risk of Bias A B C D E F G
1.3.1 All					
Austin 2002	0.727678571	0.029743132	3.9%	0.73 [0.67 , 0.79]	
Baldin 2017	0.384615385	0.067466001	3.0%	0.38 [0.25 , 0.52]	
Beretta 2017	0.421052632	0.040046627	3.7%	0.42 [0.34 , 0.50]	
Bora 1995	0.421768707	0.040731397	3.7%	0.42 [0.34 , 0.50]	
Camfield 1985	0.464285714	0.038477304	3.7%	0.46 [0.39 , 0.54]	
Chen 2016	0.462686567	0.043072978	3.6%	0.46 [0.38 , 0.55]	
Daoud 2004	0.328301887	0.028847011	3.9%	0.33 [0.27 , 0.38]	
Elwes 1985	0.691729323	0.04004132	3.7%	0.69 [0.61 , 0.77]	
Gilad 1996	0.436781609	0.053175424	3.4%	0.44 [0.33 , 0.54]	
Hart 1990	0.42961165	0.024387919	4.0%	0.43 [0.38 , 0.48]	
Hopkins 1988	0.490196078	0.02474893	4.0%	0.49 [0.44 , 0.54]	
Huang 2008	0.387387387	0.046238551	3.6%	0.39 [0.30 , 0.48]	
Hui 2001	0.371212121	0.042050987	3.7%	0.37 [0.29 , 0.45]	
Inaloo 2008	0.461538462	0.039913425	3.7%	0.46 [0.38 , 0.54]	
Jason 2018	0.20242915	0.025566583	4.0%	0.20 [0.15 , 0.25]	
Lawn 2015	0.419799499	0.01747063	4.1%	0.42 [0.39 , 0.45]	
Lin 2014	0.565217391	0.073091172	2.9%	0.57 [0.42 , 0.71]	
Marson 2005	0.32038835	0.017378054	4.1%	0.32 [0.29 , 0.35]	
Mizrogi 2015	0.547945205	0.058250905	3.3%	0.55 [0.43 , 0.66]	
Musicco 1997	0.353221957	0.023350408	4.0%	0.35 [0.31 , 0.40]	
Schreiner 2003	0.312101911	0.036979449	3.8%	0.31 [0.24 , 0.38]	
Scotoni 2004	0.366197183	0.033009943	3.9%	0.37 [0.30 , 0.43]	
Shinnar 2000	0.371007371	0.02394511	4.0%	0.37 [0.32 , 0.42]	
Van Donselaar 1991	0.397350993	0.039822718	3.7%	0.40 [0.32 , 0.48]	
Winckler 2004	0.513761468	0.047873172	3.5%	0.51 [0.42 , 0.61]	
Zhang 2014	0.378378378	0.056378089	3.3%	0.38 [0.27 , 0.49]	
Zhang 2017	0.452631579	0.036110666	3.8%	0.45 [0.38 , 0.52]	
Subtotal (95% CI)			**100.0%**	**0.43 [0.39 , 0.47]**	
Heterogeneity: Tau² = 0.01; Chi² = 316.22, df = 26 (P < 0.00001); I² = 92%					
Test for overall effect: Z = 19.54 (P < 0.00001)					
1.3.2 Adult					
Baldin 2017	0.384615385	0.067466001	5.7%	0.38 [0.25 , 0.52]	
Bora 1995	0.421768707	0.040731397	10.7%	0.42 [0.34 , 0.50]	
Gilad 1996	0.436781609	0.053175424	7.9%	0.44 [0.33 , 0.54]	
Hopkins 1988	0.490196078	0.02474893	15.6%	0.49 [0.44 , 0.54]	
Huang 2008	0.387387387	0.046238551	9.3%	0.39 [0.30 , 0.48]	
Hui 2001	0.371212121	0.042050987	10.3%	0.37 [0.29 , 0.45]	
Lawn 2015	0.419799499	0.01747063	18.0%	0.42 [0.39 , 0.45]	
Schreiner 2003	0.312101911	0.036979449	11.7%	0.31 [0.24 , 0.38]	
Van Donselaar 1991	0.397350993	0.039822718	10.9%	0.40 [0.32 , 0.48]	
Subtotal (95% CI)			**100.0%**	**0.41 [0.37 , 0.44]**	
Heterogeneity: Tau² = 0.00; Chi² = 19.04, df = 8 (P = 0.01); I² = 58%					
Test for overall effect: Z = 21.67 (P < 0.00001)					
1.3.3 Paediatric					
Austin 2002	0.727678571	0.029743132	8.7%	0.73 [0.67 , 0.79]	
Camfield 1985	0.464285714	0.038477304	8.4%	0.46 [0.39 , 0.54]	
Daoud 2004	0.328301887	0.028847011	8.7%	0.33 [0.27 , 0.38]	
Inaloo 2008	0.461538462	0.039913425	8.4%	0.46 [0.38 , 0.54]	
Jason 2018	0.20242915	0.025566583	8.7%	0.20 [0.15 , 0.25]	
Lin 2014	0.565217391	0.073091172	7.3%	0.57 [0.42 , 0.71]	
Mizrogi 2015	0.547945205	0.058250905	7.8%	0.55 [0.43 , 0.66]	
Scotoni 2004	0.366197183	0.033009943	8.6%	0.37 [0.30 , 0.43]	
Shinnar 2000	0.371007371	0.02394511	8.8%	0.37 [0.32 , 0.42]	
Winckler 2004	0.513761468	0.047873172	8.2%	0.51 [0.42 , 0.61]	
Zhang 2014	0.378378378	0.056378089	7.9%	0.38 [0.27 , 0.49]	
Zhang 2017	0.452631579	0.036110666	8.5%	0.45 [0.38 , 0.52]	
Subtotal (95% CI)			**100.0%**	**0.45 [0.36 , 0.54]**	
Heterogeneity: Tau² = 0.02; Chi² = 212.43, df = 11 (P < 0.00001); I² = 95%					
Test for overall effect: Z = 9.79 (P < 0.00001)					

