Individualised prediction model of seizure recurrence and long-term outcome after antiepileptic drug withdrawal – an Individual Participant Data meta-analysis.

Herm J Lamberink, MD[1], Willem M Otte, PhD[1,2,3], Ada T Geerts, PhD[4], Milen Pavlovic, MD[5], Julio Ramos-Lizana, MD[6], Prof. Anthony G Marson, MD[7], Jan Overweg, MD[8], Letícia Sauma, MD[9], Prof. Luigi M Specchio, MD[10], Prof. Michael Tennison, MD[11], Prof. Tania MO Cardoso, MD[9], Prof. Shlomo Shinnar, MD[12], Prof. Dieter Schmidt, MD[13], Karin Geleijns, MD[1], Prof. Kees PJ Braun, MD[1]

Affiliations:

(1) Department of Child Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands; (2) Biomedical MR Imaging and Spectroscopy Group, Center for Image Sciences, University Medical Center Utrecht, Utrecht, The Netherlands; (3) Stichting Epilepsie Instellingen Nederland - SEIN, Heemstede, The Netherlands; (4) Erasmus Medical Center–Sophia Children's Hospital, Rotterdam, The Netherlands; (5) Al Sabah Hospital, Pediatric Neurology Unit, Kuwait; (6) Pediatric Neurology Unit, Department of Pediatrics, Torrecárdenas Hospital, Almería, Spain; (7) Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom; (8) Meer en Bosch - de Cruquiushoeve, Heemstede, The Netherlands; (9) Department of Neurology, University of Campinas, Campinas, Brazil; (10) Clinic of Neurology, University of Foggia, Ospedali Riuniti, Foggia, Italy; (11) Department of Neurology, University of North Carolina, United States of America; (12) Departments of Neurology, Pediatrics and Epidemiology and Population Health, Montefiore Medical Center, Albert Einstein College of Medicine, New York, United States of America; (13) Epilepsy Research Group, Berlin, Germany

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Corresponding author: Prof. dr. K.P. Braun, Professor of Child Neurology, Division Neurosciences, Brain Center Rudolf Magnus, Dept. Child Neurology, University Medical Center Utrecht, room no KC 03.063.0, P.O. Box 85090, 3508 AB, Utrecht, the Netherlands. T: +31 88 75 543 41, k.braun@umcutrecht.nl

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Abstract

Background. People with epilepsy who became seizure-free while taking antiepileptic drugs (AEDs) may consider discontinuing their medication, with the possibility of increased quality of life due to the elimination of adverse events. The risk, however, is seizure recurrence. Factors related to long-term seizure outcome have not been studied widely. The objective of the study was to identify predictors of both outcomes, and produce nomograms for individualised outcome estimation.

Methods. A systematic review identified candidate predictors and eligible articles, using PubMed and EMBASE databases with a last update in November 2014. Eligibility criteria were: cohort with seizure-free patients with epilepsy, AED withdrawal, information regarding seizure recurrences during and after withdrawal. Risk of bias was assessed using the Quality in Prognosis Studies system. Data analysis was based on individual participant data. Survival curves and proportional hazards were computed. The strongest predictors were selected with backward selection. Models were converted to nomograms and an Excel tool to determine individual risks.

Findings. Forty-five studies with 7082 patients were identified; ten studies (22%) - with 1769 patients (25%) were included. Median follow-up was five years (interquartile range 3-10, maximum 23 years). Prospective, retrospective studies and randomised controlled trials were included, covering non-selected and selected populations of both children and adults. Relapse occurred in 812 (46%) of patients, 9% had seizures in their last year of follow-up suggesting enduring seizure control was not (yet) regained. Independent predictors of seizure recurrence were: epilepsy duration before remission, seizure-free interval before AED withdrawal, age at onset of epilepsy, history of febrile seizures, number of seizures before remission, absence of a self-limiting epilepsy syndrome, developmental delay, epileptiform abnormality on EEG before withdrawal. Independent predictors of seizures in the last year of follow-up were: epilepsy duration before remission, seizure-free interval before AED withdrawal, number of AEDs before withdrawal, female sex, family history of epilepsy, number of seizures before remission, focal seizures, epileptiform abnormality on EEG before withdrawal. Adjusted concordance-statistics were 0·65 (95% CI 0.65-0.66) and 0·71 (95% CI 0.70-0.71), respectively. Validation was stable across the individual study populations.

Interpretation. Presented nomograms are evidence-based tools with robust performance across populations of children and adults. The nomograms allow for predicting the outcome of drug withdrawal for the individual patient, including both the risk of relapse and the chance of long-term seizure-

freedom. Main limitations are the absence of a control group continuing AED treatment and the definition of long-term seizure freedom.

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INTRODUCTION

Antiepileptic drugs (AEDs) suppress seizures in 65-85% of people with epilepsy[1]. Because of the fear of seizure relapse many people continue AED treatment even when free from seizures and despite the side effects. Up to 88% of patients experience – often multiple – adverse effects from AEDs[2,3]. As a result, quality of life of seizure-free patients is significantly better when AEDs are discontinued[4], provided they remain seizure-free.

A meta-analysis estimated that the cumulative seizure recurrence rate after AED withdrawal is around 34 percent[5]. From those who experience seizure recurrence, about 80% will be able to control seizures by reinstating AED treatment[6]. The remaining 20% of people will develop treatment refractory epilepsy, although there is no convincing evidence that this refractoriness occurs as a consequence of AED withdrawal. Nonetheless, some have debated whether AED withdrawal would be safe at all[7,8].

The dilemma between overtreatment and side effects on the one hand, and the risk of seizure recurrence on the other, is one that should be considered with every seizure-free patient. However, a robust tool to guide the decision to withdraw AEDs is missing. Twenty-five predictors of seizure outcome have been identified in the past, but the published populations, methods and results were too variable to distil a definite set of independent predictors[5]. While many studies focused on predictors of seizure recurrence, only a few studied factors related to refractory epilepsy[6]. A major limitation of prognostic meta-analysis using published aggregate data is that effect sizes associated with individual predictors cannot be produced due to different methods and reporting of the original studies. A method to overcome this issue is through a meta-analysis of Individual Participant Data (IPD) in which the original data from previous studies are combined and more accurate, adjusted, statistics can be computed on a large dataset[9].

In this IPD meta-analysis of 1769 patients we aimed to (1) identify independent predictors of seizure recurrence and (2) long-term seizure outcome, and ultimately, (3) provide an evidence-based tool, using nomograms, to predict the short-, and long-term seizure outcome in an individual seizure-free patient who faces the decision to withdraw AEDs.

METHODS

Article selection

To select articles eligible for this study, a systematic search of the databases of PubMed and EMBASE was employed on 6-11-2014. Inclusion criteria for articles were: original full-text article of a cohort of seizure free patients who started AED withdrawal, information regarding seizure recurrences during and after AED withdrawal. Surgical cohorts and reports with <30 patients have been excluded, as well as publications on acute symptomatic seizures because this is beyond the scope of the objective. No limitation concerning the year of publication was used. Unpublished data were not explored. Search queries are presented in Appendix 1. Reference lists were checked for missed literature. Two independent researchers (HJL and KG) selected the studies. Differences in article inclusion were solved through discussion. After selecting eligible articles, contact details of authors were gathered from recent articles or Internet. Authors were asked to collaborate. A second request was sent to non-responders six weeks later. Authors who agreed to collaborate were requested to provide anonymous individual participant data concerning baseline, outcome and candidate predictor variables. Aggregate data from non-included studies were not used. The Dutch Medical Research Involving Human Subjects Act did not apply and ethical approval and informed consent was not needed.

Outcome variables

Two distinct outcome variables were used, corresponding with the two main research questions. The first was the occurrence and timing of seizure recurrence, at two and five years, after initiation of AED withdrawal. The second was long-term seizure outcome, with favourable outcome defined as complete seizure-freedom in the last year of follow-up, suggesting either no recurrence, or recurrence with subsequent regain of seizure control. For those with unfavourable long-term outcome, time to event was defined as the interval between initiation of AED withdrawal and seizure recurrence; for patients seizure-free at last follow-up, irrespective of the presence of seizure recurrence, censoring time was the maximum follow-up duration.

Predictor variables

The selection of candidate predictors was based on a systematic review on the predictors of seizure recurrence after AED withdrawal[5], which identified 25 significant predictors. Three pairs of variables

measured similar constructs and were therefore reduced to three single variables, resulting in a final list of 22 variables for the analysis. All studied variables are listed in table 1. Information on variable definitions can be found in Appendix 2.

Quality assessment

The quality of data as presented in the original publication of the collaborators was previously assessed in a systematic review[5], with an adjusted version of the Quality in Prognosis Studies system[10]. Potential for bias was classified as low, moderate or high for the categories 'study participation', 'study attrition', 'prognostic factor measurement', and 'outcome measurement'.

Statistical analysis

A detailed overview of statistical methods can be found in Appendix 2.

In short: missing data were dealt with by multiple imputations. Random-effects proportional hazards regression was performed to study prognostic factors. A selection of strongest contributing predictors was made through backward selection of variables using Akaike information criterion combined with manual removal of least contributing predictors, until the most optimal model was selected. Calibration plots were created, and for validation a concordance statistic (c-statistic) was computed and adjusted for optimism by using 200 bootstrap samples. Internal-external cross-validation (IECV) was performed to assess validity of the model across the different populations.

