EARLY PREDICTORS OF SEIZURE OUTCOME IN NEWLY DIAGNOSED EPILEPSY

A Systematic Review of Prognosis Studies

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DECLARATION

I hereby declare that the work described herein is original and my own, except where due acknowledgement has been made to the work of others. This thesis was completed while enrolled in the School of Public Health at the University of Sydney, under the supervision of Dr Alexandra Martiniuk and Professor Craig Anderson based at the George Institute for Global Health in Sydney who provided invaluable advice and many suggestions for the improvement of the study and this document. I certify that this thesis has not already been submitted, wholly or in part, for a higher degree to any other university or institution. All the help received in preparing this thesis, all material from published sources, and all material copied from the work of others have been properly acknowledged and referenced.

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Folarin Oluseye (Seye) ABIMBOLA

4 August 2010

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I wish I could say like Mark Twain that if only I had more time, my thesis would have been much shorter than this; it is not in the nature of theses to be decidedly brief. I therefore express deep gratitude to my supervisors who took the pain and patience to read through and annotate with comments, chicken scratches and smiley faces the overly chatty and journalistic ramblings that made up the early drafts of the thesis.

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ABSTRACT

The physical and psychosocial consequences of seizures in epilepsy are more prevalent in people with uncontrolled seizures, and are lessened with seizure control. Early management strategies and patient counselling may be informed by the predictors of control in newly diagnosed patients. The main objective of this systematic review was to identify variables that consistently and independently predict seizure outcome in people with newly diagnosed epilepsy.

English-language publications identified from electronic databases (MEDLINE and EMBASE) and reference lists of included studies, published until March 2010 were reviewed. The publications were of nested case control and cohort studies of unselected population of at least 100 people with epilepsy with multivariate analysis of the effect on seizure outcome of predictor variables collected within the first year of diagnosis in patients followed up for at least 1 year.

The quality of included studies was appraised for their likelihood for bias in five areas: study participation, study attrition, prognostic factor measurement, outcome measurement and statistical analysis. Data from each study were independently extracted three times; at each succeeding stage, the extracted data were compared with the previous extraction and where there were discrepancies, clarification made by consulting the publication. Consistent predictors were identified in more than 1 study from different cohorts.

There were 52 studies from a total of 33 publications. Five studies predicted immediate remission of seizures; 9 studies predicted remission off antiepileptic medication; 20 studies predicted remission on or off antiepileptic medication; 12 studies predicted intractability to antiepileptic medication and 1 study developed a model to predict not achieving remission after 1 or more relapses following an initial period of remission. 5 studies externally validated models predicting seizure outcome.

Two factors reduce the chance of achieving immediate remission: *More than 1 seizure before recruitment* [RR 0.63 (95%CI 0.36-1.11)] and *remote symptomatic aetiology* [childhood-onset epilepsy: RR 0.59 (95%CI 0.41-0.86), adult-onset epilepsy: RR 0.44 (95% CI 0.26-0.77)].

Having *more than 1 seizure in the period between 6 and 12 months on medication* [RR 0.24 (95%CI 0.10-0.60)] and *intellectual disability* [RR 0.77 (95%CI 0.61-0.94)] reduce the chance of achieving remission off medication in childhood-onset epilepsy. None of the studies predicting remission off medication were of adult-onset epilepsy.

Five factors reduce the chance of achieving remission on or off medication are: *More than 1 seizure before diagnosis* [childhood-onset epilepsy: RR 0.66 (95%CI 0.46-0.95), adult-onset-epilepsy: 0.81 (95%CI 0.66-0.99)] for the natural logarithm of every additional seizure; *seizures in the first 6 months after the index seizure* [childhood-onset epilepsy: RR 0.50 (95%CI 0.35-

0.72), adult-onset-epilepsy: RR 0.59 (95%CI 0.50-0.70) for the natural logarithm of every additional seizure; *mixed seizure types at onset* [RR 0.70 (95%CI 0.37-1.04), adult-onset epilepsy: OR 0.23 (95% CI 0.10-0.48)]; *intellectual disability* [childhood-onset epilepsy: OR 0.40 (95%CI 0.18-0.90), adult-onset epilepsy: OR 0.10 (95%CI 0.05-0.25)]; and *remote symptomatic aetiology* [childhood-onset epilepsy: RR 0.63 (95% CI 0.47-0.84), adult-onset epilepsy: RR 0.44 (95% CI not reported)].

O*nset of seizures in infancy* [RR 5.48 (95%CI 2.10-9.64)], *intellectual disability* [OR 18.2 (95%CI 5.2-63.6)], and *remote symptomatic aetiology* [RR 5.48 (95%CI 2.10-9.64)] increase the risk of medical intractability, while *idiopathic aetiology* [RR 0.20 (95%CI 0.0-0.80)] reduces the risk of intractability in childhood-onset epilepsy. None of the studies predicting medical intractability were of adult-onset epilepsy.

The externally validated models have little predictive gain over information provided by simple prevalence rates of seizure outcome, and the models predict wrongly in about 1 out of 3 children in the development and external validation cohorts. None of the models developed in adult-onset epilepsy were externally validated.

The study suggests that onset of seizures in infancy, number of seizures (before diagnosis, in the first 6 months after diagnosis, and between 6 and 12 months on medication), intellectual disability and the aetiology of seizures are the important predictors of seizure outcome in newly diagnosed epilepsy. The study demonstrates the feasibility of systematic review with thorough quality appraisal as a means of identifying the consistent predictors of an outcome in exploratory prognostic factor studies. The review also shows the need for further studies of the prognosis of adult-onset epilepsy.

1 CHAPTER ONE: INTRODUCTION AND BACKGROUND

This chapter is in 3 parts. The first part introduces and provides an overview of the main thrust of the thesis. The second part presents a general background to prognosis studies in epilepsy and describes the benefits of early determination of the prognosis of epilepsy in newly diagnosed patients. The second part also presents a framework for classifying the different potential prognostic categories of a newly diagnosed patient with epilepsy. The third part is an overview of the role of systematic review in medicine with particular application to prognosis studies in epilepsy.

1.1 INTRODUCTION

1.1.1 DEFINITION AND EPIDEMIOLOGY OF EPILEPSY

Epilepsy is a chronic neurological disorder characterised by a recurrent tendency to have spontaneous, intermittent, abnormal electrical activity in a part of the brain, which manifest as seizures, and diagnosed as the result of a patient having a second unprovoked seizure, with at least 24 hours between the first and second seizure. This definition regards an episode of status epilepticus (a seizure lasting more than 30 minutes or repeated seizures without intervening periods of regained function or consciousness) as a single seizure.(1)

However, the definition of epilepsy as a tendency to have recurrent seizures excludes seizures that are provoked (i.e. not spontaneous, therefore “acute symptomatic”) by an obvious and immediate preceding cause e.g. an acute systemic or metabolic imbalance, drugs or toxins, or a recent cerebral damage from stroke, trauma or infection. Seizures occurring in children between 6 months and 6 years only within the context of a febrile illness without the evidence of intracranial aetiology (febrile seizures) are also excluded, as are seizures occurring only within the neonatal period.(1, 2)

The World Health Organisation (WHO) estimates the point prevalence of active epilepsy (i.e. people with continuing seizures or the need for treatment) as generally 4 to 10 per 1,000 people, and in developing countries from 6 to 10 per 1,000. It is also estimated that at least 50 million people in the world have epilepsy as 43.7 million people were reported to have epilepsy from 108 countries covering 85.4% of the world in a WHO survey.(3, 4) The mean number of people with epilepsy per 1000 population is 8.93. This varies from 7.99 in high-income countries to 9.50 in low-income countries.(3) However, the incidence of epilepsy in developing countries is about twice that in developed countries, and the WHO estimates that about 80% of the world’s epilepsy patients are in developing countries.(3)

In developed countries, new-onset seizure occurs in approximately 80 people per 100,000 in a year. The estimates of annual incidence of epilepsy in the general population range from 30 to 57 per 100,000.(5) However, the incidence rate of epilepsy has a bimodal pattern in relation to age: it is high in the paediatric population (about half of all epilepsy cases are diagnosed in childhood or adolescence), decreasing through adulthood until approximately age 60, when the incidence again begins to increase.(6, 7) With the onset of epilepsy, a chronic disorder, being common in childhood and adolescence, and due to the burden of experiencing unpredictable paroxysmal seizure events and its psychosocial implications, epilepsy contributes about 1% of the global burden of disease.(4)

1.1.2 SEIZURES IN EPILEPSY

A working knowledge of basic clinical epilepsy is assumed in this thesis. However, the following account of the clinical and pathophysiological foundations of seizures in epilepsy is based on a 2009 monograph on clinical epilepsy by Shorvon,(8) updated with the use of terminologies for seizure classification from the 2010 report of the ILAE (International League Against Epilepsy) Commission on Classification and Terminology.(9)

The term “seizure” refers to the transient clinical manifestation of an episodic, abnormal, excessive, hypersynchronous discharge of a population of epileptic cortical neurons. For a particular patient, the seizure tends to be stereotyped, although it may take many forms (mixed seizure types) in others. The form seizures in epilepsy take could be conceptualised according to how it is experienced by the patient (as a motor, somatosensory, autonomic or psychic manifestation with or without accompanying impaired level of consciousness) or more conveniently, on physiological grounds, as either focal or generalised, in relation to how seizure activity originates within the brain.

The terms “focal” and “generalised” have been used to express a dichotomous classification for seizures and epilepsy, although they do not represent a clear dichotomy in the pathophysiology of seizures.(9) In focal seizures, the paroxysmal neuronal activity giving rise to the seizure is limited to a focal area in one half of the cerebrum, with consciousness preserved, impaired or completely lost. (Figure 1)

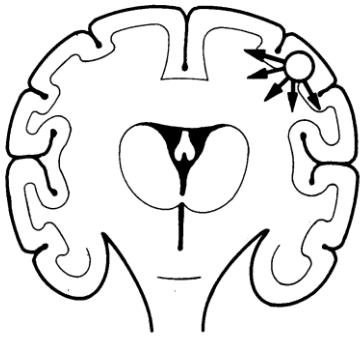


Figure 1 | Pathophysiology of Focal Seizures
[Image from Dekker 2002(10)]

For generalised seizures, the electrophysiological abnormality involves large areas of the 2 cerebral hemispheres simultaneously and synchronously. These generalised seizures are always accompanied by at least impaired level of consciousness. (Figure 2)

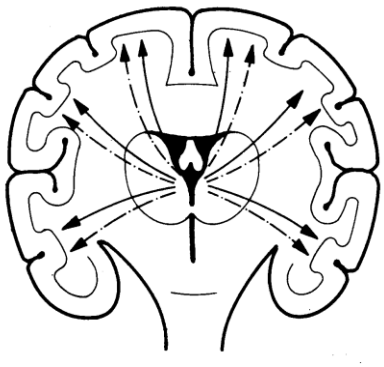


Figure 2 | Pathophysiology of Primary Generalised Seizures
[Image from Dekker 2002(10)]

The third category that blurs the distinction between focal and generalised seizures is the secondarily generalised seizures in which the initially focal neuronal discharge spreads from 1 hemisphere to the other to become generalised. (Figure 3)

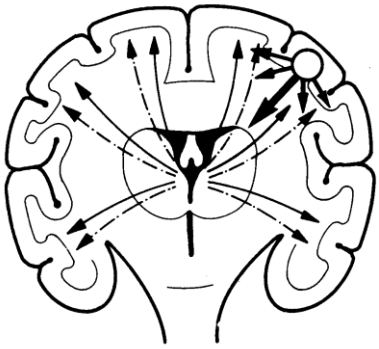


Figure 3 | Pathophysiology of Secondary Generalisation of Seizures
[Image from Dekker 2002(10)]

FOCAL SEIZURES

Focal seizures that remain localised manifest symptoms depending on the area of the cerebral cortex affected. In about 15% of patients with epilepsy the only seizure type they experience are those that start focally and remain focal with consciousness preserved, impaired or completely lost.

Focal seizures with motor manifestations occur when seizure focus is in the precentral gyrus (motor cortex) affecting the contralateral face, arm, trunk or leg characterised by rhythmical jerking or sustained spasm. The focal seizures with somatosensory or special sensory (simple hallucinations) manifestations arise in the sensory cortex, and may cause unpleasant tingling or

electric sensations in the contralateral face and/or limb. Focal seizures with sensory manifestations may originate from the visual (occipital) cortex with hallucination such as balls of light or patterns of colour, or from the temporal lobe, where hallucination may involve faces or scenes. Focal seizures with autonomic manifestations include changes in skin colour, blood pressure, heart rate, pupil size and piloerection.

Focal seizures with psychic manifestations occur especially when the focus is in the temporal lobe, with 6 categories of manifestation: 1.) *Dysphasia* when cortical speech areas of the frontal and temporoparietal lobes are affected; 2.) *Dysmnesia*, in which memory problems such as déjà vu, jamais vu, flashbacks or panoramic experiences; 3.) *Cognitive*, where dreamy states and sensations of unreality or depersonalisation is part of the seizure; 4.) *Affective*, in which fear occurs commonly, but depression, anger and irritability may also be a feature of the seizure; 5.) *Illusions*, which may be of size, weight, shape, distance or sound which occurs usually with a temporal or parieto-occipital focus; and 6.) *Hallucinations*, which may be visual, auditory, gustatory or olfactory usually due to temporal or parieto-occipital focus.

GENERALISED SEIZURES

Generalised seizures may be primary or secondarily generalised. In about 25% of patients with epilepsy, only primary generalised seizure occurs. There are 6 categories of primary generalised seizure, all accompanied with impaired consciousness from the onset of seizure activity as seizure originates extensively within cerebral cortex and subcortical structures.

However, 20% of all patients with epilepsy have primarily generalised seizures with only tonic clonic manifestation where the patient suddenly becomes rigid (tonus), then unconscious, falls if standing, and respiration is arrested with possible central cyanosis. The rigidity then becomes periodically relaxed (clonus). The patient subsequently enters a flaccid state of deep coma. When consciousness is regained, there is first a phase of confusion and disorientation following which the patient regains full memory, feeling terrible, with headache, and sleepiness. There is possibility of loss of continence occurring as well as tongue biting during the seizure.

The other types of primary generalised seizures make up the remaining 5% of patients with epilepsy having only primary generalised seizures: 1.) *Absence Seizures* occur typically as an abrupt loss of consciousness, but with preservation of muscle tone, and in its atypical form, loss of consciousness is not complete, with varying degrees of loss of muscle tone. 2.) *Myoclonic Seizures* present as brief contraction of a muscle or muscle group or several muscle groups, which may be single or repetitive and with varying severity from a twitch to severe jerking. 3.) *Clonic Seizures* are often asymmetric with irregular clonic jerking, while 4.) *Tonic Seizures*, present as tonic muscle contraction without a clonic (jerking) phase and 5.) *Atonic Seizures*, in its most severe form, manifests as a sudden complete loss of postural tone and the patient drops or, it may be more restricted, resulting in loss of tone in specific groups of muscle.

These seizures types are primary generalised. However, they may also be secondary generalised, when the seizure starts with an aura (a partial seizure). These secondary generalised seizures occur exclusively in about 60% of patients with epilepsy.

1.1.3 AETIOLOGY OF SEIZURES IN EPILEPSY

The concept for assessing, categorising and reporting on the underlying cause of epilepsy, was described in the 1989 ILAE Commission on Classification and Terminology report as being idiopathic, symptomatic, or cryptogenic.(11) In idiopathic aetiology, "there is no underlying cause other than a possible hereditary predisposition… and a presumed genetic aetiology.'' Symptomatic aetiology is "considered the consequence of a known or suspected disorder of the central nervous system (CNS). The term cryptogenic "refers to a disorder whose cause is hidden or occult… presumed to be symptomatic, but the aetiology is not known."(11)

Many human beings and other animals will have seizures in abnormal metabolic circumstances such as hyponatraemia, hypocalcaemia, hypoxia, hypo or hyperglycaemia.(5) However, the tendency to have recurrent seizures is not common to all and there are aetiological factors responsible, even though these factors cannot be identified in about 30% of patients (cryptogenic). The cause is genetic in about another 30% (idiopathic) and symptomatic (or remote symptomatic, to distinguish from acute symptomatic seizures that are excluded from the definition of epilepsy) in about 40% due to cerebrovascular disease (10-20%), malformations including hippocampal sclerosis, other neurological disorders and neurodegenerative disease (10-20%) intracranial tumour (5-10%), brain trauma (5%), cerebral infection (5%), or metabolic disorder and toxins including alcohol (5%).

The more recent 2010 report of the 2005-2009 ILAE Commission on Classification and Terminology (9) recommends more clearly defined and less confusing and conflating terms and concepts in place of the traditional terminologies. The authors of the report propose that "Genetic" replaces Idiopathic, "Structural/Metabolic" replaces symptomatic, and "Unknown Cause" replaces cryptogenic. The only major difference in the proposed use and definition of these terms relates specifically to advances in the use of genetics to better classify the aetiology of epilepsy. This thesis keeps to terminologies in current use.

1.1.4 CHALLENGES OF STUDYING THE PROGNOSIS OF EPILEPSY

DIAGNOSIS AND CASE ASCERTAINMENT

Epilepsy syndromes (epileptic seizures characterised by a consistent cluster of patient characteristics, with signs and symptoms occurring together) are organised with a complex relationship to seizure pathophysiology and aetiology.(8) The ILAE classification of epilepsy syndromes follows the pattern of aetiological classification as syndromes of epilepsy arising from focal seizures are grouped under the headings of idiopathic, symptomatic and cryptogenic

aetiology as are those arising from generalised seizures and those that are not classified either as focal or generalised. The fourth category under which epilepsy syndromes are grouped is that of "situation-related seizures" but without aetiological subdivisions. Exploration of these syndromes is however beyond the scope of this thesis.

Epilepsy, like many clinical constructs is not a singular disease entity, but a manifestation of underlying disease processes. The attempt to bring the different entities with a common tendency to have repeated seizures, albeit with a myriad of possible seizure types and aetiology and syndromes beneath one umbrella is therefore fraught with the contentious issue of classification and terminology.(12-17) This has led to repeated attempts by the International League Against Epilepsy to standardise definitions, terminologies and classification to provide a reproducible conceptual framework for organising and differentiating epileptic seizures and types of epilepsy and the standard indices for epidemiological measures of prevalence and incidence.(1, 2, 9, 11, 18)

Epilepsy is essentially a clinical diagnosis, based on eyewitness account or video recording of the seizure, as clinical examination and investigations may be normal between seizures. Patients may also not be aware of the nature of the seizure, and seizures may go unnoticed. These lead to seizures going unreported. There may also be denial of occurrence of seizures in order to avoid the stigma attached to a diagnosis of epilepsy. It is also possible that patients with infrequent seizures or mild epilepsy may not seek medical attention.(19, 20)

These factors result in difficulty with adequate case identification and case ascertainment, in determining the specific seizure type, the aetiology, and therefore the specific syndromic diagnosis of each patient's epilepsy; this extends also to the impact on epidemiological studies on populations of patients with epilepsy.(1, 2, 14, 20) However, when such syndromic diagnosis is made, the small number of patients within each group precludes much statistical analysis based on each of these groups as several epilepsy syndromes are rare.(21) Hence, much of the epidemiological studies in epilepsy do not classify patients beyond the major seizure type and aetiological classifications.