Risk of bias legend
(A) Study participation
(B) Study attrition
(C) Prognostic factor measurement
(D) Outcome measurement
(E) Study confounding
(F) Statistical analysis and reporting
(G) Overall risk of bias

ADDITIONAL TABLES

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Table 1. Characteristics of Excluded Studies *[ordered by study ID]*

Study	Reason for exclusion
Langenbruch 2019	No seizure recurrence rates
Falip-Centellas 2002	Unclear recurrence time points
Alesefir 2020	Insufficient follow-up duration
Benn 2008	Duplicate dataset
Bensken 2020	Unclear seizure recurrence rates
Binelli 1988	Full text not available for review
Bonnett 2010	Duplicate dataset
Bonnett 2014	Duplicate dataset
Brown 2015	Participants do not fulfil study inclusion criteria
Chen 2018	Participants do not fulfil study inclusion criteria
Cremo 1993	Duplicate dataset
Douw 2010	Unclear recurrence rates
Drenthen 2021	Insufficient participant number
First Seizure Trial Group 1993	Duplicate dataset
Fisch 2016	Unclear recurrence rates
Fonseca 2018	Participants do not fulfil study inclusion criteria
Gupta 1993	Full text not available for review
Haapaniemi 2014	Participants do not fulfil study inclusion criteria
Hauser 1982	Duplicate dataset
Hesdorffer 1996	Participants do not fulfil study inclusion criteria
Hesdorffer 2007	Unclear recurrence rates
Jafari 2020	Unable to access full text
Jallon 2001	Unclear recurrence rates
Jallon 2007	Duplicate dataset
Jha 2004	Unclear recurrence rates
Keret 2020	Unclear seizure recurrence rates
Khan 2020	Unclear seizure recurrence rates

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Table 1. Characteristics of Excluded Studies *[ordered by study ID]* *(Continued)*

Kim 2006	Duplicate dataset
Kim 2016	Unclear recurrence rates
Kim 2020	Unclear seizure recurrence rates
Kita 1992	Duplicate dataset
Koelfen 1991	Full text not available for review
Kollár 2006	Full text not available for review
Kotov 2020	Insufficient participant number
Koutroumanidis 2018	Insufficient number of participants
Kramer 1997	Unclear recurrence rates
Lawn 2013	Duplicate dataset
Lindsten 2000	Participants do not fulfil study inclusion criteria
Lindsten 2001a	Duplicate dataset
Lindsten 2001b	Duplicate dataset
Llaurado 2020	Unclear seizure recurrence rates
Lühdorf 1986	Participants do not fulfil study inclusion criteria
Mahler 2015	Participants do not fulfil study inclusion criteria
Maia 2017	Unclear recurrence rates
Martinović 1997	Unclear recurrence time points
Masato 1999	Full text not available for review
Matsushita 1993	Participants do not fulfil study inclusion criteria
McIntosh 2021	Insufficient follow-up duration
McManus 2021	Unclear seizure recurrence rates
McManus 2021	Unclear seizure recurrence rates
Najafi 2008	Unclear recurrence time points
Olafsson 1998	Duplicate dataset
Paliwal 2015	Unclear recurrence rates
Pathan 2014	Participants do not fulfil study inclusion criteria
Pereira 2014	Unclear recurrence time points