The funding source was the National Epilepsy Fund, which provided a grant for the doctoral studies of the first author. They had no influence on the design, execution or publication of this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Forty-five publications were identified as eligible for inclusion, 33 authors were ultimately contacted and invited to collaborate of which ten agreed to participate and provide individual participant data (flow-chart, supplementary figure 1). A total of 1771 of 7082 patients were included (25%). Many authors

provided additional, unpublished details on the cohorts, such as longer follow-up durations. No important issues that could compromise the analysis were identified in checking individual participant data from contributing cohorts. Details on the separate cohorts are given in table 2, showing a variety of populations, some with selected populations such as children with cryptogenic focal epilepsies[11], patients only on monotherapy[12], patients on monotherapy older than 13 years with exclusion of idiopathic generalised epilepsies[13], others with mostly unselected populations of children[14–18], adults[19], or both[20]. The maximum follow-up after start of AED withdrawal was 23 years, and for the patients with a seizure recurrence, the follow-up after the recurrence was a median of 3·7 years (range 0-20 years, interquartile range (IQR) 1-7 years). The median time to AED withdrawal after the last seizure was 33 months (range 3-385 months, IQR 24-48 months).

Seizure-freedom after initiation of AED withdrawal

Seizure recurrence occurred in 812 patients (46%, table 2). Figure 1 shows the survival curve for time to seizure recurrence, with an ultimate Kaplan Meier estimate of 48% seizure-free patients. The last seizure recurrence was 13 years after starting AED withdrawal. Supplementary figure 2 shows the survival curve split by EEG results. The overall recurrence rate is higher than the average reported in the literature[5]; when only published data are considered, the median of published seizure recurrence estimates of the 10 included papers was 40%, where the median of the 35 papers, which were not included, was 28% (suppl. table 1). The only other difference between included and excluded papers was the high percentage of randomised controlled trials in the current analysis (50%) compared to 11% in non-included papers (suppl. table 1). Nine percent of patients were not seizure-free in the last year of follow-up (table 2), although some of those may have had a period of seizure-freedom prior to that. Of the patients with seizure recurrence and maximum follow-up between 1 and 5 years after recurrence, 202/280 (72%) were seizure-free in the last year of follow-up. The rates were 121/152 (80%), 65/80 (81%) and 50/57 (88%) for those who relapsed and were followed 5-10 years, 10-15 years and more than 15 years after seizure recurrence, respectively.

Missing data and quality appraisal

Supplementary table 2 and suppl. figure 3 provide information on missing data. Five variables had missing values in between 30-45% of patients. Imputation was not possible for two cases because of too much missing information; these cases have been removed from further analysis, thus performed on 1769 patients. The risk of bias based on the published papers in the ten selected cohorts was scored as low to 'partly present' (suppl. table 3)[5].

Univariable proportional hazards

Univariable predictors of seizure recurrence are presented in table 1, showing 14 significant variables. With respect to the long-term outcome, defined as the presence of seizures in the last year of follow-up, ten variables were significantly related in univariate analysis.

To investigate a possible selection bias for the variable 'failure of previous AED withdrawal', baseline characteristics between positive and negative cases were investigated which showed no large difference between the groups besides a longer duration of epilepsy (median 61 vs. 24 months), and a longer seizure free interval (median 41 vs. 31 months, suppl. table 4) in the group of patients who had a previous relapse after withdrawal.

Predicting outcome by multivariable analysis

For the risk of seizure recurrence and the chance of long-term seizure-freedom, respectively, 13 and 12 independent predictors were identified in multivariable modelling (suppl. tables 5 and 6 resp.). It was possible to reduce the number of variables in each model to eight, without having an effect on the calibration plots or the validation statistics. The final reduced models with hazard ratios are found in supplementary tables 7 and 8. Independent predictors of seizure recurrence were: epilepsy duration before remission, seizure-free interval before AED withdrawal, age at onset of epilepsy, history of febrile seizures, number of seizures before remission, absence of a self-limiting epilepsy syndrome, developmental delay, epileptiform abnormality on EEG before withdrawal. Independent predictors of seizures in the last year of follow-up were: epilepsy duration before remission, seizure-free interval before AED withdrawal, number of AEDs before withdrawal, female sex, family history of epilepsy, number of seizures before remission, focal seizures, epileptiform abnormality on EEG before withdrawal.

A visual representation of these models is provided in figures 2a and 3a, which are nomograms that can be applied for direct use in clinical practice to calculate the chance of both outcome measures at specific time points in each individual patient.

For practical purposes the nomograms were translated into an Excel tool for risk calculation. It is available via the URL www.epilepsypredictiontools.info

Validation and calibration

The adjusted c-statistic for predicting seizure recurrence is 0·65 (95% CI 0·65-0·66). In the validation procedure, the c-statistic varied between 0·64 and 0·67, thus showing stability across all populations (suppl. table 9). For predicting long-term seizure-freedom, the adjusted c-statistic is 0·71 (95% CI 0·70-0·71), which varied in the validation procedure between 0·68 and 0·79 (suppl. table 10). Lastly, plotting the predicted probabilities against the observed proportions shows good calibration for both models (figures 2b and 3b; note the change of scale on both axes for figure 3b).

DISCUSSION

This prognostic IPD meta-analysis of the risks of AED withdrawal in 1769 seizure-free people with epilepsy yields clinically useful nomograms to predict individual seizure outcome. Relapse occurred in 812 (46%) of patients, while only 9% of the total cohort had seizures in the last year of follow-up. The proportion of relapsing patients that did not regain seizure-freedom decreased with longer follow-up times. The strongest predictors, included in the nomograms, were for seizure recurrence: duration of epilepsy, duration of the seizure-free interval, age at onset of seizures, history of febrile seizures, ten or more seizures before remission, the absence of a self-limiting epilepsy syndrome (such as absence-, or Rolandic epilepsy or Panayiotopoulos syndrome), IQ below 70, and epileptiform abnormality on EEG before AED withdrawal. For predicting long-term seizure outcome, the eight selected independent predictors were: duration of epilepsy, duration of the seizure-free interval, number of AEDs before withdrawal, female sex, family history of epilepsy in first or second degree, ten or more seizures before remission, the presence of focal seizures, and epileptiform abnormality on EEG before AED withdrawal. Validation -or assessment how well a prediction works on data other than that on which the model was built- is arguably the most important issue in prognostic modelling[21], and "external" validation within the available data was done through IECV[22] with good and stable performance across all cohorts.

Several clinically important implications can be drawn from the presented data. The first observation is that, although the 22 candidate predictors had all been reported as significant predictors in at least one peer-reviewed article[5], eight of these were now shown to have no consistent significant association with the outcome. The most striking example is the failure of a previous attempt to withdraw from medication. In line with a recent publication from Wolf[23], a prior seizure recurrence after AED withdrawal is not related to the outcome of a second (or third) trial. This finding is not the result of a selection bias, because (a) none of the included cohorts excluded patients with a previous failure of AED withdrawal, and (b) the baseline characteristics of those with a failed previous AED withdrawal attempt were very similar to those attempting for the first time.

Another observation is the effect of epileptiform activity on EEG before AED withdrawal, a factor which has been debated in the past[24]. Based on the analyses, EEG abnormalities are significantly associated with outcome, but in the absence of other predictive factors only increase the risks mildly. EEG abnormalities alone should thus not prevent withdrawal of medication, a notion which was already stated in 1987[19] and is in agreement with for example the 2013 Italian guideline on AED withdrawal[25].

The age at onset of epilepsy is an important predictor for seizure recurrence, but not for long-term seizure-freedom. Its association with seizure recurrence is U-shaped, with an elevated risk at birth which falls to a nadir by about 3-4 years when it begins to rise again until age 10 and plateaus until age 25; subsequently the risk continues to rise further with older ages of onset. No clear explanation for the U-shaped relation between age at onset and seizure recurrence could be found.

The duration of the seizure-free interval is negatively correlated to both seizure outcomes. Where most studies on the timing of AED withdrawal study the dichotomy "early versus late AED withdrawal", as meta-analysed in a Cochrane review[26], our analysis shows that in fact the risk decreases with every additional year of seizure-freedom. The common understanding that it is advisable to wait for "at least two years" is based on an artificial threshold, and the rule should at least be complemented by stating, "every added seizure-free year reduces the risk". The nomograms will provide insight in the best timing for the individual patient.

As a general caveat, in addition to likelihood of the outcome, there are many more considerations to be made in the decision to withdraw AEDs in seizure-free patients. When counselling patients with the use of these prediction models, a physician should be aware of the way risks are presented, as it can steer the patient towards a certain choice[27]. Other factors like fear of losing a driver's license or even a job[28], the social stigma around seizures[29,30], and the quality of life[2] are important considerations. The nomograms only provide individualised statistical chances, and can only be applied when balancing benefits and risks within the context of all these factors.

Limitations

It may appear that our models are restricted to populations with relatively high recurrence rates, with an estimated 52% of patients with seizure recurrence within 23 years after AED withdrawal. However, the ten included studies contain many different populations, from strictly selected to population-based, with recurrence rates between 26% and 63%. In the internal-external cross-validation procedure the influence of the separate populations is tested by omitting them one by one. For both the populations with low and high recurrence risks the model performance remained stable. Therefore, the high average recurrence rate is no limitation to the generalizability of the models.