STUDY DESIGN

The retrospective study design as well as hospital based studies tend to lead to bias in selecting for patients with more severe disease manifestation and course.(20, 22) Therefore prospective case ascertainment and follow up is preferred as it reduces the risk for selection bias and also allows for optimal assessment of predictors and outcome.(23)However, the difficulty and cost of ensuring prospective case ascertainment in a population based study makes the study of epidemiology and especially prognosis of epilepsy more difficult and tasking in terms of cost and logistics. Ideally, to determine the prognosis of epilepsy in a group of patients, they have to be assembled at a comparable stage in their disease progression. This is at the point where they

could be described as newly diagnosed, and better still, for each patient, at the exact point of having a second seizure, which diagnoses epilepsy.(23, 24)

MULTIVARIATE MODELS

To identify independent predictors of the outcome of newly diagnosed epilepsy, by avoiding the effect of confounders, it is imperative that multivariate analysis is conducted within a population of people with epilepsy.(23) However, the prognosis of epilepsy is dynamic:(25) some patients have a remitting course, some have a remitting-relapsing course and others a worsening course. Therefore, a multivariate analysis conducted on such a dynamic population of patients is as described by Iezzoni(26) only "a snapshot in *place* and *time*, not fundamental truth."

This thesis investigates the early predictors of the prognosis of epilepsy in newly diagnosed patients. It is a systematic review of studies that have used multivariate regression models to identify independent predictors of outcome in people with newly diagnosed epilepsy. The patients within these studies may be at different stages of the course of their epilepsy. Thus, the result of a multivariate analysis that identifies independent predictors may only be a conceptual representation, and not necessarily a true reflection of the prognosis of epilepsy.

For a model to be useful in another population, it has to be confirmed as generalisable in an external validation study of patients within another cohort. However, this external validation only answers the Iezzoni's question of place.(26, 27) The question of time in the course of the epilepsy for individual patients within a particular cohort studied can only be satisfied if all the patients in the cohort were recruited and followed at the same point in the course of the epilepsy.(27, 28) Although difficult to achieve, the point of a patient's second seizure may mark a gold standard for recruitment and commencement of follow up in prospective studies of the prognosis of epilepsy.(24)

1.1.5 OUTCOMES IN EPILEPSY

The focus of this thesis is restricted to the prognosis of epilepsy as it relates specifically to the outcome of seizure, in terms of the continued occurrence or otherwise of seizure events following the diagnosis of epilepsy and does not include circumstances or events that may result from seizures: physical effects like fracture, burns and drowning from falls or loss of consciousness, psychosocial outcome such as cognitive deficit, psychopathology (depression and anxiety), dysfunctional relationships (overprotection and overdependence in relationships), restriction in education, employment and leisure activity, and problems relating to low confidence and self-esteem leading to underachievement and social withdrawal.(8, 29-31)

These outcomes may be a result of the unpredictability of seizures or as a result of perceived or real stigma. They are however by no means less important. Indeed, these secondary psychological and social limitations that epilepsy imposes are more an issue for some patients than the occurrence of seizures.(31) The fear of death and death itself is another consequence

of epilepsy. The annual mortality in people with epilepsy is slightly higher than in the general population and there is also relatively lower life expectancy. Death may result from physical accidents resulting from seizures, status epilepticus, suicide,(32-34) or sudden unexpected death in epilepsy (SUDEP) which occurs following generalised tonic clonic seizures, commonly during sleep and possibly as a result of respiratory failure or cardiac arrhythmias.(35-37)

However, these potential consequences of seizures are reduced with control of seizures.(30, 31, 35-37) For example, the overall risk of SUDEP of 1 per 1000 per year, falls to zero with seizure remission and rises to 1 per 100 per year in patients with frequent and severe tonic clonic seizures.(8) This fact underscores the importance of this thesis in addressing the question of identifying the early predictors of seizure outcome in patients with newly diagnosed epilepsy. The results will inform management decisions that not only would help reduce the burden of seizures but may also reduce the incidence of the consequences of continued seizures.

1.1.6 ORGANISATION OF THE THESIS

The thesis is organised into 6 chapters and an appendix thus:

CHAPTER ONE

Chapter 1 introduces and provides an overview of the main thrust of the thesis. The chapter also presents a general background to prognosis studies in epilepsy and describes the benefits of early determination of the prognosis of epilepsy in newly diagnosed patients. There is also a discussion of the framework for classifying the different potential prognostic categories of a newly diagnosed patient with epilepsy. The chapter ends with an overview of the role of systematic review in medicine with particular application to prognosis studies in epilepsy.

CHAPTER TWO

Chapter 2 presents the research questions that the thesis aims to answer. The chapter also discusses the central contribution to the thesis to the systematic review and meta-analysis of prognosis studies in general and particularly to studies of prognosis in epilepsy.

CHAPTER THREE

Chapter 3 is a description of the systematic review process: eligibility criteria, the search strategy, how each category of papers was excluded, and how studies from the same cohort were handled. It also includes a discussion of the iterative process of developing the quality appraisal and data extraction forms and how the results of each study was assessed for quality i.e. tendency for bias. It also discusses the criteria for assessing the quality of externally validated predictive models. The chapter also discusses how consistent predictors of outcome were identified and the risk estimates compared across studies.

CHAPTER FOUR

Chapter 4 presents the result of the systematic review. The chapter starts by reporting the results of the process of identifying eligible publications, followed by a description of included studies, how they relate to the cohorts from which they are derived and the publications that report them, and an account of the reporting characteristics of the eligible publications. There is a detailed report of the quality appraisal of studies included from each publication. The studies were subsequently disaggregated according to the seizure outcome predicted, and each category of study is further evaluated and appraised with a view to: 1) Explaining the similarities and differences in results in relation to study characteristics and potential for bias, 2) Identifying consistent predictors and non-predictors within each outcome category, and 3) Assessing the quality and performance of externally validated models within each outcome category.

CHAPTER FIVE

Chapter 5 is a general discussion of the results of the review. The chapter is presented according to recommendations that advocate structured discussion of the results of scientific research.(38) The principal findings of 1) the literature search; 2) the quality appraisal of studies and reporting characteristics of publications; 3) the study classification; and 4) the studies within each category, were stated and interpreted. Thereafter, possible explanations for the results are presented and their implications for clinical practice are stated where applicable. There are also suggestions for future studies and the direction of future research for each set of results. The strengths of the study are highlighted, and the weaknesses are also discussed with a view to making recommendations for future studies.

CHAPTER SIX

Chapter 6 provides a summary of the key findings of the review and considers the results in the context a previous review of predictors of outcome in patients with 1 seizure.

APPENDICES

Five appendices were attached to this thesis. Appendix I is the protocol of the systematic review; Appendix II is the complete list of 154 unique citations (from MEDLINE, EMBASE and screening the references of eligible publications) with their origin indicated alongside the corresponding reasons for inclusion and exclusion; Appendix III contains three versions of the data extraction and quality appraisal form, from the first two pilot versions to the final version; Appendix IV presents the items to be considered for assessment of bias in prognosis studies as identified by Hayden et al(39); Appendix V presents the items to be considered in reporting observational studies according to the STROBE (Strengthening the reporting of Observational Studies) checklist.(40)

1.2 BACKGROUND TO PROGNOSIS STUDIES IN EPILEPSY

This second part of the chapter discusses the prognosis of epilepsy and the importance of the study of the prognosis in epilepsy.

There are different kinds of information that may arise from the study of prognosis. Fletcher et al(41) identified 4 characteristics of disorders: response (evidence of improvement), remission (disorder becomes undetectable), recurrence (return of the disorder after remission) and duration (how long the disorder lasts) all of which are amenable to prognosis studies. These studies also investigate the relationship between occurrences of outcomes and predictors in defined populations of people with disease.(23, 42)

In addition, Windeler(43)made the observation of similarity between diagnosis and prognosis, pointing out that the same factors may be responsible for diagnosis and prognosis. This particularly applies to seizure outcome in epilepsy as diagnosis of epilepsy is confirmed on the second unprovoked seizure. Therefore, while the study of seizure recurrence after the first unprovoked seizure(44) is in effect a study of diagnosis, a prognosis study considers recurrence or otherwise after a second unprovoked seizure.

The importance of prognostic research in epilepsy as in other chronic diseases is overwhelming. Altman and Lyman (45) identified the uses of prognosis studies among which are to: "1.) improve understanding of the disease process; 2.) define risk groups based on prognosis; 3.) predict disease outcome more accurately or parsimoniously; and 4.) guide clinical decision making, including treatment selection and patient counselling."

1.2.1 THE NATURAL HISTORY OF EPILEPSY

The natural history of epilepsy has important relevance for the better understanding of underlying neurobiology of the disorders that result in epilepsy, in planning and evaluating treatment strategies and health resource allocation. This segment discusses the natural history of epilepsy first with historical considerations of knowledge and attitude towards the prognosis of epilepsy, then the prognosis of epilepsy in patients who are not treated with anti-epileptic medications and evidence from patient populations who are predominantly treated with antiepileptic drugs with an emphasis on the dynamic nature of the course of epilepsy.

HISTORICAL CONSIDERATIONS

There was an early documented hint at the natural history and prognosis of epilepsy by Plato (c.429–347 BC) who wrote in *Laws* that whoever procures a slave with epilepsy had 1 year to return the slave. For him, the prognosis of epilepsy might be ascertained within 1 year, as against tuberculosis, renal stones and other chronic and mental illnesses not obvious on physical inspection of the slaves and for which the window period is much shorter at 6 months.(46, 47) Thus Plato allowed a longer period for the evolution of epilepsy compared to other diseases.

However, Hippocrates (c.460–377 BC) whose medicine had a particular focus on prognosis had earlier separated epilepsy into the prognostic categories of childhood-onset and adult-onset epilepsy: childhood onset epilepsy is initially fatal, but spontaneous remission occurs in children as they mature, and adult onset epilepsy has better prognosis as it does not lead to death. Hippocrates also thought that status epilepticus portends poor outcome and that early treatment of epilepsy could lead to better prognosis.(47, 48)

In spite of the emergence of effective anti-epileptic drugs in the late 19th century and early 20th century, accounts from Gowers(49) and Rodin(50) indicate there was much less optimism until modern times regarding seizure outcome. Kwan and Sandler(51) have suggested this may be due to much research into the prognosis of epilepsy being predominantly small-scale and hospital-based retrospective studies which tend to result in bias as the success of follow up often depends on a patient having poor seizure outcome.

SEIZURE OUTCOME IN UNTREATED POPULATIONS

More recent studies of the prognosis of epilepsy have revealed an increasingly positive message, buttressed by evidence of spontaneous remission of untreated epilepsy in some low and middle income countries with large proportion of untreated patients.(51) The treatment gap for active epilepsy exceeds 75% in low-income countries and 50% in middle-income countries whereas high-income countries have treatment gaps of less than 10%.(52)

In a study that ascertained the duration of active epilepsy at diagnosis in Malawi,(53) there was a steep progressive decline in the duration of active epilepsy at presentation. Much fewer people had epilepsy for longer than 15 years compared to those with epilepsy for a shorter duration at diagnosis. A survey in northern Ecuador showed that 31% of the total population were spontaneously seizure free for at least 12 months in the period immediately before assessment.(54) In rural China, about 40% of those in remission had never received anti-epileptic drug therapy, (55) and in rural Bolivia, after a 10 year follow up, 40% of those who have achieved 5 year remission had not taken anti-epileptic drugs for more than 1 year.(56)

While these studies are retrospective and rely on only clinical history to diagnose epilepsy with case identification and classification that may not conform to international standards, the explanation for the favourable prognosis of epilepsy from these studies cannot be entirely due to poor case ascertainment. Life expectancy is lower in low and middle income countries, and this fact may bias the result of the Malawi study. However, average life expectancy in China has been comparable to that obtainable in the other high income countries in the past 10 years.(57)

The results are also in keeping with a study from Finland in which 42% of people with untreated epilepsy achieved 2 years of remission by 10 years after onset.(58) An earlier study in Poland also found about 30% of people who had not received any anti-epileptic drug therapy had achieved remission.(59) These results may however be partly due to a selection bias as a study

in Vietnam found that the most common reason given by patients for never taking AEDs, or for deciding to discontinue, was because their seizures were too infrequent to warrant the trouble and costs of treatment, (60) a finding consistent with that from the Finnish study that patients with milder forms of epilepsy were more inclined to reject anti-epileptic drug therapy compared with those with more frequent seizures.(58)

Much has changed since the 1881 comment by Gowers(49) that "the spontaneous cessation of the disease is an event too rare to be reasonably anticipated in any given case" although he conceded to the more favourable prognosis in patients with newly diagnosed epilepsy treated with bromide. Following the introduction of bromides in 1857, was among others, phenobarbital (1912), phenytoin (1938), ethosuximide (1955), carbamazepine (1963), sodium valproate (1967),(61, 62) and subsequently the newer generation of antiepileptic drugs.(62) Most people with epilepsy in the high income countries receive antiepileptic drugs early in the course of their illness, a fact that limits what is possible in the study of prognosis of untreated epilepsy.

SEIZURE OUTCOME IN TREATED POPULATIONS

The natural history of epilepsy within populations of people that are treated with antiepileptic drugs has been extensively studied. There are reports of 65 – 80% of patients entering long-term remission on or off antiepileptic medication (21, 32, 63-70), of 45 – 55% maintaining remission off antiepileptic medication (32, 71, 72) and 10 – 20% satisfying the definition of intractable epilepsy (73-77). This thesis will explore the study characteristics that might explain the wide discrepancies in the proportion of patients with the seizure outcomes in these studies. There is also a group of patients who neither attain remission nor satisfy the definition of medical intractability identifiable in some of these studies(72, 76, 78, 79), a group which Camfield et al(80) named "something between."

Most of the studies of prognosis in epilepsy in treated populations do not provide their results in terms of seizure outcome by strategy of anti-epileptic drug treatment employed. Hence the relationship between outcome and course of antiepileptic medication is not as widely known. However, a hospital-based retrospective study by Kwan and Brodie(81) in Scotland shows that in a patient group aged between 9 to 93 years, 47% of all patients treated were seizure-free for at least 1 year at the time of last follow-up on the first AED, 13% on the second and only 4% for any further AED regime: a total of 64% of the cohort was seizure free. Moreover, similar to the report by Kwan and Brodie(81) were findings from a prospective hospital-based Dutch childhood cohort (66) in which 46% achieved remission (seizure-free for at least 1 year at 5 years of follow-up) on the first AED, 19% on the second and 9% on any further AED regime: a total of 74% of the cohort was in remission. In the childhood Dutch cohort, 58% of the patients achieved remission after the first antiepileptic drug failed compared to the Scottish cohort that comprised people aged between 9 to 93 years, where 32% achieved remission after first AED failure.(66, 81) The difference between the results of these studies may support what Hippocrates had suspected and Gowers suggested; that prognosis may be better in childhood onset epilepsy. However, this

inference is limited by the study with fewer patients in remission being a retrospective study, while in the study with better outcome, patients were prospectively identified.

In a meta-analysis (81-83) that included the Scottish study(81) involving 621 patients overall with newly diagnosed epilepsy, Wiebe(84) showed that 48% of patients became seizure free with the first AED and of those who failed the first, 27% responded to a second drug, and of those who failed a second drug 12% responded to more than 2 combined AEDs. These results relating to drug failure and number of antiepileptic drugs required to achieve remission notwithstanding, the choice of specific drug used has not been shown to significantly influence seizure outcome.(85-87)

No controlled trial has ever shown that any of the first line AEDs is better than the others in terms of achieving remission, often leaving the physician to choose which drug, mostly single, to use initially based on a case by case consideration of cost (of the drug and necessary follow-up investigations), and potential for adverse effects.(88) The AED dose is then usually increased gradually to a near toxic level before considering a second drug on account of not achieving remission, allergic or other adverse reaction. The second drug is titrated to therapeutic levels as the first drug is tapered and discontinued. Subsequent substitutions are done in similar fashion before polytherapy is considered; an approach that effectively limits the additive adverse effects of multiple antiepileptic drugs.(89)

The course of epilepsy in treated populations therefore has been shown to be good, although not as fixed as these studies might suggest. There has been evidence of a remitting-relapsing course for certain individuals who enter remission only to experience subsequent recurrence. Patients with remitting only course achieve uninterrupted terminal remission, early when within 12 months of intake or commencement of therapy or late when after 12 months as defined by Sillanpaa and Schmidt(25). There is a subset of patients running a remitting course who do not have another seizure since intake into a cohort on or off medication, a subset described as “smooth-sailing epilepsy” by Camfield et al (90)

In the Nova Scotia, Canada cohort, Camfield et al (71, 90) reported that 21% of 472 children (excluding those with absence, myoclonic, or atonic seizures) had smooth-sailing epilepsy, and an overall 48% had a remitting course. In the Dutch cohort,(66) 14% of 453 children had smooth sailing epilepsy, while altogether 41% had a remitting course. The results are similar in the Finnish cohort with 16% of the patients having smooth-sailing epilepsy and 48% overall with remitting course.(25) Those with a remitting-relapsing course have their remission interrupted by a relapse; some of them however go on to achieve terminal remission. Of the children who experienced relapse in the Finnish cohort, 58% achieved terminal remission, 52% after 1 relapse and only 6% after 2 episodes of relapse.(25)

At the other end of the spectrum are those whose seizures will become medically intractable, another fluid category. Berg et al(73) defined intractability as “failure, for lack of seizure control,

of more than 2 first-line anti-epileptic drugs with an average of more than 1 seizure per month for 18 months and more than 3 consecutive months seizure-free during that interval." In their cohort based in Connecticut, USA, 12% of children who had earlier satisfied the criteria for intractability went on to attain remission.(73)

In the Dutch cohort, 6 out of 25 (24%) children who had satisfied a similar definition of intractability at 2 years follow up, attained 1 year terminal remission at 5 years, and 18% of those who had been seizure free for 1 year during follow up did not achieve 1 year terminal remission at 5 years, and 2% had even become intractable.(66) In another childhood cohort, 4% of patients who had experienced recurrent seizures for 2 years achieved remission with each year of follow up.(91)

Therefore patients who have been seizure-free for a particular period of time at the point of assessment during follow up may not be categorised as being in such a category at a different point, as is the case for those satisfying the definition of medical intractability. The choice of end point for analysis varies from study to study. Hence the pictures we have from different studies are like snapshots, taken every 2 or so seconds, of for example the screen during a scene in a motion picture. Most things might remain in their position, but certain things, no matter how few are bound to change or be different – a shift, a change in the position of the mouth, a smile becoming stilled in a frown.