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Table 1. Characteristics of Excluded Studies *[ordered by study ID]* *(Continued)*

Potchen 2014	Participants do not fulfil study inclusion criteria
Poudel 2016	Participants do not fulfil study inclusion criteria
Pujar 2018	Participants do not fulfil study inclusion criteria
Qadri 2017	Participants do not fulfil study inclusion criteria
Ramos Lizana 2000	Participants do not fulfil study inclusion criteria
Ramos Lizana 2009	Duplicate dataset
Rozsavolgyi 2007	Full text not available for review
Saemundsen 2008	Unclear recurrence rates
Sathirapanya 2020	Unclear seizure recurrence rates
Scotoni 1999	Duplicate dataset
Shinnar 1990	Duplicate dataset
Shinnar 1993	Duplicate dataset
Shinnar 1996	Duplicate dataset
Specchio 2019	Unclear seizure recurrence rates
Stroink 1998	Duplicate dataset
Takami 2015	Participants do not fulfil study inclusion criteria
Tanabe 2005	Full text not available for review
Thoon 2006	Full text not available for review
van Donselaar 1992	Duplicate dataset
van Donselaar 1997	Unclear recurrence rates
Weber 1987	Full text not available for review
Winckler 1997	Duplicate dataset
Zhang 2016	Full text not available for review

Table 2. Summary of mortality data following a first unprovoked seizure where standardised mortality ratios (SMRs) are provided

Author	Number	Study Design	Overall SMR (time)/Subgroups
Loiseau 1999	505	1-year Prospective Cohort	4.1 (95% CI 2.5-6.2)* 0.0 (Idiopathic)** 1.6 (95% CI 0.4-4.1)

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Table 2. Summary of mortality data following a first unprovoked seizure where standardised mortality ratios (SMRs) are provided *(Continued)*

			(Cryptogenic) 6.5 (95% CI 3.8-10.5) (Remote symptomatic) 19.8 (95% CI 14.0-27.3) (Progressive conditions)
Logroscino 2008	307 291 (SS) 16 (SE)	10-year Prospective Cohort	1.3 (95% CI 0.9-1.8) 1.2 (95% CI 0.8-1.6) 2.6 (95% CI 0.8-5.3)
Bell 2016	302	Prospective cohort Median follow-up 17.0 years (IQR 10.0-24,1)	2.65 (95% CI 2.23-3.15) (SS at presentation) 5.34 (95% CI 3.32-8.59) (aged < 18 years at onset) 1.98 (95% CI 1.75-2.25) (aged > 18 years at onset) 1.89 (95% CI 1.47-2.43 (idiopathic/cryptogenic) 4.13 (95% CI 3.26-5.23) (remote symptomatic) 1.57 (95% CI 1.15-2.13) (only 1 SS notified ever) 1.49 (95% CI 1.02-2.19 (idiopathic/cryptogenic) 1.72 (95% CI 1.03-2.85) (remote symptomatic)

Table 3**.** Summary of mortality data following a first unprovoked seizure where standardised mortality ratios (SMRs) are provided
Legend:
SE – status epilepticus; SS – unprovoked single seizure; idiopathic/cryptogenic – generalised or focal seizure in which no clear cause is identified other than a presumed genetic aetiology; remote symptomatic – clearly identified preceding cause known or long-standing abnormality identified on neuroimaging; progressive conditions – identified neurological aetiology with clinical progression such as brain tumours or neurogenerative conditions.
*No deaths reported
**Includes those with idiopathic/cryptogenic and remote symptomatic aetiologies but not progressive conditions

Table 3. Studies with reported >2 years seizure recurrence rates

Study	Cohort size	Seizure recurrence
Paediatric Studies		
Arthur 2008	150	66.0% (2.5 years)
Blom 1978	71	60.6% (3 years)
Boulloche 1989	119	32.6% (3 years) 37.7% (8 years)
Camfield 1985	168	51.8% (>4.5 years)
Chan 2012	54	39.8% (7 years)
Daoud 2004	265	37% (3 years)

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Table 3. Studies with reported >2 years seizure recurrence rates *(Continued)*