A limitation is that the study population contains only people who made an attempt to withdraw AEDs, and maintaining AEDs still carries the risk of seizure recurrence and refractory epilepsy. The only two

randomised AED withdrawal trials showed that continued AED treatment is related to 7% seizure recurrence at one year[31] and 22% at two years[20], compared with 15% and 41% for the withdrawal groups, respectively. The development of refractory epilepsy may not at all be related to AED withdrawal: a follow-up study of the MRC AED withdrawal trail showed no differences between the two randomisation arms in terms of seizure control after relapse[32].

For two predictors a low number of cases were provided: (history of) epileptic encephalopathy (24 cases) and juvenile myoclonic epilepsy (JME, 30 cases). Due to the low patient numbers it cannot be concluded that these factors are not predictors of outcome. For JME patients, 26/30 experienced seizure relapse (87%) but all were seizure free at last follow-up. This suggests that only few patients can be successful at AED withdrawal (see also [33,34]). However, although most relapse, the eventual rate of regaining seizure freedom is high.

A limitation of using IPD from previously executed studies is that prognostic factors can be defined differently. For the included variables, some variation in the measurement of developmental delay and the definition of epilepsy duration was found, as described in Appendix 2. The variable "self-limiting epilepsy syndromes" was strictly defined in our protocol and not subject to different interpretation."

A last limitation is the quantification of long-term seizure-freedom chosen in the analysis. From most studies, only two outcome measures were available: seizure recurrence, and the seizure status in the last year of follow-up, both dichotomised in seizures being present or not. Although the presence of seizures in the last year of follow-up does not fully cover long-term outcome, it is the most accurate approximation of seizure control after seizure recurrence currently available.

In conclusion, the presented nomograms are helpful to calculate an individualised risk of AED withdrawal and the chance of long-term favourable seizure outcome. They may therefore help to guide person-tailored choices by the physician and patient.

Conflicts of interest

All authors declare that they have no conflicts of interest.

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Authors' contributions

HJL, WMO, DS, SS, KG and KPJB contributed to the design of the study. HJL and KG performed the literature search. Data collection was performed by HJL, ATG, MP, JR-L, AGM, JO, LS, LMS, MT, TMOC, and SS. HJL and WMO performed data analysis and created the figures. All authors contributed to the interpretation of results, reviewed and critically revised the article, and approved the final version for submission.

Research in context (box)

Evidence before this study

A systematic review of available literature was performed which identified all significant predictors of AED withdrawal outcome previously reported. A total of 25 variables were identified as significant predictor of seizure recurrence in at least one peer-reviewed article. However, differences in study design, population, and methods limited the possibility to determine which are the strongest predictors, and how to combine those to predict risks for the individual patient.

Added value of this study

This IPD meta-analysis of 1769 patients identified independent predictors of seizure relapse and eventual seizure freedom after AED withdrawal, and enabled the computation of individualized outcome risks. The nomograms are validated across various populations, and can be applied in all seizure-free patients, children and adults, in whom AED withdrawal is considered.

Implications of all the available evidence

The nomograms will improve patient consultation by providing insight in the risks of AED withdrawal, providing the patient with evidence-based risk estimates. Furthermore, future studies on prognostic factors for the outcome of AED withdrawal should correct for those found in this paper.

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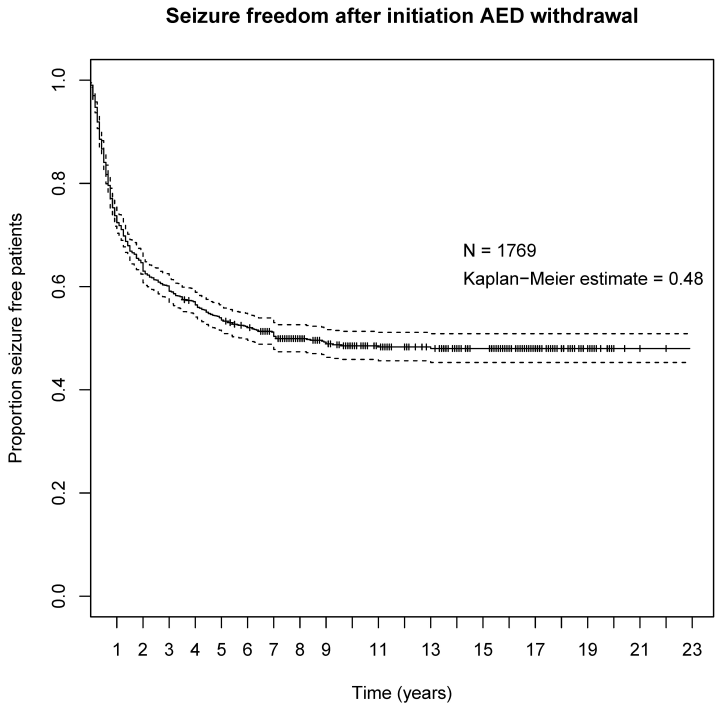


	time in years					
	0	1	2	5	10	13
Number at risk	1769	1274	1059	578	262	163
Cumulative n events	0	484	641	771	809	811
Kaplan-Meier estimate (95% CI)	1·00	0·72 (0·70 – 0·74)	0·63 (0·61 – 0·65)	0·53 (0·51 – 0·56)	0·49 (0·46 – 0·51)	0·48 (0·45 – 0·51)

Figure 1. Seizure free patients after initiation of AED withdrawal.
Survival curve of seizure free patients over time with Kaplan-Meier estimates at 1, 2, 5, 10 and 13 years (time of last event in this dataset), with seizure recurrence taken as event. Time of zero equals the start of AED withdrawal.

Table 1. Univariable predictors of seizure recurrence and the presence of seizures in the last year of follow-up

Variable	n (%)[‡]	seizure recurrence*		seizures in last year of follow-up[†]	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Female sex	842 (48%)	1·08 (0·94 - 1·24)	0·2745	1·43 (1·02 - 2·01)	**0·0391**
Age at onset epilepsy					
Childhood age at onset (0-10)	1087 (61%)	0·75 (0·60 - 0·92)	**0·0064**	1·31 (0·80 - 2·16)	0·3069
Adolescent age at onset (11-17)	387 (22%)	1·15 (0·93 - 1·42)	0·2008	1·41 (0·84 - 2·36)	0·1769
Adult age at onset (≥18)	295 (17%)	Reference		Reference	
Age at withdrawal in years[§]	15 (0-84)	1·01 (1·01 - 1·02)	**<0·0001**	1·00 (0·98 - 1·01)	0·5155
Family history of epilepsy	365/1735 (21%)	1·16 (0·98 - 1·38)	0·0828	1·55 (1·04 - 2·30)	**0·0311**
History of neonatal seizures	53/1601 (3%)	1·30 (0·91 - 1·84)	0·1440	1·77 (0·77 - 4·07)	0·1792
History of febrile seizures	199/1765 (11%)	1·27 (1·03 - 1·56)	**0·0250**	1·06 (0·61 - 1·85)	0·8424
≥ 10 seizures before remission	573/1446 (40%)	1·52 (1·29 - 1·81)	**<0·0001**	2·21 (1·15 - 3·37)	**0·0003**
Epilepsy duration before remission in years[§]	1 (0-5)	1·04 (1·03 - 1·05)	**<0·0001**	1·03 (1·01 - 1·06)	**0·0118**
Seizure free interval before AED withdrawal in years[§]	3 (2-4)	0·94 (0·91 - 0·98)	**0·0022**	0·85 (0·76 - 0·95)	**0·0057**
Number of AEDs before withdrawal[§]	1 (1-2)	1·15 (1·05 - 1·26)	**0·0035**	1·51 (1·24 - 1·83)	**<0·0001**
Failure of previous AED withdrawal	126/1246 (10%)	1·13 (0·89 - 1·44)	0·3268	1·15 (0·68 - 1·95)	0·5954
Focal seizures	833/1652 (50%)	1·13 (0·97 - 1·32)	0·1162	1·81 (1·26 - 2·56)	**0·0015**
Generalised tonic-clonic seizures	1141/1652 (69%)	1·51 (1·25 - 1·83)	**<0·0001**	1·07 (0·69 - 1·66)	0·7470
Multiple seizure types	254/1089 (23%)	1·24 (1·02 - 1·51)	**0·0334**	0·94 (0·55 - 1·59)	0·8088
Remote symptomatic aetiology	468/1649 (28%)	1·45 (1·24 - 1·70)	**<0·0001**	1·80 (1·26 - 2·56)	**0·0011**
Self-limiting epilepsy syndrome[ǀ]	183/978 (19%)	0·51 (0·39 - 0·68)	**<0·0001**	0·48 (0·25 - 0·92)	**0·0266**
History of epileptic encephalopathy	24/1142 (2%)	0·82 (0·60 - 1·12)	0·2201	0·79 (0·29 - 2·12)	0·6365
Juvenile myoclonic epilepsy	30/978 (3%)	1·27 (0·87 - 1·86)	0·2116	0·91 (0·29 - 2·87)	0·8663
Developmental delay	262/1742 (15%)	1·52 (1·27 - 1·82)	**<0·0001**	1·30 (0·82 - 2·04)	0·2622
Motor deficit	163/1736 (9%)	1·23 (0·97 - 1·54)	0·0850	0·90 (0·47 - 1·72)	0·7515
Imaging					
Normal	774/984 (73%)	Reference		Reference	
Abnormal	210/984 (20%)	1·32 (1·08 - 1·62)	**0·0076**	1·66 (0·93 - 2·98)	0·0877
Not performed	77/984 (7%)	0·86 (0·66 - 1·13)	0·2861	0·71 (0·37 - 1·36)	0·2996
EEG before withdrawal					
Normal	1207/1490 (79%)	Reference		Reference	
Epileptiform abnormality	283/1490 (18%)	1·50 (1·25 - 1·79)	**<0·0001**	1·68 (1·11 - 2·54)	**0·0144**
Not performed	46/1490 (3%)	0·71 (0·39 - 1·27)	0·2446	1·14 (0·27 - 4·78)	0·8562

Analysis performed with proportional hazards regression including a random effects term to correct for heterogeneity between populations. Bold p-values indicate significant outcomes.