This is the state of affairs in prognosis research in epilepsy. While research does not tell exactly what the prognosis of epilepsy is – it will take a report on each patient in a cohort to achieve that – we at least have snapshots from which we hope we might understand the specific predictors of each state covered in the snapshots. Several prognostic factors identifiable at the time of diagnosis have been shown to distinguish between those most and least likely to experience a particular seizure outcome. They include symptomatic aetiology, history of status epilepticus, multiple types of seizures, younger age of onset, having many seizures before initiating medication, and failure to respond early to medication.(21, 32, 63-79, 81, 92-107)

1.2.2 WHEN TO COMMENCE OR DISCONTINUE MEDICATION

This segment presents information from previous studies regarding making the decision about if and when to commence anti-epileptic medication in patients with epileptic seizures.

Antiepileptic medication is readily availability in high income countries where much of the studies of the prognosis of epilepsy studies have been conducted. Hence, there has been little opportunity to study the course of untreated epilepsy. Ethical considerations have also limited prognostic research that may help determine the proportion and characteristics of people with epilepsy who enter spontaneous remission. However, it has been shown in clinical trials that antiepileptic drug prophylaxis in patients with severe head injury(108, 109) and craniotomy(110) only suppress immediate seizures, but not the ultimate development of epilepsy in those at risk.

The Italian FIRST (First Seizure Trial) study randomised 419 people with a first tonic-clonic seizure into immediate and delayed (until after a recurrence i.e. diagnosis of epilepsy) AED treatment groups without significant long term difference in probability of achieving remission.(111) In the MESS Trial, 1443 people with single or infrequent seizures for whom indication to commence treatment was not clear were randomly assigned to immediate or delayed (until physician and patient agree AED is necessary) treatment. Immediate AED therapy reduced the occurrence of seizures in the first 2 years, but did not affect long-term prognosis in this group of patients.(98)

However, in the short term, next to the prognostic category of people with epilepsy who will enter spontaneous remission is the group of those who will enter remission only with AEDs and continue in remission even after the drugs are withdrawn. This category can only be determined in studies designed to phase out the use of AEDs in patients in remission. Much of prognosis research in epilepsy had been on determining the predictors of successful AED withdrawal. The decision to discontinue AEDs may be more difficult than the decision to start the drugs.(112) The benefit of seizure prevention in the short term does outweigh the risk of potential adverse effects, the cost, stigma and inconvenience associated with AEDs.(113)

However, the question as to whether the benefits of AEDs still outweigh the drawbacks of AEDs arises for patients in long-term remission. The possibility of the development of serious adverse events is a strong argument for discontinuing AEDs, especially in children in remission who in their formative years are on drugs that affect their cognition, and women in their child-bearing years who are in remission and intend to have children as teratogenicity is a potential problem with most of first line AEDs.(112) The discontinuation of AEDs is considered in the light of implications of recurrence for patient safety, driving privileges, employment and liability.(113) It is important to understand the predictors of recurrence clearly before embarking on AED withdrawal.

With rate of relapse following AED discontinuation ranging from 12 to 63%(113) in a wide array of studies with different designs, Berg and Shinnar(114) conducted a meta-analysis of 25 studies that met strict inclusion criteria, and found that the risk of relapse was 25% (95%CI 21% to 30%) after 1 year of initiating AED withdrawal, and 29% (95%CI 24% to 34%) after 2 years. The meta-analysis also found that the rate of relapse was higher in adult-onset epilepsy compared to childhood-onset epilepsy. The patients with remote symptomatic epilepsy and those with abnormal EEG also had a higher rate of relapse. However, the meta-analysis by Berg and Shinnar(114) addresses relapse after initiating withdrawal, and not after completion. Therefore, it does not quite tell us the percentage of patients who remain in remission after completing the AED withdrawal process. In the Nova Scotia Canada cohort 48% of the entire cohort was able to discontinue AED therapy and remain in remission(71). This was in keeping with the British MRC Antiepileptic Drug Withdrawal Study which showed that within the group of patients with at

least 2 years terminal remission randomised to slow discontinuation of AEDs, about 50% were successfully discontinued(115).

Further analysis and follow up of the MRC study cohort showed that the rate of seizure recurrence after AED withdrawal was same for all the drugs used in the cohort (phenobarbitone, phenytoin, and sodium valproate) except cabamazepine for which the rate of recurrence is lower(116) It was also found that AED discontinuation does not modify the long-term prognosis of a person's epilepsy, although it increases the risk of seizure 2 years following discontinuation, (117) a finding that further confirms the time dependent beneficial effects of antiepileptic drugs.

1.2.3 WHEN TO CONSIDER OTHER INTERVENTIONS

This segment clarifies the definitions of uncontrolled seizures adopted for the purpose of this thesis and presents the literature describing the justification for early consideration of non-pharmacological interventions such as epilepsy surgery and ketogenic diet in people with medically intractable seizures.

DEFINITIONS OF UNCONTROLLED SEIZURES

Most studies refer to uncontrolled seizures using the term intractable or refractory, and some other studies use both terms interchangeably.(72-79) The definition of intractability is usually a variation on a “failure, for lack of seizure control, of more than 2 first-line anti-epileptic drugs with an average of more than 1 seizure per month for 18 months (some 2 years) and no more than 3 consecutive months seizure-free during that interval”(78) The variations on this definition of intractability is adopted in this thesis as well as the use of the term “intractability”.

However, the fact that the term i*ntractable* is often used interchangeably with *refractory* is a source of confusion. In this thesis, the term refractory is used to denote the category of patients who had not achieved at least 1 year seizure-free period immediately before the last assessment. This is in keeping with the definition from Semah et al(103), Kwan and Brodie(81), Stephen et al(118) and Hui et al(97). The broader category defined as refractory therefore also effectively includes within it patients who will fulfil the criteria for intractability.

SEIZURES BEGET SEIZURES

The 1881 aphorism by Gowers that “seizures beget seizures”(49) may be wrong in much of human epilepsy. However, there are certain patients for whom it does seem apposite. First in this category is evidence from a study by Hauser and Lee(119) that in a first unprovoked seizure cohort, individuals with low risk for seizure recurrence in the cohort (idiopathic/cryptogenic aetiology) demonstrated a significant increase in risk for seizure recurrence with increasing numbers of seizures. However, since the majority of these patients will ultimately achieve remission and discontinue AED successfully, the authors argued with merit that there must be competing forces that increase or decrease risk for seizure recurrence, of which the number of previous seizures is only 1 of several contributors.

In a further analysis of the Nova Scotia, Canada cohort by Camfield et al(120) children with more than 10 seizures (who were also more likely to have focal seizures associated with impaired consciousness) were less likely to enter remission. Shorvon and Reynolds(121) had earlier shown that the number of focal seizures associated with impaired consciousness occurring prior to treatment was dramatically different: 20 (range 2-180) in those who achieved remission and 73 (range 20-960) in those whose seizures did not remit.(122) These 2 studies suggest that Gowers' "seizures beget seizures" may also be true for patients having focal seizures associated with impaired consciousness. Hence, considered alongside the argument for competing forces by Hauser and Lee(119), Gowers may have been at least partly right in these specific groups of patients.

The continued occurrence of seizures also changes the structure of the brain. Multani et al(123) have shown that changes in neuronal ultrastructure are associated with relatively large numbers of seizures over long periods of time. They used computerized 3-dimensional image analysis to evaluate the features of neurons removed as part of surgery for mesial temporal lobe epilepsy (TLE). More synaptic neuronal elements were lost and the 3-dimensional complexity of the neurons was simplified in direct relation to the total lifetime number of seizures and the distance of the brain tissue away from the seizure focus. Three groups that prospectively assessed every 3 to 4 years the degree of cerebral atrophy with magnetic resonance imaging (MRI) in patients with chronic(124) and temporal lobe epilepsy(125, 126) demonstrated progressive cerebral atrophy in these patients but not in those with newly diagnosed epilepsy or those whose seizure are controlled.

PSYCHOSOCIAL ASPECTS OF UNCONTROLLED SEIZURES

The continued occurrence of seizures is undesirable for reasons beyond the possibility of the seizures begetting further seizures. Numbered among other reasons why uncontrolled seizures are undesirable is the psychosocial impact on the lives of people with epilepsy.

In a cross-sectional study (N=696) by Jacoby et al(30) of British adults, 44% of 168 people with frequent seizures (1 or more seizures per month in the past 3 months) had Hospital Anxiety and Depression Scale (HADS)(127) case defining score for anxiety, compared to 13% of 350 without current seizures. The depression case defining score on the HADS was met by 21% of patients with frequent seizures compared to 4% without current seizures. In the same study, 62% of people with frequent seizures felt stigmatised compared to 25% of those without current seizures. Also, fewer people with frequent seizures were married, employed or had a sense of social support. The fact that this study is cross-sectional study and does not use any of the more usual definitions of uncontrolled seizures limits inferences that could be made from these results.

However, Thompson et al(128) in a case-control study using the Patient Health Questionnaire-9,(129) to determine clinically significant depression in another study in adults, also showed that clinically depressed people with epilepsy were significantly less likely than non-depressed ones to be married or employed and more likely to report comorbid medical problems and active seizures in the past 6 months. This study is also limited by being a cross-sectional analysis.

In a prospective cohort study by Camfield et al(130) conducted on the intellectually normal children within the Nova Scotia cohort, the proportion with 8 different adverse psychosocial outcomes were reported thus – 34% had experienced school failure, 34% used special education facilities, there was mental health consultation in 22%, unemployment in 20%, social isolation in 27%, undesired pregnancy in 12%, 5% were on psychotropic medication and 2% had been convicted. When the children were divided into those with bad social outcome (1 or more of the 8 adverse factors) and good social outcome (none of the adverse factors), stepwise logistic regression analysis showed that more than 21 seizures before treatment was an independent predictor of bad social outcome. Sillanpaa et al (32, 69) also showed in prospective Finnish cohort that childhood-onset epilepsy is significantly associated with increased risk for considerable psychosocial, vocational, and cognitive dysfunction, persisting into adulthood.

Jokeit and Ebner(131) found that the duration of epilepsy predicted global cognitive impairment in a cross-section of adults with intractable temporal lobe epilepsy, where after correcting for educational level the duration of epilepsy remained a more important independent predictor of cognitive dysfunction than age, age of onset, site of epilepsy, aetiology, use of AEDs, and occurrence of generalized seizures. Nolan et al(132) has confirmed this finding in a prospective study of childhood epilepsy in Sydney, Australia with earlier age of onset as covariate of longer duration of epilepsy. The exact same covariates were found by Pavone et al(133) among children with the more benign absence epilepsy. In the Sydney childhood epilepsy series, higher frequency of seizures, generalized symptomatic epilepsies, and larger number of AEDs were also independently associated with lower overall intelligence.

These outcomes may be due to the seizures themselves or to toxic effects of anti-epileptic drugs. It has been conclusively proved in 2 placebo-controlled, randomized trials involving healthy adults(134) and people with epilepsy(135) that antiepileptic drugs contribute to cognitive dysfunction, the major effects being impaired attention, vigilance, and psychomotor speed.(136) These effects increase with higher dosages and number of antiepileptic drugs(137) and subjective health status is affected more negatively by adverse effects of antiepileptic medication than seizure frequency.(138)

The cause of these psychosocial outcomes is likely to be a complex interplay of underlying neurologic abnormalities, effects of recurrent seizures, AED toxicity, and psychosocial factors which are more prevalent in people with intractable seizures.(134-138) Therefore if ongoing seizures, or the psychosocial factors and long running high doses of AEDs which are in themselves consequences of persistent seizures, are responsible for cognitive dysfunction and

dysfunctional adaptation to life, then earlier non-pharmacological interventions could reduce these immediate and long-term outcomes.(139)

ECONOMIC IMPLICATIONS OF CONTINUED SEIZURES

There is also an economic argument to be made for early non-pharmacological intervention. Heaney and Begley(140) in a systematic review of economic evaluation of epilepsy management identified 3 published studies of the cost effectiveness of epilepsy surgery.(141-143) The incremental cost of surgery was estimated at US$16,000 to US$27,000 per QALY (Quality Adjusted Life Years), and the cost per seizure-free patient to be about 15% of AED use over a lifetime in patients with intractable seizures. Begley et al estimate that in the United States, 80% of the cost of epilepsy is attributable to patients with medically intractable seizures, which form less than 20% of the total epilepsy population.(73-77) This disproportionate cost of people with medically intractable seizures is likely due to the cost of continued AED use at high doses to control seizures.

EARLY EPILEPSY SURGERY

Epilepsy surgery is any surgical procedure carried out to control seizures in epilepsy. It may be neurosurgical in which the seizure focus is resected, isolated or simulated. It may also be surgery carried out to implant stimulator device and electrodes for Vagus Nerve Stimulation (VNS) subcutaneously in the chest and neck.

Neurosurgical Epilepsy Surgery and Surgically Remediable Epilepsies

The benefit of resective surgery especially has been demonstrated repeatedly.(139) Early epilepsy surgery may be life-saving as the risk of mortality in people with intractable epilepsy is up to 5 times higher than in the general population reversing to normal in those who become seizure-free after epilepsy surgery.(37, 144, 145) The risk of SUDEP (sudden unexpected death in epilepsy) is zero with seizure remission but up to 1 per 100 per year in patients with frequent and severe tonic clonic seizures.(8) Patients who become seizure-free after surgery also had better cognitive function, social and behavioural outcome (131, 146, 147) but the effect of an older age at surgery(146, 148, 149) or longer duration of epilepsy persisted even after successful surgery.(131)

Epilepsy surgery is not without its own risks. However, careful candidate patient selection is crucial in preventing these risks. Helmsteader et al(147) posits that the dichotomy of surgical outcome is that patients either achieve remission with cognitive stability “double winners” or achieve neither “double losers,” a sad outcome observed mostly in only poorly selected candidates - older patients, and patients without hippocampal sclerosis who undergo dominant temporal lobe surgery.(150) Otherwise, neurological deficits such as hemiparesis, visual field defects, dysphasia are often temporary.(151)

Prognosis studies that focus on treatment decision making for epilepsy surgery are conducted in cohorts limited to specific seizure types, syndromes or by virtue of having intractable seizures or epilepsy surgery. (152-162) Téllez-Zenteno et al(163) have just completed a meta-analysis to investigate the surgical outcome in 697 patients with non-lesional epilepsy and 2860 patients with lesional epilepsy. They found the odds of being seizure-free to be 2.5 (95%CI 2.1, 3.0) times higher in patients with lesions identified on MRI or by histopathology. The outcome was similar when they disaggregated studies by surgery type (temporal lobe and extra-temporal lobe surgery) and by age (children and adults). A meta-analysis by Tonini et al(164) had earlier suggested that having identifiable lesions – mesial TLE, tumors, and abnormal MRI – were the strongest positive prognostic indicators of postoperative seizure remission.

Those patients with mesial temporal lobe epilepsy (TLE), localization-related epilepsies with well-circumscribed lesions, and unilateral hemispheric disorders in infants and children have been dubbed by Engel and Shewmon(165) as having “surgically remediable epilepsies.” Engel (166)had initially put up mesial TLE as the prototypical surgically remediable epilepsy syndrome, as it is the type mostly found among patients with medically intractable seizures who can expect to become free of disabling seizures postoperatively.(151, 156, 167)

The concept of “surgically remediable epilepsies” mooted by Engel and Shewmon(165) was a reaction to 2 emerging trends – the fact that new antiepileptic drugs might effectively render the definition for medically intractable epilepsy irrelevant as the introduction of new drugs makes it impractical to prove that any given patient’s seizures are intractable in spite of trying all available medications in every possible combination.(168)Secondly, the time it takes from diagnosis to surgery might have increased due to multiple drug trials in patients with little chance of remission. (139, 168) The idea of “surgically remediable epilepsies” therefore proposes to replace that of “medical intractability.” However while it is true that certain epilepsies are recognisable as surgically remediable from an early stage, it is also true that there are others who may not be so identifiable and for whom early surgery might be beneficial. In a Hong Kong, China unselected childhood epilepsy cohort, Kwong et al(76)reported that only 57%, of the children with medically intractable epilepsy had detectable abnormality on CT and/or MRI. Ko et al(79) reported 55% in a Massachusetts childhood cohort and Berg et al(73) had 20% from a cohort in Connecticut, USA.

Instead of replacing one with the other, there may be more benefit from having a standardised definition of medical intractability which allows for context specific application especially for “surgically remediable epilepsies” and which also accommodates the concept of remitting-relapsing epilepsy course. For example, on the Scottish study by Kwan and Brodie(81) only in 4% of the patients achieved remission on a third antiepileptic drug singly or in combination. This suggests that the present commonly varied definition that limits intractability to more than 2 antiepileptic drugs singly or in combination may suffice for the pragmatic purpose of timely determination of candidates for early epilepsy surgery.

Vagus Nerve Stimulation

In patients whose intractable seizures might not be neurosurgically remediable – especially when the seizures have multiple cortical foci, when seizure focus is in the dominant or eloquent hemisphere, or cannot be defined – or for other reasons not candidates for epilepsy surgery, there is the possibility of Vagal Nerve Stimulation (VNS). VNS is conducted through a surgical procedure that implants a stimulator in the chest, connected to bipolar electrodes wrapped around the left vagus nerve in the neck. Saneto et al(169) reported a prospective study of 43 children with medically intractable seizures on VNS who were followed up for more than 12 months. They achieved an overall median seizure reduction rate of 55%. 37% had at least 90% reduction. However, no patients are rendered completely seizure-free on the procedure.(8)

In a pioneering report of the analysis of follow up data of 440 participants from a series of open label adult VNS trials (with the participants also on AEDs allowing for dosage adjustment as required) between 1988 and 1995, Morris et al(170) demonstrated the efficacy and tolerability of VNS in medically intractable seizures. Following implantation of a stimulator, there was more than a 50% reduction in seizure frequency occurring in 36.8% of patients at 1 year, in 43.2% at 2 years, and in 42.7% at 3 years. The adverse effect profile –hoarseness and paraesthesias – was tolerable with about 75% of participants still on therapy at 3 years follow up. Other adverse effects may include dyspnoea, cough, left vocal cord paralysis and lower facial muscle paresis.(8)

KETOGENIC DIET

Besides epilepsy surgery, the high fat low carbohydrate “ketogenic” diet (sometimes using medium chain triglyceride to boost ketosis), in use since 1921, is another non-pharmacological intervention to control intractable seizures. Its use is based on the theory that ketosis has antiepileptic properties in the presence of low circulating glucose level.(171) Keene(172) showed in a meta-analysis, that 15.6% of children with medically intractable seizures on ketogenic diet were seizure-free and 33% had more than 50% reduction in seizures at 6 months of follow up. However, patients often discontinue the diet and in a meta-analysis by Henderson et al(173) the reasons for discontinuing the ketogenic diet were: less than 50% seizure reduction (47%), diet restrictiveness (16%), and presence of incurrent illness or diet side effects (13%).