Kanemura 2015	87	55.2% (4 years)
Mizrogi 2015	72	57.5% (4 years)
Scotoni 2004	213	43% (3 years)
Shinnar 2000	407	43% (5 years) 46% (10 years)
Zhang 2017	190	48% (3 years) 52% (4 years) 52% (5 years)
Adult Studies		
Bora 1995	147	44.1% (3 years) 47.0% (4 years)
Gilad 1996	87	44.8% (3 years)*
Hopkins 1988	408	52% (3 years)
Hui 2001	132	42% (3 years) 47% (4 years)
Mahamud 2020	743**	31% (5 years)
Lawn 2015	798	51% (5 years) 59% (10 years)
Paediatric and Adult		
Hart 1990/Bell 2016	302	46% (3 years) 57% (5 years) 61% (10 years) 62% (15 years) 62% (20 years) 64% (25 years)
Beretta 2017	152	66.5% (5 years) 83.6% (10 years) 89.1% (15 years)
Chen 2016	134	51.3% (>2 years)
Elwes 1985	133	71% (3 years)
Hauser 1990	208	29% (3 years)

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Table 3. Studies with reported >2 years seizure recurrence rates *(Continued)*

		35% (5 years)
Logroscino 2008	291	40.5% (10 years)
Marson 2005	1443	53%(5 years)*
		56% (8 years)*

*Treated and untreated combined

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

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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 search strategy

This includes the search filters recommended by the Cochrane Prognosis Methods Group (Geersing 2012).

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

2. (unprovoked or untreated).tw.

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$).tw.

8. 6 or 7

9. exp Epilepsy/ or epilep*.tw. 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

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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

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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]

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Appendix 4. ClinicalTrials.gov search strategy

diagnosis OR prognosis OR risk 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. ICTRP search strategy

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

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Appendix 6. Preliminary study selection, data extraction, and risk of bias forms

We will use a modified version of the quality assessment strategy recommended by bias to assess the quality of included studies (Hayden 2013). This assessment will cover six domains of potential bias: study participation, study attrition, prognostic factors measurement (as detailed above), outcome measurement (seizure recurrence, death), study confounding, statistical analysis, and reporting. Our approach will assess 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 will provide 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	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. seizure after traumatic brain injury), 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). Comprehensive description would include demographic (age, sex, date of seizure), relevant comorbidities 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.
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

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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	
Definition of the PF	Potential PFs, such as specific electroencephalogram (EEG) findings and specific neuro-imaging 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 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

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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 following a single seizure (such as important medical comorbidities, like ischaemic heart disease and diabetes mellitus) are measured.
Definition of the confounding factor	Clear definition 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

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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

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CONTRIBUTIONS OF AUTHORS

AN and GA developed the protocol with input from other named authors.
AN and GA carried out data extraction, quality assessment and data synthesis with the support of SJN, LB and AGM.

DECLARATIONS OF INTEREST

AN: has received speaker honoraria from Eisai Ltd and UCB Pharma.
GA: none known
SJN: none known
LB: none known
AP: none known
JWS: JWS's department has received grants from UCB Pharma. He has received honoraria from Zobenix, Arvelle and UCB for participating on an advisory board for drug development.
AGM: a consortium of pharmaceutical companies (GSK, EISAI, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to the University of Liverpool. Professor Marson is funded in part by the NIHR Applied Research Collaboration, North West Coast (NIHR ARC NWC). Professor Marson is a National Institute for Health and Care Research (NIHR) Senior Investigator. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care. Professor Marson is the Co-ordinating Editor of the Cochrane Epilepsy Group; however, he was not involved in the editorial process of this review.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

To minimise delay, two review authors (GA & AN) rather than a single review author, performed the selection of relevant full texts from the abstracts generated from the search due to the large number of articles generated by the search.

We pragmatically decided to include randomised controlled trials in addition to observational cohort studies as initially described in the protocol. This decision was taken as not including randomised controlled trials would mean that landmark studies of recurrence rates in

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first seizure such as the FIRST study and the MESS study would not have been included in this review. These differences in the methodology of the studies is reflected in the risk of bias assessment of these studies and is addressed in the discussion section of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [therapeutic use]; Case-Control Studies; Cohort Studies; *Epilepsies, Partial [drug therapy]; *Epilepsy [drug therapy]; Prognosis; Prospective Studies; Retrospective Studies; Seizures [diagnosis] [drug therapy] [etiology]

MeSH check words

Adult; Child; Humans

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