*heterogeneity: relative risk between studies ranged between 1·29 and 1·45; [†]heterogeneity: relative risk between studies ranged between 1·95 and 2·66; [‡]based on available information before imputations, the denominator indicates total number of complete cases; [§]median (IQR); [ǀ]formerly called "benign course", e.g. absence epilepsy, benign epilepsy with centrotemporal spikes (Rolandic epilepsy), Panayiotopoulos syndrome

Table 2. Baseline characteristics

	Total (n = 1769)	Cardoso (n = 99)	Geerts (n = 133)	MRC (n = 510)	Overweg (n = 65)	Pavlovic (n = 52)	Ramos-Lizana (n = 216)	Serra (n = 57)	Shinnar (n = 264)	Specchio (n = 256)	Tennison (n = 119)
Year publication	-	2003	2005	1991	1987	2012	2010	2005	1994	2002	1994
Study design	-	RCT*	RCT[†]	RCT[‡]	pros	retro	pros	RCT[§]	pros	pros	RCT[ǀ]
Country	-	Brazil	The Netherlands	United Kingdom	The Netherlands	Serbia	Spain	Brazil	United States of America	Italy	United States of America
Follow-up in years, median (IQR)	5·3 (3 - 10)	9·0 (7·3 – 13·3)	10·9 (10 – 11·3)	5·0 (4 – 5·9)	3·0 (2·7 – 3·3)	3·0 (2 - 6)	4·5 (2·3 – 7·5)	2·3 (1·8 – 5)	16·1 (15·3 – 17·7)	2·0 (0·7 – 4)	2·4 (1·3 – 4·2)
Follow-up after seizure recurrence in years, median (IQR)	3·7 (0·6 – 6·8)	7·8 (5·4 – 11·9)	9·4 (7·7 – 10·4)	3·9 (2·6 – 4·9)	2·5 (1·8 – 2·8)	2·0 (1 – 5·2)	4·0 (2·6 – 5·9)	3·9 (2·2 – 5·7)	14·8 (11·3 – 16·9)	0 (0 – 0)	0 (0 – 1·8) [¶]
Female sex, %	842 (48 %)	46 (46%)	69 (52%)	260 (51%)	25 (38%)	16 (31%)	96 (44%)	25 (44%)	128 (48%)	130 (51%)	47 (39%)
Polytherapy, %	464/1753 (26%)	47 (47%)	22 (17%)	86 (17%)	46 (71%)	10 (19%)	40 (19%)	29 (51%)	13 (5%)	130 (51%)	41 (34%)
Aetiology, remote symptomatic, %	468/1649 (28%)	72 (73%)	42 (32%)	134 (26%)	13 (20%)	0 (0%)	55 (25%)	18 (32%)	97 (37%)	37 (14%)	missing
Age at onset epilepsy in years, median (IQR)	8 (4 – 14)	14 (9 – 22)	7 (4 - 10)	14 (7 – 24)	10 (6 – 14)	7 (5 - 9)	5 (1 - 8)	4 (1 – 8)	5 (2 – 9)	12 (7 – 17)	3 (1 – 6)
Age at withdrawal in years, median (IQR) [**]	15 (10 - 26)	26 (21 – 36)	8 (5 - 11)	27 (18 – 43)	29 (22 – 24)	14 (11 - 16)	8 (4 - 10)	10 (7 – 13)	12 (8 – 16)	22 (17 – 30)	11 (8 – 14)
Epilepsy duration before remission in months, median (IQR)	23 (4 - 72)	8 (3 – 15)	19 (5 - 43)	53 (10 – 143)	157 (94 – 240)	1 (0 - 12)	0 (0 - 6)	23 (10 – 46)	21 (5 – 55)	47 (11 – 108)	35 (12 – 74)
Seizure-free interval before AED withdrawal in months, median (IQR)	33 (24 - 48)	40 (27 - 38)	6 (6 - 12)	41 (29 – 70)	63 (48 – 85)	48 (36 - 60)	25 (23 - 27)	24 (24 – 33)	30 (26 – 42)	36 (36 – 60)	24 (24 – 48)
Previously failed withdrawal attempt, %[††]	126/1246 (10%)	27/99 (27%)	0/133	60/510 (12%)	4/51 (8%)	0/52	0/0	3/57 (5%)	22/264 (8%)	0/0	10/80 (13%)
Epileptiform EEG before withdrawal, %[††]	283/1536 (18%)	12/99 (12%)	72/133 (54%)	85/457 (19%)	31/64 (48%)	0/41	0/171	0/41	0/158	55/256 (21%)	28/116 (24%)
Seizure outcome											
Number of recurrences, %	812 (46%)	53 (54%)	71 (53%)	235 (46%)	39 (60%)	19 (37%)	56 (26%)	23 (40%)	110 (42%)	160 (63%)	46 (39%)
Seizures in last year of follow-up, %[††]	136/1455 (9%)	16/98 (16%)	17/129 (14%)	60/495 (12%)	12/60 (20%)	0/47	6/211 (3%)	9/56 (16%)	11/258 (4%)	5/101 (5%)	[¶]

RCT, randomised controlled trial; pros, prospective; retro, retrospective

*randomised for: AED reduction versus complete AED discontinuation. Seizure free patients from reduction group later completely withdrew from AEDs; [†]randomised for: AED withdrawal after 6 or 12 months of seizure freedom; [‡]randomised for: AED withdrawal versus no AED withdrawal, in current analysis only withdrawal patients were included; [§]randomised for: taper duration of 1 month versus 6 months; [ǀ]randomised for: six-week versus nine month AED taper period; [¶]in most cases follow-up was ceased after seizure recurrence, so that the final seizure outcome could not be reported; [**]988 patients (56%) were below 18 years old at withdrawal; [††]incomplete cases, the denominator shows the number of patients with available information