The only RCT comparing the ketogenic diet against no change in treatment reported on 3 month seizure outcome in children with medically intractable seizures.(174) After 3 months, the mean percentage of baseline seizures was significantly (75%) lower in the diet group than in the controls. Also, 38% of children in the diet group had greater than 50% seizure reduction compared with 6% control; 7% in the diet group had greater than 90% reduction in seizure frequency compared with none among the controls.

Therefore, although with relatively poorer results, but wider applicability and less invasiveness, VNS and the ketogenic diet remain viable and appropriate options in patients with non-surgically remediable medically intractable seizures.

1.2.4 THE SEIZURE OUTCOME OF EPILEPSY

The ultimate goal of the prognosis studies is to define specific risk groups based on prognosis and to predict different categories of seizure outcome more "accurately or parsimoniously" in order to provide tools for making informed treatment decision and patient counselling.(45)

Kwan and Sander(51) came up with an epidemiological synthesis of prognosis studies of the natural history of treated and untreated epilepsy that suggests there are 3 prognostic groups (see Figure 4). Group 1 (20–30%) are the patients with excellent prognosis. There is long term remission after a period of seizures, with or without AEDs. The primary aim of AED therapy in this group therefore is to suppress seizures until remission occurs, and patients are successfully weaned off AEDs. For group 2 (20–30%) seizure remission occurs and is maintained only with AEDs. In group 3 (30–40%) there is continuing seizures despite AEDs with some patients having frequent enough to qualifying them as being medically intractable.

Figure 4 | Natural History of Newly Diagnosed Epilepsy
Group 1 will enter "Spontaneous" remission (20-30%), 2 remains in remission only on AED treatment (20-30%) and 3 continues to have seizures (30-40%) [Adapted from Kwan and Sandler(51)]

However, a further interpretation of available evidence and patterns of seizure outcome suggest that this view could be further broken down to achieve a finer granularity in the prognostic groups that people with newly diagnosed epilepsy could be predicted to belong at the point of, or within 1 year of diagnosis. Group 1 is the group of patients who would enter remission with or without AED therapy, those who would automatically achieve remission even if they did not have access to AEDs.

Sub-Group 1A therefore will represent those with immediate spontaneous remission (ISR). (Figure 5) They will not have a third seizure, i.e. upon starting AED or being recruited into the cohort under consideration they enter terminal remission immediately, and will not relapse after complete AED withdrawal. In a New York childhood first seizure cohort, Shinnar et al(24) reported that out of 182 children who had a second seizure, 28% did not have a third seizure (second recurrence) at 5 years follow up, meaning they could be effectively considered as having entered into immediate remission.

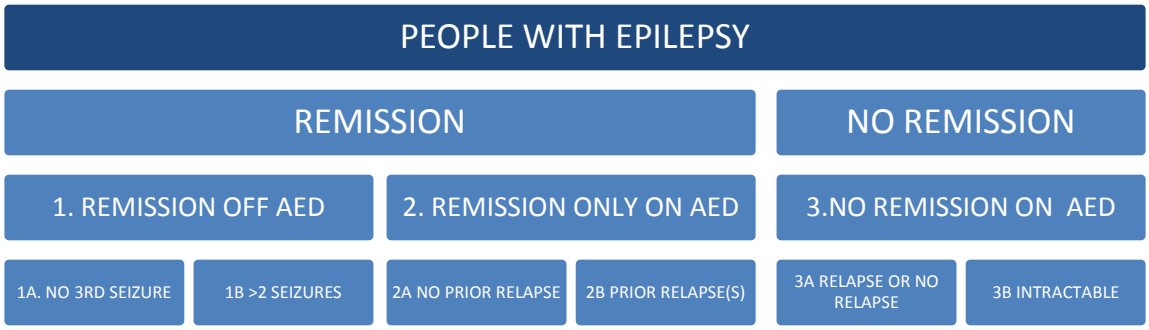


Figure 5 | Natural History of Newly Diagnosed Epilepsy (with additional granularity)
Sub-Group 1A will not have a second recurrence (third seizure) and will remain in remission after complete AED withdrawal. 1B enters remission, although not immediately and remain in remission after complete AED withdrawal). 2A achieves and stays in remission only on continued AED. 2B has 1 or more periods of relapse, but achieves remission ultimately and stays in remission only on continued AED. 3A has 2 different categories within it: i – those who have 1 or more periods of relapse, but do not achieve remission ultimately, ii – those who have never achieved remission, but who do not fulfil the criteria for medically intractable seizures. Sub-Group 3B medically intractable seizure which could also have within it the 2 categories of: i –those whose seizures will remit on non-pharmacological intervention, and ii – those who will never achieve remission no matter what is done.

Hauser et al(175) reported that 27% did not have a second recurrence after 4 years of follow up in an all age cohort in Minnesota. Treatment did not influence the rate of second recurrence in both studies, although for Hauser et al(175) the risk of additional seizures in those with 2 previous seizures is greater than the risk of adverse effects of antiepileptic drugs. Neither study investigated the subset of these patients who are successfully taken off antiepileptic drugs. Hence the proportion of patients within this Sub-Group may be less than they have reported.

Sub-Group 1b thus represents those who although they do not enter remission immediately, ultimately do so, and who alongside those who enter immediate remission, will remain in remission on antiepileptic drug withdrawal. There is however no study from which an estimate of the proportion of patients who will be in this group could be derived. It does however fill an important conceptual space within the range of temporal outcomes of seizures in newly diagnosed epilepsy.

Notwithstanding their original eligibility into any of the Sub-Groups of Group 1, those who cannot be successfully weaned off antiepileptic drugs belong in Group 2. It could also be imagined that those within Sub-Group 2A are those whose epilepsy alongside the whole of group 1 did run a remitting course only that they could not be taken off AED. Those in Sub-Group 2B arrived in remission after a remitting-relapsing course. People in Sub-Group 2B made up 20% of the Finnish cohort.(25)

Group 3 comprises those patients who will not enter terminal remission either because after a remitting-relapsing course they do not achieve terminal remission (14% of Sillanpaa et al's Finnish childhood cohort) or because they continue to have seizures from diagnosis in spite of AEDs i.e. they never experience remission. Within this group will be those (Sub-Group 3A) who will continue to have seizures, not frequent or debilitating enough to be described as intractable

and those (Sub-Group 3b) who will fulfil the definition of medically intractable seizures (10-20%) (73-77).

Further subdivision of 3B would give us the 2 categories of those whose seizures will remit on non-pharmacological intervention, and those who will never achieve remission no matter the intervention. Sub-Group 3A will also have a sub-population of those who ran a remitting-relapsing course within it. Therefore the whole of Sub-Group 2B and part of Sub-Group 3A is made of patients running a remitting-relapsing course, which also indicates that the boundary between the 2 Groups will be a potential area of cross-over activity, and certainly an area where multivariate regression snapshots will capture different pictures in time.

One group that may exist but is not covered is of newly diagnosed patients who initially enter immediate spontaneous remission and then go on to have a remitting-relapsing course, but are eventually successfully weaned off AEDs. However, evidence from Sillanpaa et al(25) suggest that it is unlikely that such individuals exist. They show that the number of years before entering 5-year remission is an independent predictor of relapse. Therefore there is a low probability that a patient with immediate spontaneous remission will go on to have a remitting-relapsing course, and if they do, it may be ill advised to wean them off AEDs.

The ideal prognosis study in unselected populations of people with epilepsy will be a prospective cohort which is followed up long enough and in good detail to achieve this level of granularity in making out different prognosis groups that will help inform treatment decisions and patient counselling regarding issues of if and when to start antiepileptic drugs, if and when to discontinue antiepileptic drugs and if and when to consider non-pharmacological intervention. The ideal study will also use multivariable approach to analyse for prognostic factors that will help guide these decisions, and also provide externally validated tools (models) to estimate outcome probabilities based on combinations of these predictors.(23)

1.3 SYSTEMATIC REVIEWS OF PROGNOSIS STUDIES

The third part of this introductory chapter presents an overview of the role of systematic review in medical research with its application to observational studies in general and prognosis studies in particular.

1.3.1 THE ROLE OF SYSTEMATIC REVIEWS

In an exposition on the role of systematic review in health research, Chalmers(176) opened his foreword to *Systematic Reviews in Health Care: Meta-analysis in Context*[1] by quoting the physicist Lord Rayleigh: "If, as is sometimes supposed, science consisted in nothing but the laborious accumulation of facts, it would soon come to a standstill, crushed, as it were, under its own weight… The work which deserves but I am afraid does not always receive the most credit is that [of] *introducing order and coherence* in which not only facts are presented, but their relation to old ones is pointed out."

The introduction of order and coherence into a body of research is the central role of systematic reviews. Cook et al(178) defined systematic review as "the application of scientific strategies that limit bias by the systematic assembly, critical appraisal and synthesis of all relevant studies on a specific topic" and meta-analysis as "a systematic review that employs statistical methods to combine and summarize the results of several studies." The need for this method of research arose out of the fact that science itself is a cumulative process. The fast pace, and almost exponential increase in the accumulation of scientific papers resulted in a tendency to lose information in an abundant mass of facts, necessitating that the results of research be synthesised.(179)

However, the traditional /narrative review, synonymous with expert opinion has been shown to have a tendency to reflect a singular, often biased opinion that also may lag behind and even contradict research evidence.(180-184). Murlow in 1987 was the first to highlight that the review of clinical research was largely poor and unscientific.(182) Murlow reviewed a sample of traditional/narrative clinical reviews published in 4 leading American medical journals, and demonstrated that most fell short of the standards for systematic reviews. McAlister et al(181) did a follow up 10 years later, and found that the situation had only improved marginally.

There is a metaphorical view of systematic review as an epidemiological study, one in which the subjects are published and unpublished studies rather than humans. The data collection involves taking a representative sample of a well-defined population (of studies) or identifying every member of the population if an unbiased sample is impossible.(185) Systematic reviews start like all epidemiological studies with a good question, followed by developing a protocol to answer that question, collecting, synthesising and analysing the data to arrive at objective conclusions.

[1] The book "Systematic Reviews in Health Care: Meta-analysis in Context" has had a defining role in the emergence of systematic review and meta-analysis as a central and important tool in health research. (177)

1.3.2 HISTORY OF RESEARCH SYNTHESIS IN MEDICINE

The application of systematic reviews and meta-analysis lagged in medicine, behind the social science research fields of education and psychology. In 1933, Peters(186)published a systematic review of a series of experiments on the impact of moral instruction on modifying character “in order to bring them together into a single form so that we may draw inferences from the whole set.” It was a psychologist, Glass(187) who coined the term meta-analysis “to refer to the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings.” In these roles systematic review and meta-analysis helped separate the wheat from the chaff of available research, performing interpretative functions as well as serving as a means of systematising existing accumulated knowledge.

Nevertheless, medicine had much earlier, albeit isolated attempts at systematic review. In 1753, James Lind, a Scottish naval surgeon, who had to deal with a series of reports about scurvy came up with a treatise containing “an inquiry into the nature, causes, and cure, of that disease together with a critical and chronological view of what has been published on the subject." For him, "it became requisite to exhibit a full and impartial view of what had hitherto been published on the scurvy” and “to remove a great deal of rubbish."(179) Two 18th century European journals [*Medical and Philosophical Commentaries (Edinburgh)* and *Comentarii de Rebus in Scientia Naturali et Medicina Gestis (Leipzig)]* published critical appraisals of available research evidence.(188)

However, the 20th century pioneer of research synthesis in medicine was Pearson.(179) In their 1904 review of a typhoid vaccine, Simpson and Pearson(189) extracted data and conducted a meta-analysis of correlation coefficients in 2 groups from 11 selected studies of immunity and mortality among British soldiers serving in various parts of the world. In another typhoid review 3 years later in 1907, Goldberger(190) analysed available data on bacteriuria in typhoid fever in Washington DC, in strict adherence to yet-to-be-formulated criteria for systematic reviews and meta-analysis.

The terms systematic review and meta-analysis have not always meant what they presently mean. The idea of research synthesis has gone through periods of evolution over which these terms and others including “research synthesis” have connoted different things. The term research synthesis was and is sometimes still used extensively by the social scientists who led the development of the science and practice of review in the second half of the 20th century.(179) Although the term “systematic review” was used during the first half of the 20th century, even before "research synthesis,"(191) it is uncertain whether it was in the same sense of what it grew to mean during the second half of the century.(179)

However, the term systematic review slowly gained wider usage and the method became more popular and recognised, reaching a tipping point in the late 1990s owing to the earlier use of the term by Cochrane(192) in his foreword to a popular 1989 compilation of research syntheses in

maternal health,(193) the creation of the Cochrane Collaboration in the early 1990s, and the promotion of “systematic review” in contradistinction to meta-analysis, in the first and second editions of *Systematic Reviews in Health Care: Meta-analysis in Context.* (194, 195)

1.3.3 CRITICISMS OF RESEARCH SYNTHESIS IN MEDICINE

Nonetheless, there have been epistemological challenges to the claims of the systematic review process to objectivity.(196)This view concedes to systematic review its assertion of methodical discipline in adhering to an explicit and auditable protocol. The contention is that this “procedural objectivity” does not remove the subjectivity of the process(197) as search results,(198) quality assessment,(199) data extraction(197) and review conclusions(200) all vary with reviewers. The objectivity of the process is then, it was argued, only in its “disciplined subjectivity.”(196)

However, on the other end of the spectrum, there is the challenge that over-adherence to protocols has sometimes lead to “empty reviews”(201) in cases where no studies meet inclusion criteria, with authors missing the opportunity to offer insight into the quality of studies so excluded. The contention here is that “bad” research can yield “good” evidence.”(202)

The same subjectivity charge has also been levelled against meta-analysis,(203) especially in the interpretation of funnel plots(204) and the use of quality scores.(203)The idea of quantitative statistical synthesis (meta-analysis) has drawn strident negative responses.(176) Expressions like "shmeta-analysis"(205) “an exercise in mega-silliness”(206) and “statistical alchemy for the 21st century”(207) were a rare display of invective in the medical literature. However, the effort at distinguishing systematic review from meta-analysis by the editors of *Systematic Reviews in Health Care: Meta-analysis in Context* (194, 195) and others was “to prevent the former being discredited by poor versions of the latter”(208). They set meta-analysis in proper context as an optional addendum to the systematic review process only to be used with proper discretion.

1.3.4 SYSTEMATIC REVIEW OF OBSERVATIONAL STUDIES

These criticisms especially of meta-analysis were more directed at reviews of observational epidemiology, than of interventional studies. From only 4 identifiable in the 1985 publication year(209) to over 400 published in 1996,(210) the use of meta-analysis in observational studies is now about as common as in randomised controlled trials. In a random sample of meta-analyses published available on MEDLINE search in 1999, Egger et al(211) found that 40% of the meta-analyses were based on observational studies (mainly cohort and case-control) studies, a result that is in keeping with an earlier analysis by the same group, of studies published and available on MEDLINE search in 1995.(212)

While the randomised controlled trial (RCT) remains the gold standard in the evaluation of intervention, aetiological and prognostic hypotheses can hardly be tested in randomised experiments; it is often only by observational studies or laboratory experiments that these could

be investigated.(212) However, in meta-analysis, the assumption of random variation in the results between studies, while it may be plausible in RCTs (as they are conducted in usually homogenous groups of patients and within largely regulated settings) is not quite as plausible in observational studies where estimates of association may deviate from true underlying relationships beyond variation due to chance, as it is a design that is more susceptible to the effects of confounding, and the influence of biases.(185, 212)

The most important threat to the validity of results from a well conducted cohort study is confounding, while a plethora of biases may plague the case-control studies. Even in instances where confounding factors have been allowed for in statistical analysis, residual confounding, where the confounder is unknown, unsuspected or could be reliably or precisely assessed may remain.(211-214) Therefore, the systematic review of observational studies is for these reasons encouraged over meta-analysis which however remains particularly attractive as it results in precise and definite risk estimates when the magnitude of the underlying risks are small or when the results from individual studies disagree.(212)

However, the more specific application of systematic review and meta-analysis to prognostic factor studies, while it shares the issues that plague that of observational studies in general, also presents its own unique problems:(45, 211, 215) greater difficulty in identifying all relevant studies compared to RCTs, the problem of publication bias (it is less likely that non-significant results will be reported), and many of the studies are retrospective thereby increasing the probability of bias.

There is the issue of inadequate and incomplete reporting of methods and outcome measures, and the lack of recognised criteria for quality assessment. There is also wide variation and inconsistency in study design, inclusion criteria into cohorts, methods of assessing prognostic variables, approach to handling continuous variables, the choice of variables to adjust for, methods of statistical analysis and adjustment for confounders, length of follow up, and the presentation of results by different time points during follow up.(215)

1.3.5 SYSTEMATIC REVIEWS OF PROGNOSIS STUDIES IN EPILEPSY

The conduct of prognosis studies in general has been frequently criticised within the medical literature.(23, 39, 45, 216, 217) The contention has often been that in spite of its methodological demands, prognostic studies are usually not protocol driven, small sized, widely heterogeneous in characteristics of patients, choice and number of predictor variables, outcome and follow up measures, and often prognostic analyses are conducted post-hoc in studies designed for quite another purpose. However, the same issues are not restricted to prognosis research alone, but have broader implications for observational studies generally.(218, 219)

The results of prognostic studies are therefore largely fraught with limitations, and with the attendant uncertainty about the reliability of conclusions of their synthesis.(42, 217) This led to

the creation a new Cochrane Prognosis Methods Group in 2008 aimed at providing support and a forum for discussion to facilitate and improve the quality of systematic reviews of prognosis research.(220) Systematic review of prognosis studies with special focus on methodology is therefore a burgeoning field of interest, and there have been efforts at ensuring the quality of such reviews. Hayden et al(39) have developed a set of criteria, for quality assessment through a meta-review of systematic reviews of prognosis studies. These criteria were adapted for use in the quality appraisal of studies included in this review.

Hitherto, the systematic reviews in the literature of observational studies in epilepsy have only focused on the incidence and prevalence of epilepsy generally(221) and with regional focus – Asia(222), Latin America(223), Middle East and North Africa(224), Europe(225) and sub-Saharan Africa(226). However, these studies, when they do, only make passing reference to the methods and/or results of prognosis studies. Ross et al also systematically reviewed the literature, but on management issues in epilepsy from 1980 to 1999.(227)The studies on prognosis were therefore only partly considered and only in passing, without methodological rigour or consideration of prognostic factors.

The studies on AED withdrawal have also been extensively reviewed(113) with meta-analysis of prognostic factors conducted(114), as are of studies considering seizure outcome following epilepsy surgery (163, 164)and the use of ketogenic diet.(173) However, in spite of the amount of work that has gone into analysing prognosis in newly diagnosed epilepsy, there has been no systematic review of these studies and neither has there been a meta-analysis of the prognostic factors in patients with newly diagnosed epilepsy. However, beyond seizure outcome, no systematic review has also considered other prognostic outcomes, especially of psychosocial outcomes following newly diagnosed epilepsy, important as they are.

2 CHAPTER TWO: THE AIMS AND SIGNIFICANCE OF THIS THESIS

This chapter presents the research question that the thesis aims to answer. The chapter also discusses the central contribution of the thesis to the systematic review and meta-analysis of prognosis studies in general and particularly to studies of prognosis in epilepsy.

The seizure outcome of epilepsy is varied. Epilepsy itself is a multi-aetiological and diverse disorder. The first seizure brings with it the opening of a fresh chapter in the life of the patient, with tough decisions to be made for the patient and for clinicians especially of when or whether to start AEDs as they carry risks of acute idiosyncratic reactions, dose-related and chronic toxic effects, and teratogenicity. For some of the patients newly diagnosed with epilepsy, the benefits of treatment will far outweigh the risks associated with treatment, but there are those for whom this risk to benefit ratio is more finely balanced.(98) There is also the group of patients that may be candidates for non-pharmacological intervention as they will develop drug-resistant intractable seizures.

There is thus the need for studies that identify independent predictors of seizure outcome. These studies have appeared and accumulated in the medical literature. The studies are of different quality and they employ varying methods, study population, outcome definition, and duration of follow up. It is therefore useful to systematically identify all these studies, review their methods and synthesise the results of those studies that have identified the independent factors which consistently predict clinically relevant seizure outcomes in patients that have been newly diagnosed with epilepsy early in the course of the disease.

There is a greater tendency for publication bias in observational research compared to randomised trials(228) and particularly in prognosis studies, as it is more probable that studies showing a strong, statistically significant prognostic ability will be published. This can lead to invalid results and incorrect inferences.(229)There are also the biases associated with observational studies. This systematic review will therefore thoroughly assess for quality of each study in a reproducible manner, based on indices that reflect how prone the studies are to different types of bias.

The systematic review method has been applied extensively to confirmatory prognostic factor studies investigating contribution of one variable to an outcome. The methods for reviewing exploratory studies that set out to identify the independent contribution of a range of variables to an outcome have received less attention in the literature. However, studies of prognostic factors in epilepsy are of the type that investigates more than 1 variable as there are no already extensively established set of prognostic variables for seizure outcome in epilepsy. This type of study presents its own unique issues and difficulties for the reviewer. Therefore this review also

offers an opportunity to explore these issues and to contribute to the understanding of how a reviewer might confront these difficulties.

This thesis aims to answer the following questions:

1. What is the quality of prognosis studies that have attempted to identify independent predictors of seizure outcome among unselected population patients with newly diagnosed epilepsy?
2. What is the effect of study quality, especially potential risk for bias, on the results of the prognosis studies?
3. Which factors have been consistently identified as independent predictors of seizure outcome and which factors have been consistently identified as non-predictors?
4. Do satisfactory seizure outcome prediction models already exist?

The thesis also proposes to develop a classification scheme for prognostic factor studies in newly diagnosed patients with epilepsy so that future studies can be fitted into the scheme and their results interpreted more easily and readily within the context of previous studies of the same category.

This thesis contributes to the present understanding of the methods of systematic review of prognostic factor studies by developing and using a transparent and reproducible method of quality appraisal and by showing how multiple prognostic variables might be handled in a systematic review of studies that do not specifically investigate one particular prognostic variable.

3 CHAPTER THREE: METHODS

This chapter has within it a description of the systematic review process: eligibility criteria, the search strategy, how each category of papers was excluded, and how studies from the same cohort were handled. It also includes a discussion of the iterative process of developing the quality appraisal and data extraction forms and how the results of each study were assessed for quality i.e. tendency for bias. It also discusses the criteria for assessing the quality of externally validated predictive models. This chapter also includes how predictor variables that are consistent, independent predictors of particular outcomes were identified and categorised and results compared in a meta-analysis where possible.

The guidelines for the design, performance and reporting for meta-analyses of observational studies published by the MOOSE group(210) are followed in this systematic review and meta-analysis. One of the defining characteristics of the systematic review – which itself is a retrospective study subject to its own selection bias – is its fidelity to an *a priori* protocol. This protocol is presented in Appendix I.

3.1 ELIGIBILITY CRITERIA

For a systematic review of observational studies such as this, an overly strict set of inclusion and exclusion criteria especially relating to study design may be unduly limiting. Having a strong opinion about the best study design to answer the review questions may lead to selection bias as it does not necessarily mean that these types of studies exist or that studies of better design and higher quality are not available.(230) Therefore, published prospective and retrospective studies – randomised controlled trials, cohort studies, nested case control studies and case-control studies – of unselected (unrestricted) populations of people with newly diagnosed epilepsy that assess the independent effect of predictors of seizure outcome using multivariate regression analysis were sought for inclusion in the review, excluding as ineligible, case series and cross-sectional studies.

Newly diagnosed epilepsy was defined as epilepsy within the first year for the purpose of this review. Therefore only studies with predictor variables collected within the first year of onset, diagnosis, presentation or treatment, depending on how intake is defined in each study. Majority of patients in the studies will also have been followed up prospectively or retrospectively for at least 1 year.

There is no consensus on sample size estimations for multivariable models. However the standard rule of thumb is 10 or more events per variable (EPV) in the model to allow a robust estimation of regression coefficients(231), a value supported by a simulation study,(232) although a more recent study showed that it could be a bit lower(233). Since about 30% (21, 32, 51, 63-70) of patients with newly diagnosed epilepsy will not achieve seizure remission despite

continued antiepileptic drug therapy, a study of association of 2 to 3 predictor variables with 30% outcome rate requires at least 100 patients to achieve an EPV of 10 or more. Therefore to be eligible, the studies also included must have at least 100 patients,(234) a figure also in keeping with an inclusion criterion in a systematic review of prognosis studies by Hemingway and Marmot.(235)

Only studies published in English language were included in the review. The decision to include only English-language studies was made, considering the time, logistic and cost constraints of translation, and also with the awareness that the influence of bias due to language of publication is disputed, and its effect, when and where shown, has been little, and has been considered only in reviews and meta-analyses of intervention studies.(236-239)

3.2 SEARCH STRATEGY

There is no widely acknowledged optimal database and strategy for searching the literature for prognostic studies.(45, 215) However, in a study to ascertain how many databases would be necessary to ensure comprehensive coverage of observational studies in diabetes, Royle et al,(240) found that no additional articles from English language journals were retrieved from any database beyond MEDLINE and EMBASE.They found that MEDLINE alone retrieved about 94% of all the articles retrieved from both databases and the overlap in journal coverage between MEDLINE and EMBASE was 59%. In a much earlier study considering journal coverage, Smith et al(241) in 1992 found the overlap between MEDLINE and EMBASE to be 34%. Therefore these 2 databases were searched to ensure comprehensive retrieval of prognosis studies in epilepsy for potential inclusion in the review. With the wide overlap between MEDLINE and EMBASE, and the fact that the indexing of search terms in EMBASE is more extensive with more synonyms, compared to MEDLINE,(242) a more focused strategy was developed for searching EMBASE using terms specific to study design and analysis.(243)

3.2.1 MEDLINE

To develop search strategies that optimise the yield for prognostic studies in MEDLINE(244) and EMBASE(245), Wilczynski et al (244, 245) used Ovid's search engine syntax for combination of terms. The terms for best sensitivity (keeping specificity ≥50%) in MEDLINE (sensitivity 90.1%, specificity 79.7%)[2] was:

incidence (MeSH)
OR explode mortality
OR follow-up studies (MeSH)
OR prognos (text word)*
OR predict (text word)*
OR course (text word)

[2] Sensitivity is the proportion of high quality articles that were retrieved while Specificity is the proportion of low quality articles not retrieved

This result served as a guide in deciding the search strategy for the study. The process that generated this result was not limited by specific clinical/disease terms. Therefore the performance of the search may be improved by combining the search terms with content specific terms using the Boolean 'AND'. In a search from inception to March 2010, the terms identified by Wilczynski et al(244) were combined with:

explode epilepsy (MeSH)
OR explode seizure (MeSH)
OR seizure disorder (text word)

3.2.2 EMBASE

The reason why it is difficult to formulate search strategy for observational studies is that there are many study designs and the terminology is not standardized.(246) Furlan et al(243)therefore set out to identify terms in MEDLINE and EMBASE related to study design and analysis that could help reverse identify relevant nonrandomized studies in 4 systematic reviews across 4 different clinical areas. They found that text word "multivariate" was 1 of 2 terms which limit topic only searches in all 4 clinical areas. The text word "regression" (Cox regression and logistic regression) was among others common to 2 of the 4 clinical areas.

These terms identified by Furlan et al(243) focusing on terms related to study design and statistical analysis were used for the EMBASE search. The terms "multivariate" and "regression" are common to the inclusion criteria for studies to be included in the review. The terms were thus selected, in addition to "multivariable" to limit an "epilepsy" topic search. The search was from inception to March 2010, and was not limited to EMBASE records alone; it also included papers from MEDLINE present in EMBASE.

multivariate (text word)
OR multivariable
OR regression (text word)

AND

explode epilepsy (Emtree)
OR epilepsy (text word)

3.2.3 SCREENING THE RESULTS FOR ELIGIBLE PUBLICATIONS

To reduce the likelihood of missing out any publication, the full list of titles and corresponding abstracts from MEDLINE was independently screened for eligible papers by 2 reviewers (the MPhil candidate and KB[3], who has masters level training in epidemiology). Following the first

[3] Ms Kathleen Bongiovanni, who had just completed her Master in Public Health (International), volunteered to join in the first round of screening citations retrieved through MEDLINE on EndNote.

round of selection based on inclusion and exclusion criteria, the MPhil candidate returned to EndNote library and conducted a second screening of titles and abstracts to ensure completeness. However, for EMBASE, the first and second rounds of screening, selection, and elimination was conducted by the candidate. The list of references of each of the potentially eligible papers identified from MEDLINE and EMBASE was also manually searched by the MPhil candidate.

3.3 DATA EXTRACTION

In this review, individual studies (not publications) were the unit of analysis as there were papers and cohorts that contributed more than 1 study to the review. For example, a cohort might provide more than 1 study considering different categories of seizure outcome, or using different methods of multivariate regression analysis to identify independent predictors of seizure outcome.

The novel nature of the review precluded the use of any previously designed data extraction form. Therefore a data extraction form was designed and initially piloted on 3 papers. The form was redesigned and piloted on another 2 papers. Then finally, it was redesigned for a third time, and piloted on 2 papers other than the previous 5.

The main issues that had to be addressed in the versions of the quality appraisal forms concerned the areas of potential bias in prognosis studies as identified by Hayden et al(39) which were successively edited to reflect the important quality issues in the studies included. There was also a section on reporting characteristics of included studies in the third (final) version of the form. The 3 versions are in Appendix II.

Data from each study were extracted by the candidate 3 times; twice into a data extraction form (Appendix II), and during the third time, data were extracted and entered directly onto an Excel spreadsheet database. The data extracted were compared with the previous extraction at each succeeding stage and where there were discrepancies, clarification made by consulting the paper(s).

The extracted data included authors and title of study, year of publication, journal, study design, age range (including mean and standard deviation), study recruitment period, length of reported follow up, epilepsy subtypes included or excluded, method of multivariate regression analysis, investigated seizure outcome measures, and details of AED treatment and withdrawal, and how decisions about AED and the choice of drug was made. The risk estimates of the prognostic factors in the multivariable model, and corresponding confidence intervals were also extracted for each study. All data were extracted from the published studies, including obtaining related publications from the same cohort that authors have made reference to for further

details, especially of study population and methods. The authors however were not contacted for further information.

3.4 QUALITY APPRAISAL

There has been a wide range of scales, scores and checklists available to aid quality assessment especially for systematic reviews of intervention studies.(247, 248) However, the use of quality scoring in systematic review and meta-analyses is controversial as aggregate scores may inappropriately conceal and conflate the elements that define quality and may thus not directly be associated with quality.(203, 247-249) It has thus been suggested that key components of design, rather than aggregate scores themselves, may be more important.(39, 249)

In keeping with the guidelines of quality appraisal in systematic reviews and meta-analysis, (39, 178, 195, 250) each eligible study was assessed for bias. Hayden et al(39) developed extensive guidelines for assessing quality in prognosis studies on the basis of a framework of potential biases. In a meta-review that identified quality measures used in systematic reviews of prognosis studies, they pooled quality items into 6 areas of potential bias: study participation, study attrition, prognostic factor measurement, confounding measurement and account, outcome measurement and analysis. (Appendix IV)

These areas of potential bias are relevant to the purpose and question of the present systematic review and were therefore adapted in the analysis of the methods of studies being reviewed. However, the 2 areas of "prognostic factor measurement" and "confounding measurement and account" were merged into 1 as this thesis is not a review of studies investigating the prognostic value of one particular variable. These 5 areas of potential bias as identified by Hayden et al(39) are discussed.

3.4.1 STUDY PARTICIPATION

The area of study participation is concerned with adequacy of reporting and assessing how well the population recruited into each cohort is representative of people with epilepsy within the source population. This judgement is made from the authors' description of study setting, location and catchment area in the paper or a previous, referenced, publication. Therefore for each cohort, answer (Yes, Partly, or No) was provided to the question "Is the source population described?" The explicit description of inclusion/exclusion criteria and baseline characteristics of the cohort was also assessed. This included the assessment of the definition of epilepsy in each paper which according to International League against Epilepsy (ILAE) standard.(1, 2)

The combined information – from how well the cohort is representative of its source population, inclusion and exclusion criteria, and description of the baseline characteristics of the cohorts – is used to make a judgement as to whether recruitment of eligible individuals into the cohort is adequate. Those studies that attempted to prospectively ascertain all the cases of newly diagnosed epilepsy within a particular geographically defined population, with clearly

stated and appropriate inclusion and exclusion criteria are the ideal studies meeting the highest quality standard within this area of assessment.

In retrospective case ascertainment, investigators go back over a period of time and identify patients with recently diagnosed epilepsy for inclusion in the cohort. Prospective studies on the other hand use on-going surveillance to identify newly diagnosed patients when they present for medical attention, recruit them and subsequently follow them going forward. However, studies with retrospective ascertainment of cases may have a prospective follow up component to them, and some studies combined prospective and retrospective case ascertainment, followed by prospective follow up.(44)

Retrospective case ascertainment is a potential source of bias in that identifying cases for inclusion in study may depend on unfavourable outcome, as those who experience recurrence will be easier to identify than those who remain seizure-free after a second or third seizure.(44) It is also more likely that patients with prospective recruitment are more comprehensively assessed for clinical variables and history of previous seizures at the point of diagnosis, thereby avoiding under- or over-estimation of the number of seizures before clinical presentation, and ensuring the general quality of the assessment potential predictors.(44)

The inclusion of single seizure patients, patients with a single episode of status epilepticus, defining epilepsy by a third seizure, excluding patients with poor prognosis or those with excellent prognosis within epilepsy cohorts reported and analysed in the studies are also potential sources of bias. These deviations from standard inclusion and exclusion criteria were highlighted where applicable.

3.4.2 STUDY ATTRITION

This area of potential bias considers what happens after patients are recruited into the cohort i.e. the proportion of the cohort completing the study at the end of follow up or the proportion included in the analysis. The question to answer here is: are those lost during follow up similar to those who completed the study? To make this judgement however, it is important to know if there is an adequate proportion of cohort in the study analysis (76 – 100% Yes, 65 – 75% Partly, <65 No, and when it is not stated in the report – Unsure).

This is considered, together with the reasons for loss to follow up and the characteristics of the patients lost to make the judgment as to whether there are important differences between key characteristics and outcome in participants who completed the study and those who did not that may potentially bias the result of the study. For cohorts with >90% completeness of follow up, without evidence of systematic pattern to loss in follow up, it was assumed that patients lost to follow up are similar to those who completed the study.

However, not all the studies were designed to have the whole cohort included in analysis. In some studies, a case-control analysis of the cohort was conducted instead. The comparison groups in the classical cohort study of prognosis are people with a risk factor and all the other members of the cohort without the risk factor. The relative proportion of individuals with an outcome of interest in each risk factor group is then considered. The outcome groups – cases and controls – are made up of the entire cohort.(28)

A variation on this is the nested case-control study in which the whole cohort is not included in the analysis: the proportion of people with the risk factor under investigation is compared between cases and matched controls or a random sample (sub-cohort) of those without the outcome albeit from the same cohort.(251)This design shares all the advantages of the cohort over case-control study design, especially when it is a prospective cohort: collecting risk factor data before outcome, the time sequence of cause and effect, providing an unbiased estimate of relative risk,(252-255) and the fact that cases and controls are from the same cohort, notwithstanding the argument by Wacholder et al(256) that at least in theory, every case-control study takes place within a "cohort" or population, albeit difficult to define.

However, the variant of the nested case control study design available to be included in this systematic review was one in which the cases and control groups were defined by outcome, for example patients whose seizure is in remission were controls, while for example those with medically intractable seizures were treated as cases, thereby leaving out of the analysis patients who do not satisfy both definitions.(75, 76, 78, 79, 94) This group of studies will subsequently be referred to as "nested case-control" studies although technically, they are not altogether similar in design to studies that bear that name in the literature.(251, 257, 258) In the conventional nested case-control study, cases are identified in a defined cohort. For each case, a specified number of matched controls are selected from among those in the cohort without the case defining outcome.

However, especially in prognostic studies of newly diagnosed epilepsy, these studies do have the additional advantage of comparing groups that are more homogenous, compared to studies that involve the whole cohort. Within a cohort, there is a continuous range of severity of seizure outcome. An assumption inherent in logistic and Cox regression is that the outcome being considered in the analysis must be discrete. Therefore, by creating a dichotomy of outcomes – remission and intractability – and excluding from analysis patients that form a continuum between these 2 groups, nested case control studies achieve a better delineation of binary outcome categories necessary for logistic and Cox regression analyses.