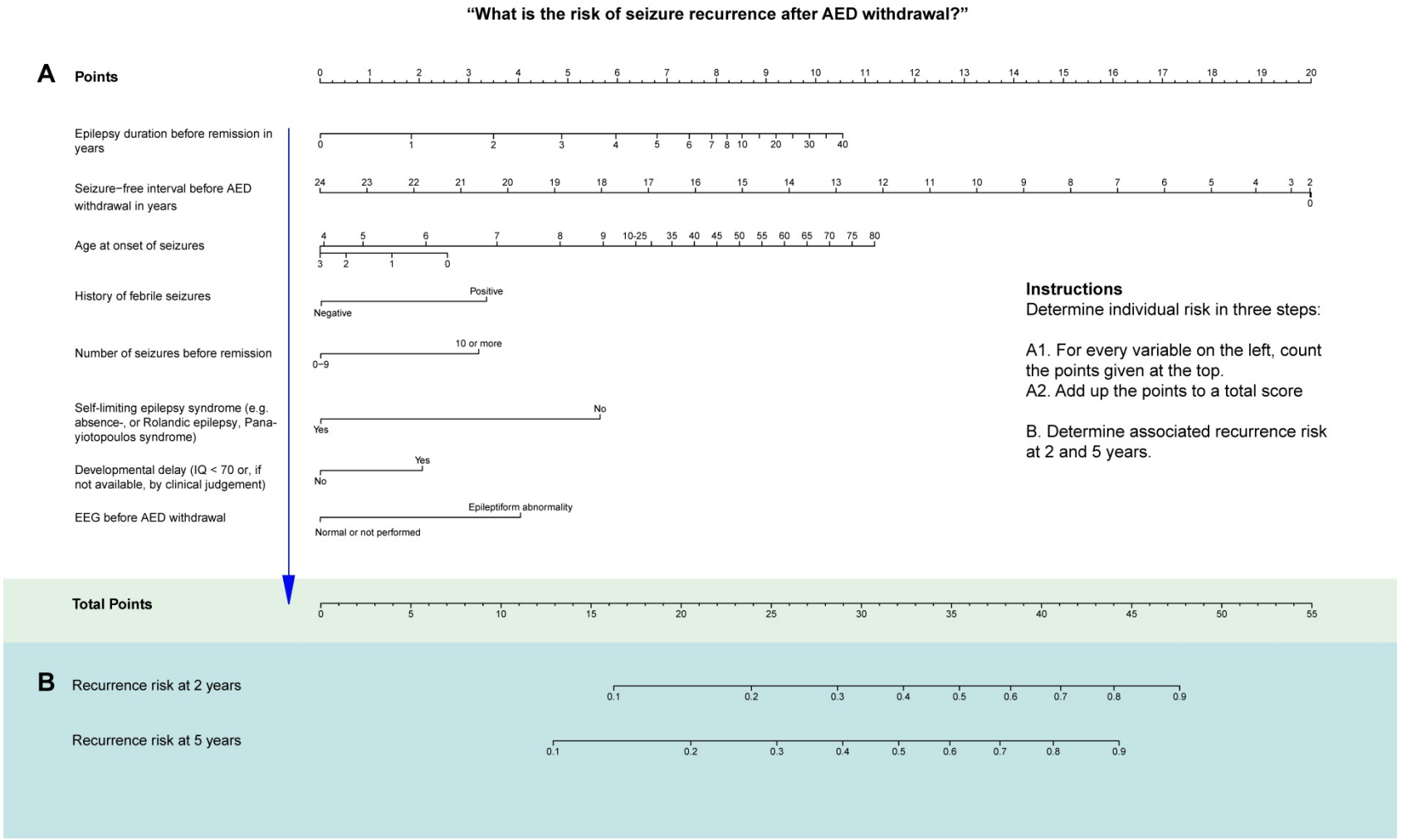


Figure 2a. Predicting seizure recurrence after AED withdrawal

Nomogram to predict seizure recurrence after AED withdrawal, validated in the ten cohorts summarised in table 1. The model is a visual representation of supplementary table 7. Example: a child whose seizures started at the age of 3 (0 points) who had active epilepsy for 1 year (2) and is seizure free since 2 years (20), with no history of febrile seizures (0), less than 10 seizures (0), no self-limiting epilepsy syndrome (5·5), no developmental delay and a normal EEG (0), has a total of 27·5 points, which corresponds to a risk of seizure recurrence of 28% and 36% at 2 and 5 years respectively.

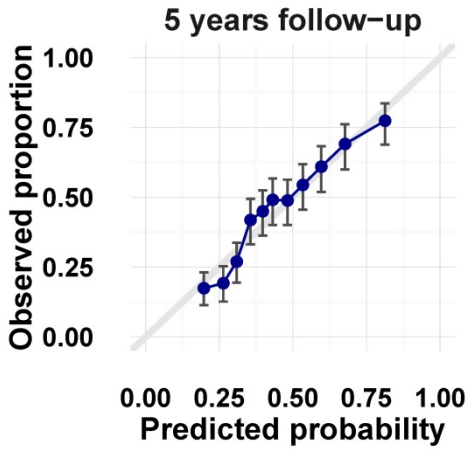


Figure 2b. Calibration plot for the prediction of seizure recurrence as modelled in figure 2a and supplementary table 7

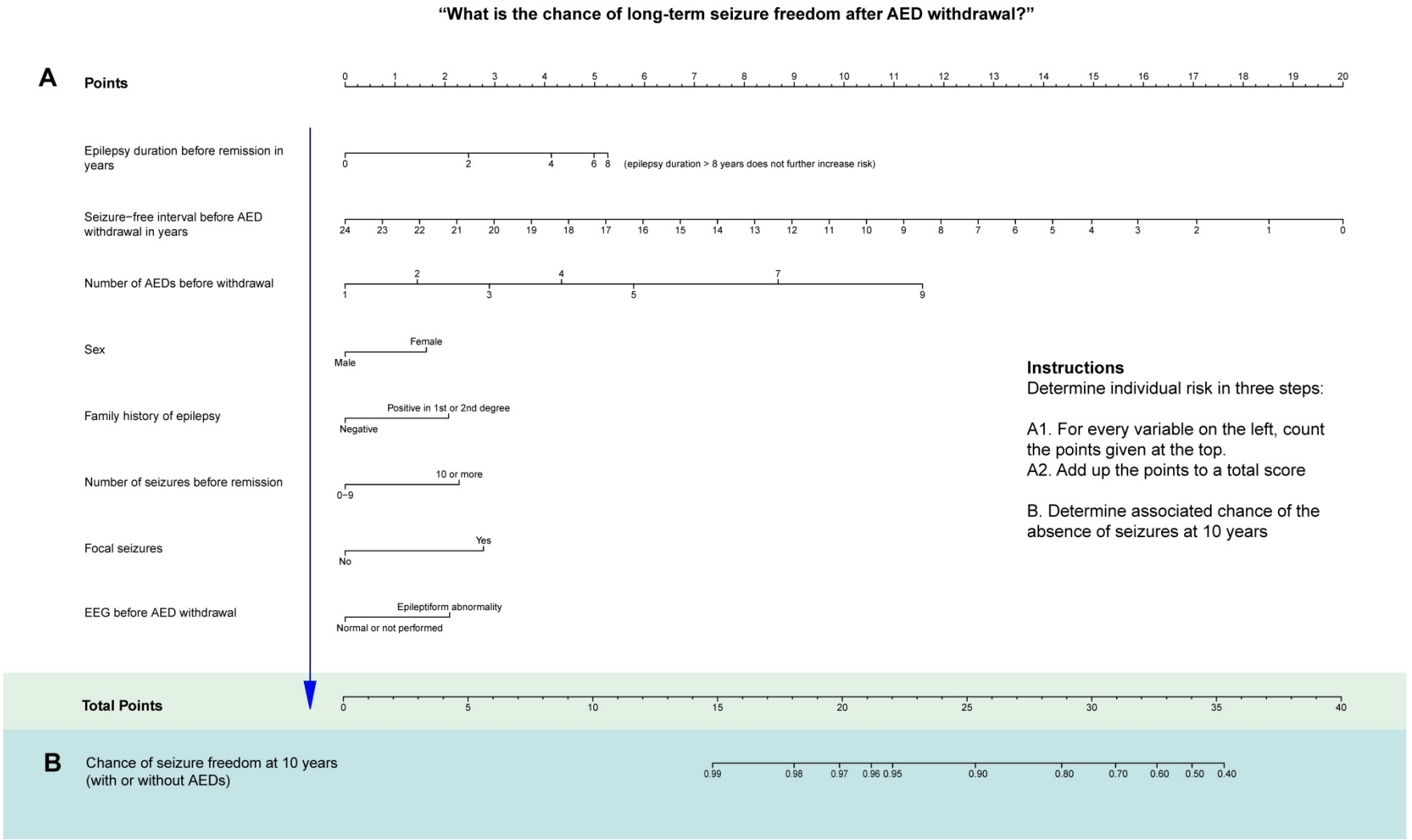


Figure 3a. Predicting seizure freedom (for at least one year) at 10 years follow-up

Nomogram to predict long-term outcome after AED withdrawal, validated in the ten cohorts summarised in table 1. The model is a visual representation of supplementary table 8. Example: a female (1·5 points) who had active seizures for 1 year (1), has been seizure free for 2 years (17), is using 1 AED (0), has no family history of epilepsy (0), had less than ten seizures in total (0), only had generalised seizures (0), and has no abnormalities on EEG before withdrawal (0), has a total of 19·5 points, which corresponds to the chance to be seizure free on the long term of 97%.