The judgment on attrition in these studies was also made with full understanding of their peculiarity in selecting, based on set criteria in each study, the cases and controls from a defined cohort. For these studies, if there was no evidence of systematic pattern to loss in follow up beyond the choice of cases and controls, it was also assumed that patients lost to follow up were similar to those who completed the study.

3.4.3 PROGNOSTIC FACTOR MEASUREMENT

The definition of each prognostic factor has to be clear and specific to avoid bias. The question was therefore asked: are the prognostic variables clearly defined? Answers were reported thus: Yes, if all the prognostic factors were clearly defined or described, Partly, if not all, and No if none of the prognostic factors were clearly defined or described.

There is also the probability that misclassification bias is introduced by virtue of the method by which prognostic factors are assessed. The second question was if the methods of assessing the prognostic factors were reliable enough to limit misclassification bias. In this case, it was reported as Yes if there was a single site with single assessor, or a fixed protocol, or if there was explicit information about training of assessors for multiple sites or if ILAE standards and definitions (1, 2, 9, 11, 18) were rigorously followed even if there were multiple assessors and there was no information on training assessors for multiple sites. In the absence of these 3 conditions, the answer was Unsure.

How adequate was the proportion of patients with complete data and how missing data were handled in each study formed the third question in this area. Missing data could be in 3 forms: missing completely at random (MCAR) when people with missing data are a random subset of the complete sample of the cohort, for example the result of some patients' brain computed tomography (CT) scan is lost accidentally. The fact that data are missing is completely explainable in terms of a random event as the probability that an observation is missing is not related to the patients' characteristics.(259, 260)

When missing data are MCAR, patients with complete data are also a random sample from the cohort. Therefore a technique like simply deleting an entire observation if it is missing on any item used in the analyses (listwise deletion) is appropriate as the only loss is statistical power, and there is no apparent potential for bias in the estimates.(260) This is also true when data are missing at random (MAR) in which case the probability that an observation is missing depends on information for that subject that is present, i.e. the reason for missing data is based on other observed patient characteristics,(259) for example if the number of seizures before treatment cannot be ascertained in a random sample of patients with cognitive impairment, it could be said to be missing at random (MAR), and could also be ignorable just like for MCAR.

However, it is not ignorable when data are missing not at random (MNAR). Here, the probability that an observation is missing depends on the value of the observation itself,(259) like when the reason that the number of seizures before AED cannot be ascertained is because the frequency of pre-treatment seizures is high, and the patient or carer cannot recollect. In this case, there would be a need to resort to the more complex imputation techniques to handle missing data.(259, 260)

Therefore the question about if the proportion of patients with complete data was adequate and how missing data were handled would have been reported in the following way: Yes when data were complete, or when less than 20% of a prognostic factor data were MCAR (missing completely at random) or MAR (missing at random) and listwise deletion or imputation was used, or when less than 10% were MNAR with listwise deletion or imputation used. Partly when MCAR and MAR was 20-30% with appropriate imputation or when MNAR was 10-20% with the use of appropriate imputation. No when MCAR, MAR was more than 30% of a prognostic factor or when MNAR (missing not at random) was greater than 20%. When these issues were not addressed or reported, the answer was Unsure.

However, most authors did not report on these issues at all. Some authors included data completeness as an inclusion criterion, making it impossible to assess if the study population is representative.

How continuous variables are handled is also important in multivariate analysis. The choice is between keeping them continuous or creating categories which may or may not be data dependent. Categorizing patients into high- and low-risk groups based on an "optimal cut-point" that maximises statistical significance or the non-data dependent division through the median into 2 equal groups without *a priori* justification often leads to bias, loss of potentially important quantitative information, loss of power and residual confounding.(261)

Therefore the question about how the continuous variables were handled was answered Yes for papers that left all the continuous prognostic factors as continuous variables. However it was Partly for those that kept some variables continuous and others categorised in a non-data dependent and/or data dependent manner. It was also Partly for those that used only non-data dependent method of categorising continuous data and No for those that used only data dependent method or in combination with non-data dependent method.

3.4.4 OUTCOME MEASUREMENT

It is also important that there is a clear operational definition of the seizure outcome being considered in the study, with a long enough time frame to limit misclassification bias as seizure outcome in newly diagnosed epilepsy has a temporal pattern, and when patients are followed up longer it is more likely that they are classified correctly in their outcome category.(25) The question about the clear definition of outcome measure is reported as Yes, Partly or No. It was Yes if the outcome was clearly defined in relation to length of follow up and seizure-free period or period of continued seizures. It was No if either the outcome was not clearly defined and if the time dimension was not explicitly stated. It was Partly if the outcome was clearly defined but the related time dimension was not stated explicitly.

The issue of being able to limit misclassification bias was assessed in a manner similar to that of prognostic factor measurement. The method of assessment was considered sufficient to limit

misclassification bias if follow up for the majority of the cohort was for at least 1 year and it was a single site with single assessor. The answer was Partly if there were 2 to 3 assessors in a site or if there was 1 assessor in 2 to 3 sites. Multiple sites or multiple assessors without information on training or standardization of outcome measure method was answered as a No.

For the third question in this area, the issue was about measuring the outcome and prognostic factors blind to each other. It was assumed that in cohorts where cases were prospectively identified, whether it was stated or not, the outcome and prognostic factors were assessed blind to each other, and for retrospective case ascertainment, the answer is Unsure, unless explicitly stated in the affirmative.

3.4.5 MULTIVARIATE REGRESSION ANALYSIS

Multivariate regression analysis is the most commonly used method to examine and adjust for variables in prognostic factor studies.(45) However, it is also commonly abused, especially as a black box that simply produces risk estimates(262) without important details of the process and sometimes, details of the results of analysis . The risk estimates tend to vary with the choice of the mathematical model, coding of variables, and method of selecting variables.(263) It is therefore important that information on the test of assumptions of model building be provided such as a test for colinearity and interactions among variables.(263) It is also important to be able to determine how sufficient the reported data are to assess the validity and reliability of the results.

Therefore, the first question here was: how detailed were the results presented? If the risk estimate or the regression coefficient was presented and the standard error or 95% confidence interval of regression coefficients of risk estimate was presented, the report was Yes. However if the result from only 1 of these 2 was presented, it was reported as Partly, and if neither, the report was No.

The next question concerns whether the method of selecting variables to be included in the final model was described. The choice of variables to retain in a regression analysis could be made by forward selection (starting with a priori recognised predictor variables) or backward elimination (starting with all available predictors, and could be all variables used in univariate analysis, or only variables significant at ($P < 0.05$) in univariate analysis) or using the computer automatic selection stepwise procedure (forward or backward), with different criteria for inclusion or exclusion of a variable in the model. Important variables from clinical experience or previous studies may be forced into the model as well as significance level fixed for prognostic factors to retain or eliminate, in a forward or backward stepwise manner, manually or in automated algorithms. Did the authors specify how predictor variables were selected? Was there a preliminary screen based on the univariate association? Was some form of stepwise analysis used, and if not, was colinearity between variables assessed? For this item, the answer is Yes if it was stated that there was a stepwise selection of variables, and No if it was not so stated.

The risk estimates may however be unreliable if outcome events are too few relative to the number of independent variables, leading to a situation where regression coefficients for individual prognostic factors may represent spurious associations, or the effects estimated with low precision.(231, 263) Therefore the rule of thumb, of having at least 10 events per variable (EPV) is a liberal way of assessing if or not there is over-fitting of the data. This is done by computing the ratio of the number of predictors in the model and number of patients with less common outcome.(231)However it has been shown by Vittinghoff et al(233) that the rule of 10 could be relaxed a little.

Other issues related to statistical analysis that were also assessed include if the authors attempted to justify study sample size, the number of patients lost to follow up and how loss to follow up was treated in analysis.(263)

3.4.6 SUMMARY OF POTENTIAL FOR BIAS IN STUDIES

To assess the quality of each study, 1 summary measure of judgement about each of the 5 potential areas of bias (study participation, study attrition, prognostic factor measurement, outcome measurement and multivariate analysis) was constructed for each of the individual studies included.

The summary assessment for quality of study participation was the report of how adequately the eligible individuals were recruitment of into each cohort, which is the answer to the third question in the area of study participation. However, for study attrition, cohorts with >90% completeness of follow up and nested case control studies, without evidence of systematic pattern to loss in follow up, were assessed as adequate. Otherwise, studies were assessed based on their report of how similar those lost to follow up are to those who are included in the analysis. For studies with minimum follow up > 20 years, the rules were relaxed to allow for more than 10% attrition rate.

To be assessed as adequate, methods that were assessed as sufficient to limit misclassification bias must be used for prognostic factor measurement. The factors would at least be “partly” defined and continuous variables at least “partly” kept continuous or have adequate proportion of patients with complete data. The outcome must first be clearly defined, and the method of measure must also be sufficient to limit misclassification bias, or measured blind to prognostic factors and vice versa. Multivariate analysis was considered to be adequate only if the EPV was at least 9.

3.5 SYNTHESIS OF RESULTS

The consistently identified independent predictor variables were considered for synthesis. This does not involve the statistical pooling of risk estimates; only the statistical conversion of risk estimates into formats that would facilitate comparison in order to ascertain the consistency of

exposure-outcome relationship across different studies, and to make a decision on the least biased risk estimate(s) for each outcome.(264) Variables that were found to be an independent predictor in more than 1 study from different cohorts were considered to be consistent predictors. On the other hand, the variables that were examined, but not retained in the model in more than 1 study from different cohorts were considered as consistent non-predictors.

Hazard (or rate) ratio (HR) was assumed to be a reasonable approximation of the relative risk (RR), as they are both simple quotients of "exposed" and "unexposed" quantities; HR a ratio of rates and RR a ratio of probabilities.(265) However, the similarity or disparity of these measures depends on the influence of the length of follow-up, which may impact on the average rate of the occurrence of the seizure outcome of interest, and the risk of the "exposed" group relative to the referent group.(265)

When association is weak and events are uncommon, relative risk, hazard rate ratio, and odds ratio (OR) are good numerical approximations of one another; their disparity increases as events increase and as risk departs from unity. However, the odds ratio is more subject to the influence of these factors (265-267) as the hazard ratio reasonably approximates relative risk under a much wider range of circumstances. Therefore, in studies where odds ratio was the risk estimate, the Zhang-Yu equation(266) was used to shrink the odds ratio towards unity (in the direction of relative risk), when event rate exceeds 10%, and/or odds ratio is greater than 2.5 or less than 0.5.(265-267)

The Zhang-Yu equation(266) is such that in a cohort study, if P_0 is the incidence of the outcome of interest in the non-exposed group and P_1 is the incidence in the exposed group:

Odds Ratio (OR) = $(P_1/1-P_1)/ (P_0/1-P_0)$

Therefore $(P_1/P_0) = OR/ [(1 - P_0) + (P_0 \times OR)]$

However, since relative risk (RR) = P_1/P_0

The corrected RR = $OR/ [(1 - P_0) + (P_0 \times OR)]$ (Zhang-Yu Equation)

Zhang and Yu(266) proposed the formula to estimate the risk ratio from the odds ratio in cohort and cross-sectional studies with univariate and multivariable analyses. They validated the formula with a simulation incorporating 2 confounding variables and it was shown that the relative risk estimates were close approximations to the true relative risk. The equation was recommended for use, and has been used in several meta-analyses.(265, 268-271)

The equation shows that as P_0 approaches zero, the denominator approaches 1 and RR approaches OR. This situation in which OR approximates RR obtains when the outcome is rare. However, as P_0 approaches 1, RR approaches 1 regardless of the value of OR, which shows the

large differences that occur between RR and OR when the outcome is common. When OR equals 1, then RR also equals 1, regardless of the value of P_0. For all P_0 greater than zero and less than 1, RR is less than OR when OR exceeds 1, and RR is greater than OR when OR is less than 1. Therefore, as expected, the estimated relative risk is always closer to unity than the odds ratio. (272)

3.6 EXTERNALLY VALIDATED PROGNOSTIC MODELS

For studies with prognostic models that were externally validated, further quality appraisal will be conducted with particular reference to the models. Laupacis et al(273) suggested additional criteria specific to prognostic models in their 1997 paper which was an addition to previous criteria suggested by Wasson et al (274) in 1985, many of which were again identified in the more recent work Hayden et al(39). The factors peculiar to prognostic models from Laupacis et al(273) that were not already discussed as one of the potential areas of bias from the study by Hayden et al(39) are the sensibility of the model and its performance on internal and external validation and in clinical practice. The models were assessed for their performance in internal and external validation using the 2 parameters of calibration and discrimination.(23, 27, 275)

3.6.1 CALIBRATION AND DISCRIMINATION

The performance of binary outcome models is usually assessed in terms of calibration and discrimination. The calibration of a model is its ability to have predicted probabilities that agree with the observed proportions of events over the whole range of probabilities. Calibration could be investigated by plotting the observed proportions of events against the predicted risks for groups defined by ranges of individual predicted risks, usually in 10 groups. Ideally, the plot shows a 45 degree line in internal validation i.e. the slope is 1.(23) There is however a loss in the calibration when the model is externally validated in another population. The statistical tests sometimes used to assess calibration include Hosmer-Lemeshow test(276) and the calibration component of the Brier score.(277)

The 2 probabilities that are often used to express the performance of binary tests were used to assess the accuracy of the models as reported in internal and external validation studies: 1.) Sensitivity or true positive rate (TPR) which is the proportion of actual positives [patients with outcome, i.e. true positives (TP) and false negatives (FN)] that the model correctly identifies as true positive (TP) (i.e. the percentage of newly diagnosed epilepsy patients that will enter remission who are correctly identified by the model); 2.) Specificity or true negative rate (TNR) which is the proportion of actual negatives [patients without outcome, i.e. true negatives (TN) and false positives (FP)] which are correctly identified as true negative (TN) (i.e. the percentage of newly diagnosed epilepsy patients that will not enter remission who are identified by the model).(278)

However, 2 more clinically important probabilities were also used in assessing the accuracy of the models. Positive Predictive Value (PPV) refers to the percentage of the true positive (TP)

among all those that the model correctly (TP) or incorrectly (FP) identified as positive (i.e. PPV = TP/TP+FP); Negative Predictive Value (NPV) is the percentage of true negatives (TN) among all those that the model correctly (TN) or incorrectly (FN) identifies as negative (i.e. NPV = TN/TN+FN). The summary of the accuracy of the model is the proportion of patients within the cohort with correct prediction, either positive (P) or negative (N) (i.e. TP+TN/P+N) The positive and negative predictive values, unlike sensitivity and specificity change with pre-test probability i.e. with the proportion of patients with the outcome within the cohort.(279) Therefore the PPV and NPV measure in external validation reflect the accuracy of the model in a different cohort, and a possible difference in pre-test probability.(279) PPV and NPV were computed from available data when they were not explicitly provided.

However, before these probabilities are determined for a particular model, the ROC (receiver operating characteristic) curve of the model in the development sample is plotted. The ROC curve is a plot of the true positive rate (or sensitivity) versus the false negative rate (or 1−specificity) as the cut-off point that assigns a higher probability of outcome in the model is progressively varied. In effect, it is a comparison of 2 operating characteristics (true positive rate and false positive rate) as the discrimination criterion changes.(278)

The area under ROC (receiver operating characteristic) curve (AUC) is used to assess the ability of a model to discriminate between individuals with and without the outcome being predicted. The AUC represents the chance that given 2 patients, one who will develop an outcome and the other who will not, the model will assign a higher probability of having the outcome to the patient who will develop, for example, the seizure outcome of interest.(23, 275) The AUC for a prognostic model is typically between about 0.60 and 0.85 (the values are higher in diagnostic settings) (275) and it is usually deemed good if >0.70 and poor when <0.70 for prognostic models. (107, 280)

The other purpose of the ROC curve is that it allows for the detection of an optimal cut-off point, at which the combination of true and false positive rates is best for the purpose of the model. Therefore values above this point will indicate a higher probability of the indicated outcome, and lower values indicate lower probability of outcome. Ideally, this point is chosen to assess the accuracy of the model in predicting outcome in the development cohort and in the external validation, and the probabilities that assess accuracy at the cut-off point (sensitivity, specificity, positive predictive values, negative predictive value and the proportion of patients in each cohort with correct prediction) are computed.(107)

3.6.2 INTERNAL VALIDATION

Although not explicitly stated and only implied by Laupacis et al,(273) internal validation is important in assessing the performance of the model. However, internal validation does not provide information about the model's performance in another population. A model is internally validated by splitting the dataset randomly into 2 parts. The model is developed using the first

part and its predictive accuracy is assessed on the second portion. If the available data are limited, the model can be developed on the whole dataset and techniques of data re-use, such as cross validation and bootstrapping, applied to assess performance.(27) In this review, the results of the internal validation of the models that were subsequently subjected to external validation were assessed for calibration and discrimination.

3.6.3 EXTERNAL VALIDATION

It is important to validate a model intended for clinical use in a group of patients different from the group in which it was derived, and preferably with different clinicians. This examines the generalisability of the model.(27, 231, 273)This could be external in place and/or external in time. When validation is external only in time, it is otherwise called temporal validation. In this case, the performance of a model is prospectively evaluated on subsequent patients from the same centre.(27, 281) However, a higher hierarchy of validation is when it is external both in time and place,(281)as it is the only form of validation that could confirm the wider generalisability of the model. The results of the external validation were assessed for calibration and discrimination.

3.6.4 SENSIBILITY

The evaluation of sensibility was based on judgment rather than statistical methods:

Is the model clinically sensible? Clinicians should think that the items in the model are clinically sensible and that no important items are missing. It is difficult to determine which factors are important in the prognosis of seizure outcomes in epilepsy, but this was determined retrospectively following this systematic review. It was then subsequently documented whether these variables were included in the model(234)

Is the model easy to use? This includes consideration of factors like time needed to apply the model, and how simple it is to use. Models that require extensive calculations may be less likely to be used than models with simpler scoring schemes.(216) Laupacis et al(273) are of the opinion that prognostic models that recommend a course of action are more likely to be used compared with those that simply describe the probability of an outcome. Therefore, it was also assessed if the model was only reported as outcome probability or the authors also recommend accompanying course of action. These 3 indices of sensibility were assessed and reported.

3.6.5 EFFECTS OF USE ON CLINICAL PRACTICE

This refers to the prospective evaluation of the effect on clinical practice of using the prognostic model in a patient population other than the one in which it was developed and validated to show if physicians and patients are willing to use the model and how its use affects patient behaviour and clinical outcomes. This is best done in randomised trials.(282) These criteria apply to models that could be used to predict seizure outcomes in epilepsy, and were therefore used in the analysis of methods of the studies with externally validated prognostic models.