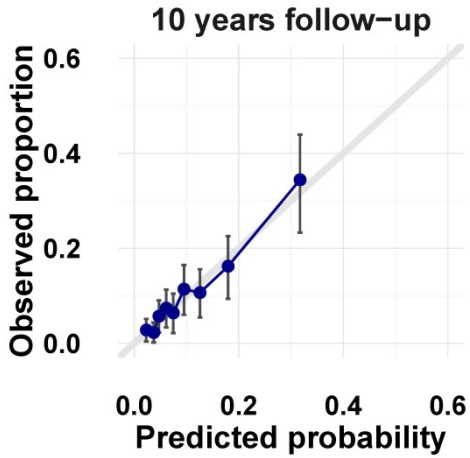
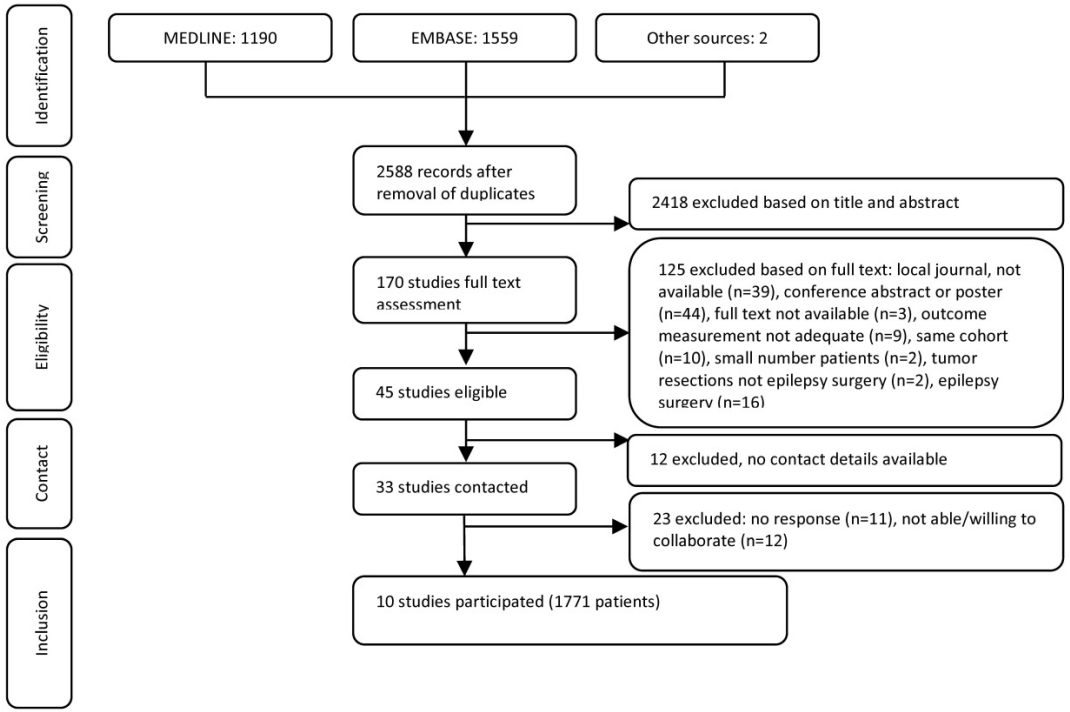
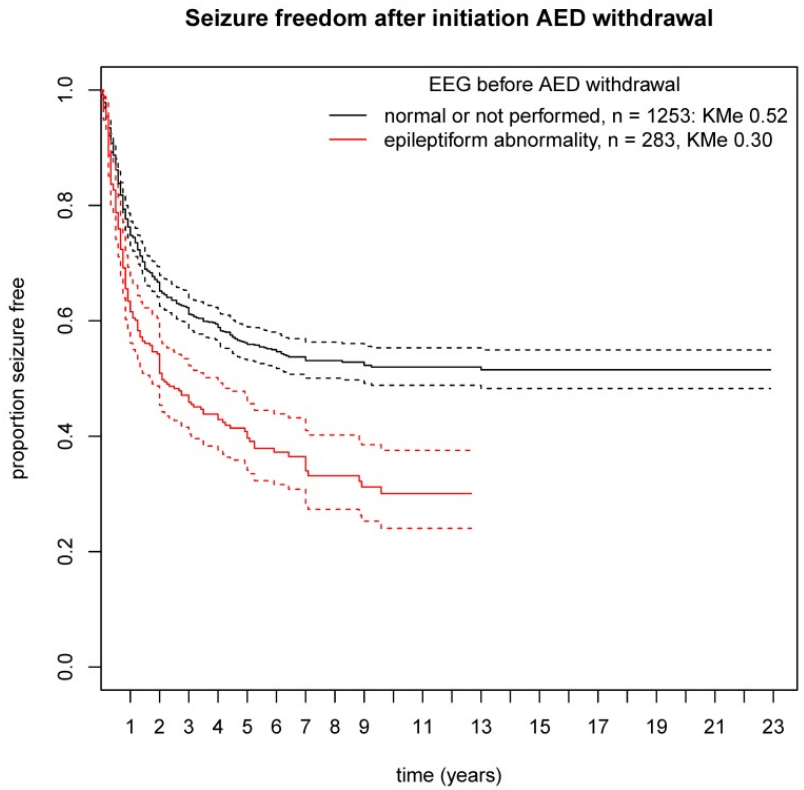


Figure 3b. Calibration plot for the prediction long-term seizure freedom as modelled in figure 3a and supplementary table 8

Supplementary figures and tables with the manuscript "Individualised prediction model of seizure recurrence and long-term outcome after antiepileptic drug withdrawal – an Individual Participant Data meta-analysis."



Supplementary figure 1. Flow-chart article inclusion



	time in years					
	0	1	2	5	10	13
Normal or not performed, number at risk/ cumulative number of events	1253	934/ 313	764/ 427	406/ 513	178/ 533	111/ 534
Epileptiform abnormality, number at risk/ cumulative number of events	283	174/ 108	147/ 137	71/ 163	27/ 175	

Supplementary figure 2. Seizure free patients after initiation of AED withdrawal, separated by EEG results before AED withdrawal.
Survival curve of seizure free patients over time with Kaplan-Meier estimates at 1, 2, 5, 10 and 13 years (time of last event in this dataset), with seizure recurrence taken as event. Time of zero equals the start of AED withdrawal. KMe = Kaplan-Meier estimate.

Supplementary table 1. Comparing follow-up and seizure recurrence rate between included studies and non-participating studies

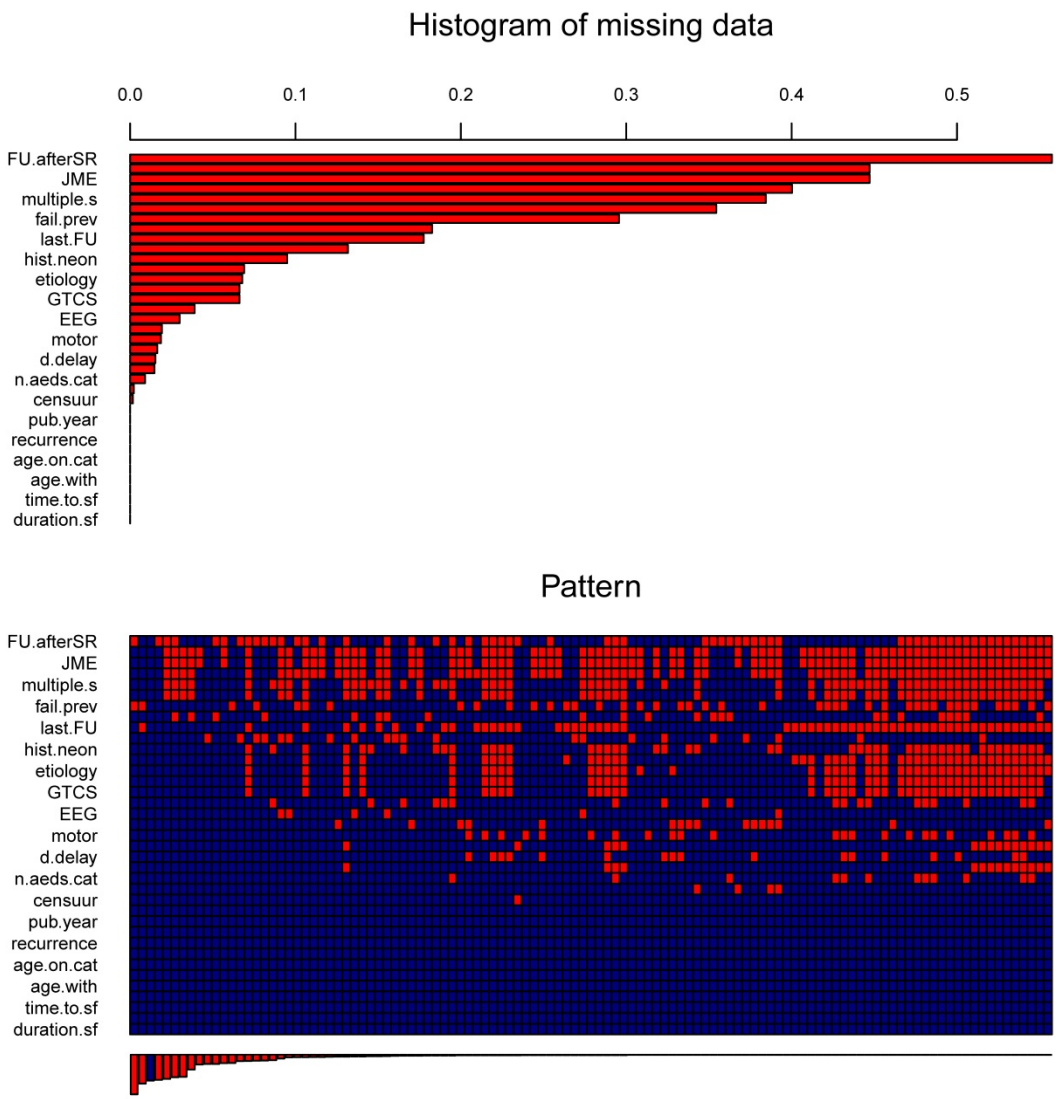
Variable	All studies (n=45 cohorts, 7082 patients)	Included studies (n=10 cohorts, 17 patients)	Non-participating studies (n=35 cohorts, 5311 patients)
Follow-up duration in months, median (range; IQR)	48 (12 – 408; 31 – 66)	44 (24 – 129; 36 – 56)	48 (12 – 408; 30 – 68)
Seizure recurrence rate, median (range; IQR)	30% (10 – 66; 25 – 40)	40% (26 – 66; 36 – 48)*	28% (10 – 63; 22 – 37)
Year of publication, median (range; IQR)	1999 (1981 – 2014; 1993 – 2006)	2002 (1987 – 2012; 1994 – 2005)	1999 (1981 – 2014; 1992 – 2007)
Ages included			
Only adults	2 (4%)	1 (10%)	1 (3%)
Only children	28 (62%)	5 (50%)	23 (66%)
Both adults and children	15 (33%)	4 (40%)	11 (31%)
Type of population			
Population based	3 (7%)	1 (10%)	2 (6%)
Secondary care	7 (16%)	1 (10%)	6 (17%)
Specialised centre	32 (71%)	7 (70%)	25 (71%)
Mixed	1 (2%)	1 (10%)	0
Unclear	2 (4%)	0	2 (6%)
Design			
Retrospective	12 (27%)	1 (10%)	11 (31%)
Prospective	24 (53%)	4 (40%)	20 (57%)
RCT	9 (20%)	5 (50%)	4 (11%)

IQR = interquartile range. RCT = Randomised controlled trial

*medians were calculated from data available from published results as available from our previous systematic review (Lamberink, 2015), not with the available individual patient data (IPD). Because the IPD contained longer follow-up than published results, the recurrence rate reported elsewhere in the current publication is higher.

Supplementary table 2. Missing data before imputations

Variable	n missing values	% missing values
Censor variable	3	0·2%
History of febrile seizures	4	0·2%
Number of AEDs. categorical	16	0·9%
Follow-up	26	1·5%
Developmental delay	27	1·5%
Motor deficit	33	1·9%
Family history of epilepsy	34	1·9%
EEG, general abnormalities	53	3·0%
Number of AEDs. numerical	69	3·9%
Focal seizures	117	6·6%
Generalised tonic-clonic seizures	117	6·6%
Aetiology	120	6·7%
History of neonatal seizures	168	9·4%
EEG, specific epileptiform abnormalities	233	13·1%
Seizure status at last follow-up	314	17·7%
Total number of seizures	323	18·2%
Failure of previous withdrawal attempt	523	29·4%
Epileptic encephalopathy	627	35·2%
Multiple seizure types	680	38·2%
Imaging	708	39·8%
Self-limiting epilepsy syndromes	791	44·5%
Juvenile myoclonic epilepsy	791	44·5%



Supplementary figure 3. Missing data before imputations

Supplementary table 3. Quality appraisal of prognostic studies (Hayden *et al*., 2006)

Publication	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement
Cardoso, 2003	+/-	+/-	+	+
Geerts, 2005	+	+	+	+
MRC, 1991	+	+	+/-	+
Overweg, 1987	+/-	+/-	+	+
Pavlovic, 2012	+	-	+/-	+
Ramos-Lizana, 2010	+	+	+	+
Sauma, 2005	+/-	+	+	+
Shinnar, 1994	+	+	+	+
Specchio, 2002	+	-	+	+
Tennison, 1994	+	+	+	+

'+' = bias is sufficiently limited; '±' = potential for bias is partly present; '-' = high potential for bias.
Adapted from: Lamberink HJ, Otte WM, Geleijns K, Braun KPJ. Antiepileptic drug withdrawal in medically and surgically treated patients: a meta-analysis of seizure recurrence and systematic review of its predictors. *Epileptic Disorders* 2015; 17(3):211-228 with permission from John Libbey Eurotext

Supplementary table 4. Baseline differences between patients with a history of seizure recurrence after AED withdrawal and those attempting for the first time

	No previous attempt (n = 1120)	Failure previous attempt of AED withdrawal (n = 126)
FU in months (median, IQR)	73 (47-137)	71 (54-149)
Seizure recurrence	508 (45%)	64 (51%)
FU after seizure recurrence in months (median, IQR)	59 (33-120)	60 (48-118)
Seizures at last follow-up	108/1016 (11%)	15/115 (13%)
Sex, female	526 (47%)	69 (55%)
Age at onset (median, IQR)	9 (4-15)	9 (3-18)
Age at onset ≥ 11	460 (41%)	53 (42%)
Age at withdrawal (median, IQR)	16 (10-27)	22 (15-37)
Duration of epilepsy, months (median, IQR)	24 (5-68)	61 (19-116)
Seizure free interval, months (median, IQR)	31 (24-48)	41 (48-62)
Number of AEDs (median, IQR)	1 (1-1)	1 (1-1)
History of febrile seizures	122/1116 (11%)	16 (13%)
Family history	249/1096 (23%)	37/123 (29%)
≥ ten seizures before remission	320/834 (38%)	40/96 (42%)
Benign	69/481 (14%)	0
Focal seizures	526/1050 (50%)	65/116 (56%)
Developmental delay	185/1103 (17%)	10/125 (8%)
EEG epileptiform abnormality	194/945 (21%)	18/113 (16%)

FU = follow-up

Supplementary table 5. Full prediction model 1: predicting seizure recurrence

Variable	HR (95% CI)	p-value
Epilepsy duration before remission in years	*	*
Seizure free interval before AED withdrawal in years	*	*
Age at onset of epilepsy	*	*
Family history of epilepsy	1·22 (1·03 - 1·45)	0·0252
History of febrile seizures	1·38 (1·11 - 1·70)	0·0033
≥ 10 seizures before remission	1·35 (1·13 - 1·60)	0·0008
Generalised tonic-clonic seizures	1·19 (0·97 - 1·46)	0·0940
Multiple seizure types	1·13 (0·90 - 1·42)	0·2779
Self-limiting epilepsy syndrome †	0·57 (0·43 - 0·77)	0·0004
History of epileptic encephalopathy	0·69 (0·50 - 0·93)	0·0172
Juvenile Myoclonic Epilepsy	1·37 (0·98 - 1·93)	0·0664
Developmental delay	1·31 (1·05 - 1·63)	0·0160
Epileptiform abnormality on EEG before withdrawal	1·48 (1·23 - 1·77)	<0·0001

Predictors in model selected by backward selection. Adjusted c-statistic = 0·66 (95% CI 0·65-0·66), bootstrap-corrected for 1·8% optimism

*not linearly related to outcome, no estimate available. For influence on model, see nomogram in figure 2; †formerly called "benign course", e.g. absence epilepsy, benign epilepsy with centrotemporal spikes (Rolandic epilepsy), Panayiotopoulos syndrome

Supplementary table 6. Full prediction model 2: predicting seizures in last year of follow-up

Variable	HR	p-value
Epilepsy duration before remission in years	*	*
Seizure free interval before AED withdrawal in years	*	*
Number of AEDs before withdrawal (per AED)	1·34 (1·09 - 1·64)	0·0060
Female sex	1·48 (1·04 - 2·10)	0·0302
Family history of epilepsy	1·65 (1·10 - 2·47)	0·0161
≥ 10 seizures before remission	1·65 (1·03 - 2·64)	0·0366
Remote symptomatic aetiology	1·67 (1·08 - 2·59)	0·0219
Focal seizures	1·75 (1·19 - 2·57)	0·0042
Self-limiting epilepsy syndrome †	0·62 (0·34 - 1·13)	0·1173
Juvenile myoclonic epilepsy	1·82 (0·61 - 5·44)	0·2759
Motor deficit	0·56 (0·28 - 1·13)	0·1047
Epileptiform abnormality on EEG before withdrawal	1·68 (1·11 - 2·54)	0·0140

Predictors in model selected by backward selection. Adjusted c-statistic = 0·71 (95% CI 0·70 – 0·71), bootstrap-corrected for 3·5% optimism

*not linearly related to outcome, no estimate available. For influence on model, see nomogram in figure 4

Supplementary table 7. Final prediction model 1: predicting seizure recurrence

Variable	HR (95% CI)	p-value
Epilepsy duration before remission in years	*	*
Seizure free interval before AED withdrawal in years	*	*
Age at onset of epilepsy	*	*
History of febrile seizures	1·40 (1·13 - 1·73)	0·0020
≥ 10 seizures before remission	1·38 (1·17 - 1·63)	0·0002
Self-limiting epilepsy syndrome †	0·57 (0·44 - 0·72)	<0·0001
Developmental delay	1·23 (1·01 - 1·50)	0·0420
Epileptiform abnormality on EEG before withdrawal	1·50 (1·25 - 1·80)	<0·0001

The number of variables of the full model from supplementary table 5 was reduced. Adjusted c-statistic = 0·65 (95% CI 0·65-0·66), bootstrap-corrected for 1·4% optimism. Random effects 1·01.
*not linearly related to outcome, no estimate available. For influence on model, see nomogram in figure 2; †formerly called "benign course", e.g. absence epilepsy, benign epilepsy with centrotemporal spikes (Rolandic epilepsy), Panayiotopoulos syndrome

Supplementary table 8. Final prediction model 2: predicting seizures in last year of follow-up

Variable	HR	p-value
Epilepsy duration before remission in years	*	*
Seizure free interval before AED withdrawal in years	*	*
Number of AEDs before withdrawal (per AED)	1·37 (1·11 - 1·69)	0·0031
Female sex	1·42 (1·01 - 2·01)	0·0437
Family history of epilepsy	1·56 (1·04 - 2·33)	0·0302
≥ 10 seizures before remission	1·62 (1·04 - 2·51)	0·0315
Focal seizures	1·82 (1·26 - 2·64)	0·0016
Epileptiform abnormality on EEG before withdrawal	1·57 (1·04 - 2·36)	0·0313

The number of variables of the full model from supplementary table 6 was reduced. Adjusted c-statistic = 0·71 (95% CI 0·70 – 0·71), bootstrap-corrected for 3·5% optimism. Random effects 1·65.
*not linearly related to outcome, no estimate available. For influence on model, see nomogram in figure 3

Supplementary table 9. Internal-external cross-validation for prediction of seizure recurrence