4 CHAPTER FOUR: RESULTS

This chapter presents the result of the systematic review. The chapter starts by reporting the results of the process of identifying eligible publications, followed by a description of included studies, how they relate to the cohorts from which they are derived and the publications that report them, and an account of the reporting characteristics of each of the eligible publications. There is a detailed report of the quality appraisal of studies included from each publication. The studies were subsequently disaggregated according to the seizure outcome predicted, and each category of study is further evaluated and appraised with a view to: 1) Understanding and explaining similarities and differences in results in relation to each study's peculiar characteristics and potential for bias, 2) Identifying consistent independent predictors and non-predictors within each outcome category, and 3) Assessing the quality and performance of externally validated prognostic models within each outcome category.

4.1 IDENTIFYING ELIGIBLE PUBLICATIONS

When the search terms were run through MEDLINE, (from inception to March 2010) 14,967 citations were identified and exported to EndNote citation management software.

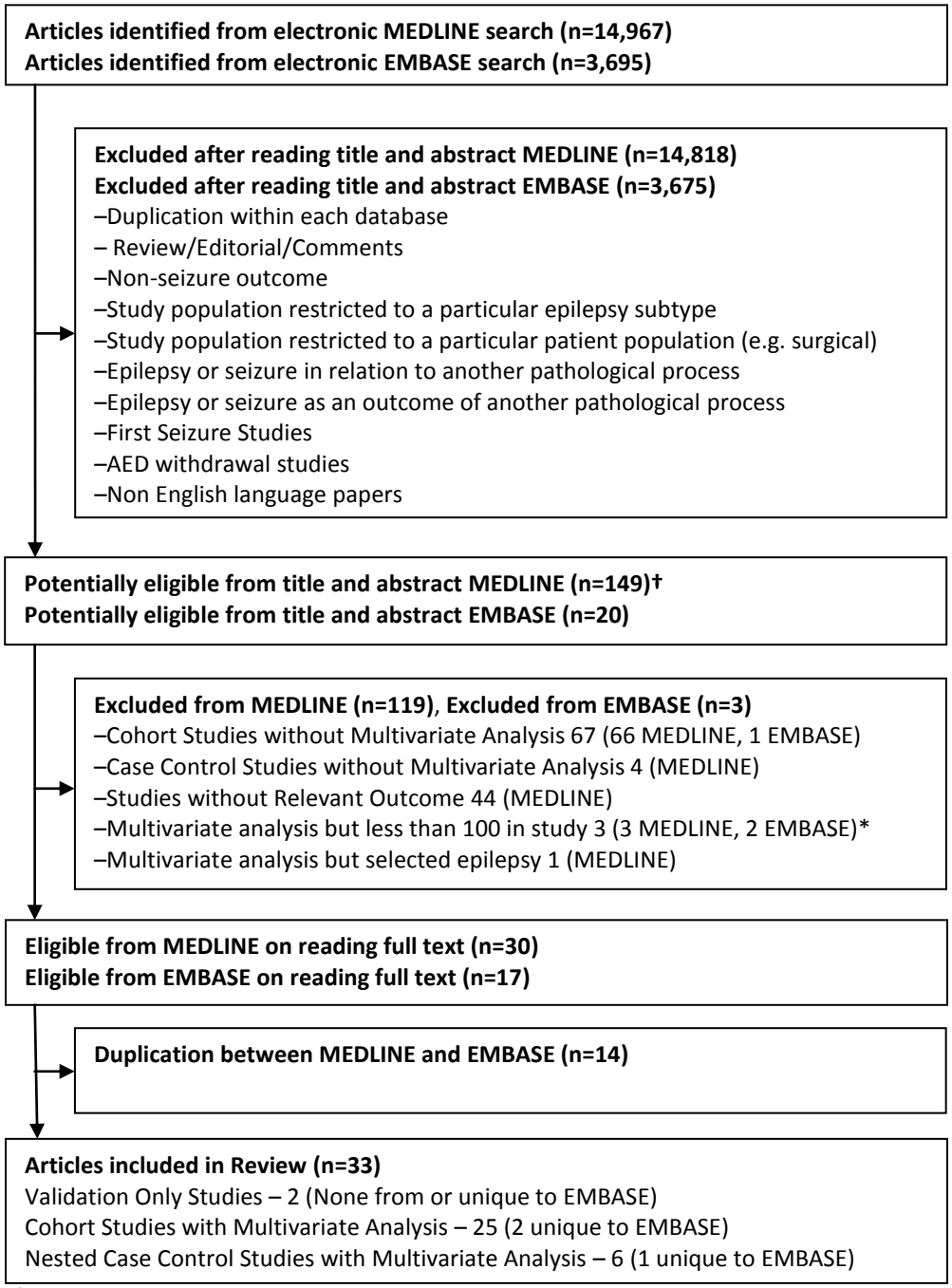
Following the first round of screening, 144 potentially eligible papers were identified after eliminating duplications, review articles, editorials and commentaries, and papers with non-seizure outcome. Papers with the study population restricted to a particular epilepsy subtype (e.g. partial epilepsy or mesial temporal lobe epilepsy) or patient population (e.g. pre-operative or post-operative epilepsy surgery candidates) were also eliminated. There were also papers in which epilepsy or seizure was studied as an outcome of or in relation to another pathological process (e.g. head trauma or autism) which were also eliminated. Reports of first seizure studies without follow up to the second seizure and beyond, and studies of AED withdrawal were also eliminated as were non-English language articles. (Figure 6)

The second round of screening yielded an additional 5 potentially eligible papers. Then the full text of all 149 papers was assessed and 44 studies without relevant outcome, mostly non-seizure outcome were eliminated, as were 66 prospective or retrospective cohort and 4 case control studies without multivariate regression analysis to control for confounding. There were also 3 papers with multivariate regression analysis modelled on less than 100 participants,(50, 92, 102) and 2 papers reporting studies with multivariate regression analysis modelled on more than 100 patients but with a selected epilepsy population such as excluding patients with remote symptomatic aetiology(67) and including only patients with focal seizures(103); these papers were also eliminated.

A total of 119 papers were eliminated, leaving 30 eligible papers. A manual search through the list of references of each of the eligible papers yielded only 1 potentially eligible title, which

turned out to be a case control study without multivariable control for confounding, and so was eliminated. The full citation details of the papers are in Appendix II.

Figure 6 | Flow diagram of the systematic review



† The number selected after 3 rounds of screening

*The 2 papers eliminated from EMBASE were the same as 2 of the 3 eliminated from MEDLINE

The EMBASE search (from inception to March 2010) returned 3,695 papers, expectedly much fewer than the broader MEDLINE search. After screening the title and abstracts, 20 papers remained following the elimination of duplications, review articles, editorials and commentaries, and papers with non-seizure outcome. Papers reporting studies restricted to a particular epilepsy subtype or patient population and in which epilepsy or seizure was studied only as an outcome of or in relation to another pathological process were also eliminated. Reports of first seizure studies without follow up to the second seizure and beyond and studies of AED withdrawal were also eliminated as were non-English language papers as in the MEDLINE search. No additional potentially eligible papers were identified during the second screening of the search results.

The full text of these 20 papers revealed that there was 1 paper reporting a cohort study but without multivariate control for confounding. There were also 2 papers with multivariate regression analysis to control for predictors of seizure outcome, but in fewer than 100 patients.(92, 102) These same 2 papers were also eliminated for the same reason from the MEDLINE search result. Of the 17 eligible papers from the EMBASE search, 14 had already been identified from the MEDLINE search, making 47% of the 30 identified from MEDLINE. The additional EMBASE effort contributed 3 papers of the total 33 (9%), 2 of which were published in 2010. There were no additional papers identified from the list of references of the 3 papers. (Appendix II)

4.2 DESCRIPTIVE CHARACTERISTICS OF ELIGIBLE PUBLICATIONS

Of the 33 publications included, 2 publications exclusively reported on external validation of prognostic models developed independently in a Dutch cohort and a cohort from Nova Scotia. The first was a validation of the first Nova Scotia model in patients within the Turku, Finland cohort.(105) The second was a temporal validation of the first set of models developed from the Dutch cohort at 2 years follow up.(107)

However, of the other 31 publications, 23 were reports of multivariate regression analysis conducted on entire cohorts,(21, 24, 32, 63-66, 68-74, 77, 93, 95, 97-101, 104) 7 were case control analyses of populations nested within cohorts defined by seizure outcome(25, 75, 76, 78, 79, 94, 96) and 1 was an analysis of a combination of 2 existing cohorts,(106) which also contains an external validation study of prognostic models derived from both cohorts. The study combined individual patient data from the Dutch and Nova Scotia cohorts, with different inclusion criteria from the original publications reporting studies on these cohorts to develop a model from each newly constituted cohort and a third model from the combined population. The model from each cohort was internally validated on the cohort within which it was developed, and then cross-validated externally on the other cohort.

The general characteristics of the eligible publications are reported in Table 1, showing that more than 80% were published in the last fifteen years, and almost a third were published in a single journal, *Epilepsia*. Only 2 (6%) papers were published in non-neurology journals – *New England Journal of Medicine* (NEJM) and *Acta Paediatrica* (formerly named *Acta Paediatrica Scandinavica*). Thirty of the papers were from countries with high income economies, while the rest are from the 3 contiguous low-and middle- income countries (LMICs) of Bangladesh, India and Nepal as defined in the World Bank's 2010 World Development Indicators.(283)

Table 1 | Eligible Publications by Year, Journal and Country

Category	Characteristic	Number
Year of Publication		
	2006 – 2010	8
	2001 – 2005	9
	1996 – 2000	10
	1991 – 1995	4
	1986 – 1990	2
Publishing Journal		
	Epilepsia	10
	Seizure	3
	Brain	3
	Pediatric Neurology	2
	Annals of Neurology	2
	Acta Neurologica Scandinavica	2
	Others with 1 publication	11
Journal Category		
	General Medical	1
	General Neurological	12
	General Paediatric	2
	Paediatric Neurology	4
	Epilepsy	13
	Other (Neurophysiology)	1
Country of Cohort*		
	Finland	6
	Italy	4
	Netherlands	4
	United Kingdom	2†
	USA	6
	Canada	3
	China (Hong Kong)	2
	Others with 1 publication‡	7

**The sum of this category is 34 instead of 33 as 1 publication is based on 2 cohorts from different countries*
†The second UK publication is from a multinational cohort with 50% of patients from the UK
‡Four of the 7 countries with 1 publication each are non-European –Bangladesh, India, Nepal and Saudi Arabia; the others are Norway, Spain and Sweden

There were 47 eligible multivariable regression analyses in all, considering different categories of seizure outcome (Table 2 and Table 3). Each of the 3 publications from low-and middle-income countries arose from 1 cohort in each of Bangladesh, India and Nepal, with each publication reporting the only study from each cohort. The same is true for the studies and cohorts from Hong Kong as well as Saudi Arabia. However, there were 24 eligible studies from the 10 European cohorts, and 18 studies from 7 North American cohorts. One cohort,(98) originally from the MESS trial(284) (a randomised controlled trial of the effect of early AED use on seizure outcome) was multi-national from 9 European countries (United Kingdom, Hungary, Italy, Netherlands, Poland, Portugal, Slovakia, Turkey and Yugoslavia), 2 South American countries (Brazil and Chile), India, and Israel. However, as 50% of the cohort was from the United Kingdom (UK) alone,(284) this study was categorised as European. In all, there was no cohort from Australasia; neither was there a cohort containing an African population.

Eight (35%) out of a total of 23 unique cohorts were population based cohorts; 5 of the population based cohorts were European (out of 10) while the remaining 3 were based in North America (out of 7) (Table 2 and Table 3).

Table 2 | Descriptive Characteristics of Cohorts, Publications and Studies (European Cohorts)

Cohort Recruitment Period Setting	Age of Population	Decision on AED Regimen	Study Design	Seizure Outcome	Method of Analysis (Risk Estimate)	Publication
Turku, Finland *1961-1964, Population*	Children (<15 years)	Physician's Discretion	**Mixed Cohort**	**Remission on or off AED**	**Logistic (OR)**	**Sillanpaa, 1990**
			Mixed Cohort	**Remission on or off AED**	**Logistic (OR)**	**Sillanpaa, 1993**
			Mixed Cohort	**Remission on or off AED**	**Cox (HR)**	**Sillanpaa, 1998**
			Mixed Cohort	**Remission off AED**	**Cox (HR)**	**Sillanpaa, 1998**
			Prospective Cohort	**Remission off AED**	**Cox (HR)**	**Sillanpaa, 1998**
			Prospective Cohort	**No Remission after Relapse**	**Logistic (OR)**	**Sillanpaa, 2006**
			Prospective Cohort	**Remission on or off AED**	**Cox (HR)**	**Sillanpaa, 2009**
DSEC, The Netherlands *1988-1992, Hospital*	Children (<16 years)	Physician's Discretion	**Prospective Cohort**	**Remission on or off AED**	**Logistic (OR)**	**Arts, 1999**
			Prospective Cohort	**Remission on or off AED**	**Logistic (OR)**	**Arts, 1999**
			Prospective Cohort	**Remission on or off AED**	**Logistic (OR)**	**Arts, 2005**
			Prospective Cohort	**Remission on or off AED**	**Logistic (OR)**	**Arts, 2005**
			Prospective Cohort	**Remission off AED**	**Logistic (OR)**	**Geelhoed, 2005**
NGPSE, UK *1984-1987, Population*	Children and Adults (>5 years)	Not Stated / Unclear	**Prospective Cohort**	**Remission on or off AED**	**Cox (HR)**	**MacDonald, 2000**
			Prospective Cohort	**Remission on or off AED**	**Cox (HR)**	**MacDonald, 2000**
MESS, UK (50%) *1993-2000, Hospital*	Children and Adults	Randomised	**Mixed Cohort**	**Early Remission**	**Cox (HR)**	**Kim, 2006**
CGSE, Italy *1982-1985, Hospital*	Children and Adults	Physician's Discretion	**Mixed Cohort**	**Early Remission**	**Cox (HR)**	**CGSE, 1988**
			Mixed Cohort	**Remission on or off AED**	**Cox (HR)**	**CGSE, 1992**
			Mixed Cohort	**Remission on or off AED**	**Cox (HR)**	**CGSE, 1992**
Copparo, Italy *1964-1984, Population*	Children (<19 years)	Not Stated / Unclear	**Prospective Cohort**	**Intractability**	**Logistic (OR)**	**Casetta, 1999**
Bari & Monza, Italy *1989-1999, Hospital*	Children and Adults	Physician's Discretion	**Mixed Cohort**	**Early Remission**	**Logistic (OR)**	**Del Felice, 2010**
Västerbotten, Sweden *1985-1987, Population*	Adults	Physician's Discretion	**Mixed Cohort**	**Early Remission**	**Cox (HR)**	**Lindsten, 2001**
Akershus, Norway *1987-1994, Population*	Adults	Not Stated / Unclear	**Retrospective Cohort**	**Remission on or off AED**	**Logistic (OR)**	**Lossius, 1999**
Almeria, Spain *1994-2004, Hospital*	Children (<14 years)	Physician's Discretion	**Mixed Cohort**	**Intractability**	**Logistic (OR)**	**Ramos-Lizana,2009**

Mixed Cohort – Combined prospective and retrospective case ascertainment; OR – Odds Ratio; HR – Hazard Ratio

Table 3 | Descriptive Characteristics of Cohorts, Publications and Studies (Other Cohorts)

Cohort Recruitment Period, Setting	Age of Population	Decision on AED Regimen	Study Design	Seizure Outcome	Method of Analysis (Risk Estimate)	Publication
Nova Scotia, Canada *1977-1985, Population*	Children (<16 years)	Physician's Discretion	**Mixed Cohort**	**Remission off AED**	**Logistic (OR)**	**Camfield, 1993**
			Mixed Cohort	**Remission off AED**	**Logistic (OR)**	**Camfield, 1993**
			Mixed Cohort	**Remission off AED**	**Logistic (OR)**	**Geelhoed, 2005**
DSEC and Nova Scotia	Children (<16 years)	Physician's Discretion	**Mixed Cohort**	**Remission off AED**	**Logistic (OR)**	**Geelhoed, 2005**
Montreal, Canada *1991-2000, Hospital*	Children (2 -17 years)	Not Stated / Unclear	**Retrospective Cohort**	**Remission off AED**	**Cox (HR)**	**Oskoui, 2005**
			Retrospective Cohort	**Remission off AED**	**Cox (HR)**	**Oskoui, 2005**
			Retrospective Cohort	**Intractability**	**Logistic (OR)**	**Oskoui, 2005**
			Retrospective Cohort	**Intractability**	**Logistic (OR)**	**Oskoui, 2005**
			Retrospective Cohort	**Intractability**	**Logistic (OR)**	**Oskoui, 2005**
			Retrospective Cohort	**Intractability**	**Logistic (OR)**	**Oskoui, 2005**
New York, USA *1983-1993, Hospital*	Children (<19 years)	Not Stated / Unclear	**Prospective Cohort**	**Early Remission**	**Cox (HR)**	**Shinnar, 2000**
			Prospective Cohort	**Remission on or off AED**	**Cox (HR)**	**Shinnar, 2000**
Connecticut, USA *1993-1997, Population*	Children (<15 years)	Protocol	**Prospective Cohort**	**Intractability**	**Cox (HR)**	**Berg, 2001a**
			Prospective Cohort	**Remission on or off AED**	**Cox (HR)**	**Berg, 2001b**
Boston, USA *Not Stated, Hospital*	Children (<18 years)	Not Stated / Unclear	**Retrospective Cohort**	**Intractability**	**Logistic (OR)**	**Ko, 1999**
			Retrospective Cohort	**Intractability**	**Logistic (OR)**	**Ko, 1999**
Rochester, USA *1935-1978, Population*	Children and Adults	Not Stated / Unclear	**Retrospective Cohort**	**Remission on or off AED**	**Cox (HR)**	**Shafer, 1988**
New Haven, USA *Not Stated, Hospital*	Children (Not Stated)	Not Stated / Unclear	**Retrospective Cohort**	**Intractability**	**Logistic (OR)**	**Berg, 1996**
Hong Kong, China I *1997-NS, Hospital*	Adults	Protocol	**Mixed Cohort**	**Remission on or off AED**	**Logistic (OR)**	**Hui, 2007**
Hong Kong, China II *1982-1997, Hospital*	Children and Adults	Not Stated / Unclear	**Mixed Cohort**	**Intractability**	**Logistic (OR)**	**Kwong, 2003**
Riyadh, Saudi Arabia *1994-1996, Hospital*	Adults	Protocol	**Mixed Cohort**	**Remission on or off AED**	**Logistic (OR)**	**Abduljabbar, 1998**
Dhaka, Bangladesh *1996-NS, Hospital*	Children (<15 years)	Protocol	**Retrospective Cohort**	**Remission on or off AED**	**Logistic (OR)**	**Banu 2003**
New Delhi, India *Not Stated, Hospital*	Children (Not Stated)	Not Stated / Unclear	**Mixed Cohort**	**Intractability**	**Logistic (OR)**	**Chawla, 2002**
Kathmandu, Nepal *1995-NS, Hospital*	Children and Adults	Physician's Discretion	**Retrospective Cohort**	**Remission on or off AED**	**Logistic (OR)**	**Lohani, 2010**

Mixed Cohort – Combined prospective and retrospective case ascertainment; OR – Odds Ratio; HR – Hazard Ratio

4.3 REPORTING CHARACTERISTICS OF ELIGIBLE PUBLICATIONS

Table 4 presents the results of 10 reporting characteristics of the 31 eligible publications reporting multivariate analysis. The publications are assessed based on information documented within them or within referenced publication(s).