Omitted study	C-statistic (remaining studies)*	C-statistic (omitted study)*
Cardoso	0·655	0·656
Geerts	0·645	0·649
MRC	0·674	0·665
Overweg	0·648	0·650
Pavlovic	0·650	0·652
Ramos-Lizana	0·648	0·638
Serra	0·646	0·651
Shinnar	0·643	0·642
Specchio	0·649	0·645
Tennison	0·648	0·649

To assess the IECV, one study was omitted after which the model was fitted on the nine remaining studies. A c-statistic was computed on the nine studies, after which the model was forced onto the omitted study, where again a c-statistic was computed.
*c-statistic is corrected for optimism similar to the overall c-statistic in suppl. tables 5-8

Supplementary table 10. Internal-external cross-validation for prediction of seizures in last year of follow-up

Omitted study	C-statistic (remaining studies)*	C-statistic (omitted study)*
Cardoso	0·704	0·700
Geerts	0·715	0·713
MRC	0·785	0·787
Overweg	0·711	0·714
Pavlovic	0·704	0·709
Ramos-Lizana	0·693	0·683
Serra	0·716	0·702
Shinnar	0·717	0·720
Specchio	0·716	0·711
Tennison	0·717	0·715

To assess the IECV, one study was omitted after which the model was fitted on the nine remaining studies. A c-statistic was computed on the nine studies, after which the model was forced onto the omitted study, where again a c-statistic was computed.
*c-statistic is corrected for optimism similar to the overall c-statistic in suppl. tables 5-8

APPENDIX 1

Search strategy in PubMed and EMBASE databases, as last executed until November 6, 2014

MEDLINE: (antiepileptic*[tiab] OR AED*[tiab] OR anticonvulsant*[tiab] OR anticonvulsants[MeSH]) AND (stop[tiab] OR stopping[tiab] OR reduction[tiab] OR discontinuation[tiab] OR withdrawal[tiab]) AND ("seizure free"[tiab] OR "seizure-free"[tiab] OR recurrence[tiab] OR relapse[tiab] OR remission[tiab])

EMBASE: ('anticonvulsive agent'/exp OR antiepileptic:ti:ab OR antiepileptica:ti:ab OR AED:ti:ab OR AEDs:ti:ab OR anticonvulsant:ti:ab OR anticonvulsants:ti:ab) AND ('drug withdrawal'/exp OR stop:ti:ab OR stopping:ti:ab OR reduction:ti:ab OR discontinuation:ti:ab OR withdrawal:ti:ab OR titration:ti:ab) AND ('recurrence risk'/exp OR 'seizure free':ti:ab OR 'seizure-free':ti:ab OR recurrence:ti:ab OR relapse:ti:ab OR remission:ti:ab) NOT [Medline]/lim

APPENDIX 2

Supplementary methods

Data extraction and data transformation

Study-level data that were sought: country, type of population (population-based, secondary care, specialised centre, mixed), years of recruitment, study design.

Participant data that were requested:
1) basic information: follow-up after start of AED withdrawal in months, in case of RCT treatment allocation.
2) outcome variables: seizure recurrence, time to seizure recurrence in months, seizure status at last follow-up (presence of seizures in the last year including auras)
3) potential predictors: sex (male/female), age at onset of epilepsy (years), age at withdrawal (years), family history in 1st or 2nd degree, history of neonatal seizures, history of febrile seizures, number of seizures before remission (less than 10/10 or more), epilepsy duration before remission (interval between first and last seizure in months), seizure free interval before AED withdrawal (interval from last seizure to start AED withdrawal), failure of a previous AED withdrawal attempt, number of AEDs before withdrawal, presence of focal seizures, presence of generalised tonic-clonic seizures, presence of multiple seizure types, aetiology (remote symptomatic/ proven genetic/ unknown), presence of Juvenile Myoclonic Epilepsy, presence of a self-limiting epilepsy syndrome (absence epilepsy, benign epilepsy with centro-temporal spikes, Panayiotopoulos syndrome), presence or history of epileptic encephalopathy (West syndrome, Ohtahara syndrome, Lennox-Gastaut syndrome, ESES, Landau-Kleffner), developmental delay, motor deficits on neurological examination, imaging (normal, structural laesion, imaging not performed), EEG before AED withdrawal (normal, general abnormality, not performed), epileptiform EEG before AED withdrawal (normal, epileptiform abnormality, not performed).

Data with variable definitions or data transformation:
Developmental delay: IQ below 70 (4 studies, n=698), IQ below 70 or clinical judgement (1 study, n=52), clinical judgement and necessity for specialised schooling (3 studies, n=899), IQ between 70 and 80 (1 study, n=65), Denver scale (1 study, n=57).

Imaging: many advances in imaging have come about in the past decades, resulting in a proportion of patients who have not been evaluated with MRI but with CT-scan. MRI scans have improved in accuracy over the years.

Aetiology: in 2010 the ILAE proposed a new approach to aetiology, in which the term ‘remote symptomatic’ is not used anymore. Since most included studies are older than the new definition, the old dichotomy of remote symptomatic versus not remotely symptomatic was used.

Number of AEDs: one study (Pavlovic, n=52) only had binary information available, multi- versus polytherapy. For the other studies, a new variable with this dichotomy was created next to the continuous variable, for the purpose of imputing the 52 missing values.

EEG abnormality: six studies provided information on both general and specific EEG abnormalities (Cardoso, Geerts, MRC, Overweg, Specchio, Tennison , n=1182). Four studies only had information on general EEG abnormalities (Pavlovic, Ramos, Serra, Shinnar, n=589). For the latter four, a new variable was created in which the categories “normal EEG” and “not performed” were kept, the category “abnormal” was set to missing and imputed to create the variable “epileptiform EEG before AED withdrawal”.

Epilepsy duration: two studies (Pavlovic, Ramos, n=268) formulated this as the interval between start treatment and the last seizure, which was accepted as an approximation of the interval between the first and last seizure.

Self-limiting epilepsy syndromes: the definition of 'Benign childhood epilepsies' has been debated. Therefore, we chose to define this group of syndromes as including absence epilepsy, Rolandic epilepsy, or Panayiotopoulos syndrome. Patients with Juvenile Myoclonic Epilepsy are not included.

Statistical analysis

Missing information was analysed and imputed using Multiple Imputations using Chained Equations (MICE, number of imputations = 20)[1], which provides more accurate summary statistics than deleting cases with missing data[2]. Continuous variables were imputed using predictive mean matching; logistic regression was used for imputing categorical variables. Baseline characteristics were computed before imputations were performed. If follow-up after a seizure recurrence was less than a year, the second outcome parameter could not be established, in which case the value was reported as 'missing', after which it was imputed to estimate the outcome most accurately[3].

To account for the variation in follow-up among participants, analyses were performed with a variation on the Cox proportional hazards model. The standard Cox model has shown disadvantages concerning heterogeneity between groups, as it can be seen as a fixed-effect model which does not adjust for between-study heterogeneity. To account for this heterogeneity, a shared frailty model was used, which is a random-effects extension of the Cox proportional hazards model[4]. As an indication of heterogeneity, the random-effects statistic reported in this paper is the approximate hazard ratio between two equally sized prognostic groups from different cohorts.

The assumption of linearity was assessed by inspection of martingale residuals and if violated corrected by restricted cubic splines with three to five knots. In the survival analyses we assumed censoring to be non-informative, and the assumption of proportional hazards was not violated as tested by statistical and visual inspection of Schoenfeld residuals[5]. Multi-collinearity was checked through a correlation matrix, after which age at withdrawal was removed from the models because of collinearity with age at onset of seizures (Pearson's r = 0·80).

A selection of strongest contributing predictors was made through backward selection of variables using Akaike information criterion (AIC) combined with manual removal of least contributing predictors, until the most optimal model was selected. For the purpose of creating a prediction model, categorical variables with three categories were reduced to binary variables when the third category was not contributing to the model (e.g. instead of EEG before withdrawal categories "normal", "epileptiform abnormality" and "not performed", comparing "normal or not performed" with "epileptiform abnormality"). Using the final reduced model, a nomogram was created to assist the clinician in computing the individual risks for a patient.

To validate the models, concordance-statistics (c-statistics) were computed on the model and on 200 bootstrap samples to correct for optimism. The adjusted c-statistic and percentage of optimism are reported. Furthermore, internal-external cross-validation (IECV) was performed to assess validity of the model across the different populations. With this method, it can be shown that the models work similarly in the different populations, and it therefore functions as external validation[6]. To assess the calibration of the models, a graphic plotting the predicted probability versus the observed proportion was used. The plotted data points should align the diagonal grey line.

Statistical analyses were performed with R Statistical Software version 3·2·2, using packages 'MICE', 'coxme', and 'rms'.

References:

1 Van Buuren S, Groothuis-Oudshoorn K. Multivariate Imputation by Chained Equations. *J Stat Softw* 2011; 45: 1–67.

2 Marshall A, Altman DG, Royston P, Holder RL. Comparison of techniques for handling missing covariate data within prognostic modelling studies: a simulation study. *BMC Med Res Methodol* 2010; 10: 1–16.

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4 Therneau TM. coxme: Mixed Effects Cox Models. R-package Descr. 2015; 1–14.

5 Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994; 81: 515–26.
6 Ahmed I, Debray TP, Moons KG, Riley RD. Developing and validating risk prediction models in an individual participant data meta-analysis. *BMC Med Res Methodol* 2014; 14. DOI:10.1186/1471-2288-14-3.