None of the publications reported a power calculation or attempted to justify their sample size or discuss limitations that may arise as a result of sample size, whereas all the studies reported on loss to follow up albeit to differing degrees, including studies in which it was reported that no patient was lost. Only a quarter of the studies mentioned the issue of missing data in the cohort analysed. However, data completeness was generally poorly described. In several studies, absence of missing data was a criterion for inclusion in the study analysis. Of the 8 papers that reported on missing data,(66, 68, 71, 98-100, 104, 106) 3 explicitly stated the number of participants excluded from analysis for that reason, (68, 104, 106) and 2 reported the use of imputation to replace missing data.(98, 106)

In their analysis for predictors of seizure outcome, all the studies dichotomised seizure outcome. However, 3 papers (10%) failed to report the exact proportion or number of participants with the seizure outcome.(72, 98, 104) The risk estimate or regression coefficient with accompanying confidence interval or standard error was not reported for all the studies contained in 5 publications.(63, 71, 95, 104, 106) More than half (58%) of the publications reported the statistical package or software used to conduct the multivariate analysis. The report on the test of assumptions of multiple regression analysis is as follows: 2 out of 13 (15%) papers using Cox regression explicitly reported on the test of the assumption proportional hazards.(71, 72) However, only in 1 paper(65) was there a report of a test for colinearity as a consideration for including variables in analysis, while 8 papers(24, 65, 66, 73, 96, 98, 101, 104) reported a test of interaction terms.

Sixteen of the 31 (52%) publications stated the significance level, at which prognostic variables were retained or excluded from the model, while 2 reported the deliberate inclusion of prognostic factors considered to be important.(21, 65)Sixteen papers (52%) reported the use of stepwise selection of variables, backwards, forwards or a combination of both. (Table 4)

Table 4 | Reporting characteristics of publications with multivariate analysis

Reporting Characteristic	Abduljabbar, 1998	Arts, 1999	Arts, 2004	Banu, 2003	Berg, 2001a	Berg, 2001b	Camfield, 1993	CGSE, 1988	CGSE, 1992	Geelhoed, 2005	Hui, 2007	Kim, 2006;	Lindsten, 2001;	Lohani, 2010	Lossius, 1999	MacDonald, 2000	Oskoui, 2005	Ramos-Lizana, 2009	Shafer, 1988	Shinnar, 2000	Sillanpaa, 1990	Sillanpaa, 1993	Sillanpaa, 1998	Sillanpaa, 2009	Berg, 1996	Casetta, 1999	Chawla, 2002	Del Felice, 2010	Ko, 1999	Kwong, 2003	Sillanpaa, 2006	n (out of 31) with ✔
Justification of Study Size	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	**0/31**
Report on Loss to Follow Up	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	**31/31**
Report on N with Outcome	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✘	✔	✔	✘	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	**29/31**
Report of Statistical Package Used	✔	✔	✘	✔	✘	✘	✘	✔	✘	✔	✔	✘	✔	✔	✔	✘	✔	✔	✔	✘	✘	✘	✔	✔	✔	✘	✔	✔	✔	✘	✘	**18/31**
Report on/Discussion of Missing Data	✘	✘	✔	✘	✘	✘	✔	✘	✘	✔	✘	✔	✔	✔	✔	✘	✘	✘	✔	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	**8/31**
Report on Test for Collinearity	✘	✔	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	**1/31**
Report on Test for Interaction Terms	✘	✔	✔	✘	✔	✘	✘	✘	✘	✘	✘	✔	✘	✘	✘	✔	✘	✘	✔	✔	✘	✘	✘	✘	✘	✘	✘	✔	✘	✘	✘	**8/31**
Discussion of Model Assumptions	✘	✘	✘	✘	✘	✘	✔	✘	✘	✘	✘	✘	✘	✘	✘	✘	✔	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘	**2/31**
Report on Criteria for Variables in Model	✔	✔	✘	✔	✘	✔	✔	✘	✘	✔	✔	✔	✘	✔	✔	✔	✘	✔	✘	✔	✘	✘	✘	✔	✔	✘	✘	✔	✘	✘	✘	**16/31**
Report on Results of Analysis	✘	✔	✔	✔	✔	✔	✘	✘	✔	✔*	✔	✔	✔	✔	✔	✔	✔	✔	✘	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	**27/31**

✔ *- Yes (Reported);* ✘ *- No (Not Reported)*

** For Geelhoed et al 2005, reporting >1 study where reporting characteristics vary between analyses, the better reporting characteristic is chosen as summary for the paper.*

4.4 QUALITY APPRAISAL OF ELIGIBLE PUBLICATIONS

This segment of the chapter presents the results of quality items on the 31 eligible publications. The publications are assessed based on information documented within them or within referenced publication(s).

4.4.1 STUDY PARTICIPATION

Every eligible publication had documented within it or within a referenced publication, information on inclusion criteria and baseline characteristics of the patients included. However, for 7 papers little or no information on the setting from which the cohort was derived could be retrieved. Four of them provided insufficient information (78, 93, 96, 100) while the remaining 3 contained no further information beyond stating the geographical location of the cohort. Two of the 3 were reports from the same cohort (CGSE in Italy) (64, 95). The third publication was a hospital based nested case control study, (Chawla et al) (94) and it was the only publication/cohort without the necessary information to make a judgment on adequate study participation; the judgement was made in the affirmative for all 28 of the other 30 papers.

The studies reported by Ko et al(79)have a clear inversion in the proportion of cases and controls. The number of patients satisfying the definition of medical intractability in the cohort was more than 3 times (3.7) as many as those in remission on or off AED. There was also an over-representation of patients satisfying the criteria for intractability in the study reported by Berg et al 1996.(78) This however may be explained by the fact that both studies are hospital based retrospective cohorts. It was therefore concluded that recruitment of eligible individuals into these 2 studies was not adequate.

4.4.2 STUDY ATTRITION

Two out of the 24 publications reporting analysis of an entire cohort (as against nested case-control analysis) conducted their analysis on less than two thirds of the patients in the cohort,(100, 104) owing mostly to incompleteness of data as they were both retrospective studies. In the case of 1 other retrospective study,(93) it was uncertain how the cohort was constituted and if there was loss to follow up.

Two publications with less than 90% completeness of follow up (72, 98) gave details of the characteristics of patients lost to follow up. In the MESS Trial cohort(98)information from the linked paper(284)suggest that there were no important clinical differences between those who did not consent to be randomised into the study and those who consented. However in the second publication,(72) there was significant difference only in the proportion of patients within the 3 aetiologic groups (cryptogenic, idiopathic and remote symptomatic). For 4 other publications (reporting studies conducted on an entire cohort), information upon which to base such judgement was not provided, even though the studies had >10% participant attrition rate. (69, 77, 100, 104)

However, for Chawla et al,(94)a report of a nested case-control study, there was enough reason to conclude that information on how similar patients included in the analysis compared to those not included would be important. This was because the study did not provide information about how equal number (50 in each group) was selected as cases and controls.

4.4.3 PROGNOSTIC FACTORS

Twenty three of the 31 publications contained clear definition or description of the prognostic factors considered for analysis, and only partly so in the remaining 8. However, the handling of continuous variables was poorly reported, and inferences concerning this were made by a combination of observing how continuous data were reported and how the authors stated they were handled. In all, only 4 of the 31 publications contained studies in which no continuous variable was categorised.(72, 78, 79, 97)The poor reporting of missing data reflects on the ability to know if there is adequate proportion of patients with complete data. This judgement could be made for only 7 publications, 5 (63, 66, 68, 98, 106) of which had complete data, and 2 (100, 104) that did not have complete data. Also, all the publications reported on cohorts for which it was unlikely that there would be misclassification bias in assessing the prognostic factors.

4.4.4 OUTCOME MEASUREMENT

As it was for prognostic factor measurement, all the publications reported on cohorts for which it was unlikely that there is misclassification bias in assessing the chosen outcome measure, as the majority of patients were followed up for at least 1 year with the outcome clearly defined. The outcome measure was also clearly defined in all the studies reported in all the publications. Three out of 7 publications reporting studies with exclusively retrospective ascertainment of cases provided information to demonstrate that prognostic factors and outcome were assessed blind to each other.(72, 78, 104)However, for Chawla et al,(94) a mixed cohort with retrospective and prospective ascertainment of cases, the report does suggest that the assessment of the prognostic factors may not have been blind to outcome assessment at least for some of the patients in the cohort.

4.4.5 MULTIVARIATE ANALYSIS

Sixteen papers out of 31 reported the use of some kind of stepwise procedure in the model building strategy, while only 2 did not report enough data for the results of analysis. Therefore, the calculation of events per variable ratio was not possible for the 2 publications for which the proportion of patients with the outcome studied could not be retrieved.(101, 104) It was however less than 10 in studies reported in 5 publications: 9.8 for 1 of the 2 studies included in Arts et al 2004(66) , 7.5 for the study in Berg 2001a(73) 8.3 and 4 respectively for 2 categories of study reported by Oskoui et al(72), 9.5 for the study in Sillanpaa 1993(77)and 7.8 and 6.5 for the 2 studies in Ko et al(79)

Table 5 | Details of Quality Appraisal of Publications

	Abduljabbar, 1998	Arts, 1999	Arts, 2004	Banu, 2003	Berg, 2001a	Berg, 2001	Camfield, 1993	CGSE, 1988	CGSE, 1992	Geelhoed, 2005	Hui, 2007	Kim, 2006;	Lindsten, 2001	Lohani, 2010	Lossius, 1999	MacDonald, 2000	Oskoui, 2005	Ramos-Lizana, 2009	Shafer, 1988	Shinnar, 2000	Sillanpaa, 1990	Sillanpaa, 1993	Sillanpaa, 1998	Sillanpaa, 2009	Berg, 1996	Casetta, 1999	Chawla, 2002	Del Felice, 2010	Ko, 1999	Kwong, 2003	Sillanpaa, 2006
Study Participation																															
The source population was described	Y	Y	Y	P	Y	Y	Y	N	N	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	N	P	Y	Y	Y
Inclusion criteria and baseline cohort described	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Adequate recruitment of eligible individuals into cohort	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	U	Y	N	Y	Y
Study Attrition																															
There is adequate proportion of cohort in study/analysis	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	P	P	Y*	Y	Y	Y	Y	Y	Y	Y	Y
Reasons for loss and characteristics described	—	Y	Y	U	—	—	—	Y	Y	Y	—	Y	—	P	—	—	N	N	P	—	Y	Y	—	—	—	—	U	—	—	—	—
Those lost are similar to those who completed the study	—	—	—	U	—	—	—	—	—	—	—	Y	—	U	—	—	P	—	U	—	U	U	—	—	—	—	U	—	—	—	—
Prognostic Factors																															
The prognostic variables were clearly defined	P	P	P	Y	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	P	P	Y	Y	Y	P	Y	Y	Y	Y
Continuous variables were kept continuous	P	P	P	N	P	P	P	P	P	P	Y	P	N	P	P	P	Y	P	N	P	P	P	P	P	Y	P	N	P	Y	P	P
Methods sufficiently limit misclassification bias	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
There was adequate proportion of patients with complete data	Y	U	Y	U	U	U	U	U	U	Y	U	Y	U	N	Y	U	U	U	N	U	U	U	U	U	U	U	U	U	U	U	U
Outcome Measurement																															
The outcome measures are clearly defined	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Measure methods sufficiently limit misclassification bias	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Outcome & prognostic factor measured blind to each other	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	U	Y	Y
Multivariate Analysis																															
There is sufficient data to assess adequacy of the analysis	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
The model building strategy is described as being stepwise	Y	Y	N	Y	N	N	Y	Y	N	Y	N	Y	N	N	Y	Y	N	N	Y	N	Y	Y	N	N	N	N	Y	Y	N	Y	Y
There is no over-fitting the data (i.e. EPV at least 9)	Y	Y	Y*	Y	N	Y	Y	Y	Y	Y*	Y	Y	Y	Y	Y	Y*	Y*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y

Y-Yes, P-Partly, U-Unsure, N-No | Dash (–) is used when the item is not stated, while it is either not applicable or unimportant as a potential source of bias in the cohort/study being reported.

*For papers reporting >1 study where result of quality appraisal vary between studies, (Geelhoed et al, Oskoui et al and Sillanpaa et al 1998) the quality of the better study is reported in this table.

EPV – Events per Variable

4.5 STUDY CATEGORIES BY OUTCOME MEASURE

The next segment of this chapter considers each study within designated categories, classified according to the seizure outcome predicted in the study in order to facilitate comparability among studies as different seizure outcome measures were considered across studies. The 5 categories (***Type I-V***) of studies are introduced. The results are subsequently reported in relation to quality considering the following – 1) Proportion of patients with outcome; 2) Predictors of the outcome; 3) Non predictors of the outcome; and 4) Prognostic models for predicting the outcome

STUDIES PREDICTING EARLY/IMMEDIATE REMISSION (TYPE I)

Type I Studies are those that identified independent predictors of belonging or not to *Sub-Group 1A*, which is the category of patients with immediate or early spontaneous remission (ISR). These patients will not have a third seizure, i.e. upon starting AED or being recruited into the cohort under consideration they enter terminal remission immediately, and will not relapse after complete AED withdrawal. These studies (24, 95, 98, 99) typically include the entire cohort i.e. all the patients with early or immediate spontaneous remission (ISR) compared with those who did not enter ISR. (Figure 4)There was however 1 atypical study, a nested case-control study, by Del Felice et al(96) that was classified within this category. The study compares patients with early or immediate spontaneous remission (ISR) i.e. no additional seizure once AED therapy started with "late" remission i.e. those who continued to have seizures until 2 years after AED therapy was commenced with those patients. (Figure 7)

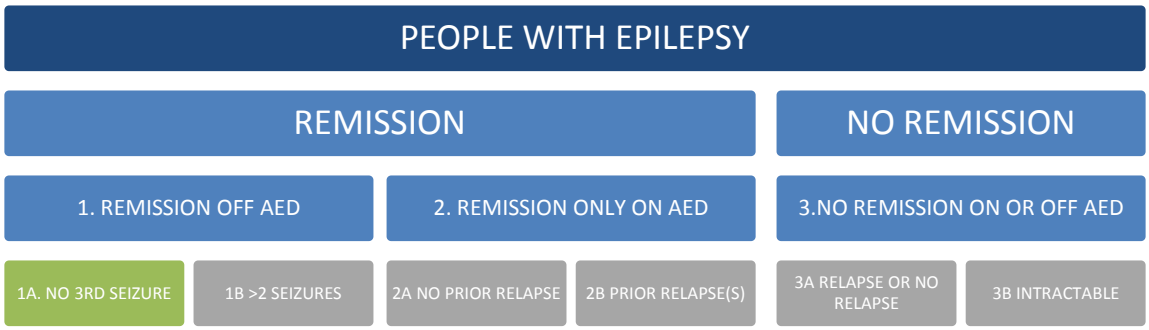


Figure 7 | Type I studies (Predicting Immediate Remission)
The colour differences (lemon and grey) in the lowest set of boxes indicate comparison groups.

STUDIES PREDICTING REMISSION OFF AED (TYPE II)

Type II Studies, illustrated in Figure 8, identified independent predictors of remission off AED, i.e. patients in prognosis *Group 1*. This group consists of patients in *Sub-Group 1A* (immediate spontaneous remission – ISR) and *Sub-Group 1B* with non-immediate spontaneous remission (NISR) i.e. patients who although do not enter remission immediately, ultimately do so, and remain in remission upon AED withdrawal. The other comparison group therefore is all the other patients on AED whether in remission or not.(32, 71, 72, 106)

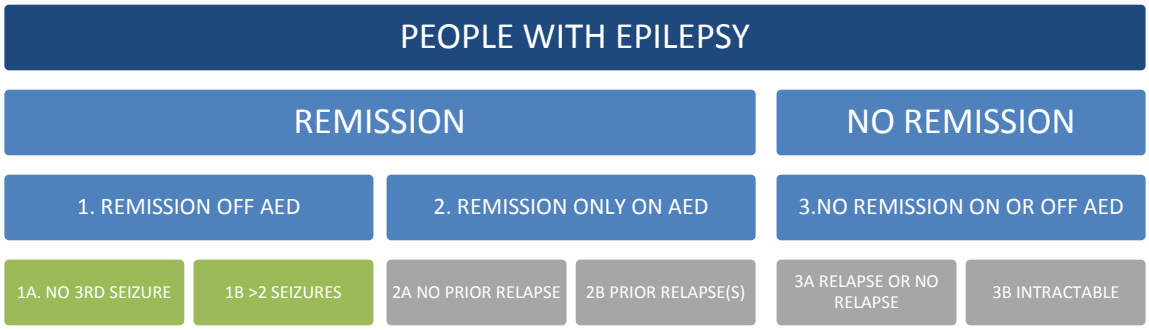


Figure 8 | Type II studies (Predicting Remission off AED)
The colour differences (lemon and grey) in the lowest set of boxes indicate comparison groups.

STUDIES PREDICTING REMISSION ON OR OFF AED (TYPE III)

Type III Studies consider as an outcome group, those patients in remission, on or off AED. These patients belong in the prognosis *Group 1* and *Group 2.* Therefore the other comparison group for this category of studies are those patients who do not enter remission either for a specified period during the course of follow up or immediately before the last follow up assessment. This is illustrated in Figure 9, and shows how the second comparison group contains patients with intractable seizures, and those who although are not in remission, do not meet the criteria for intractability.(24, 32, 63-66, 68-70, 77, 93, 97, 100, 101, 104)

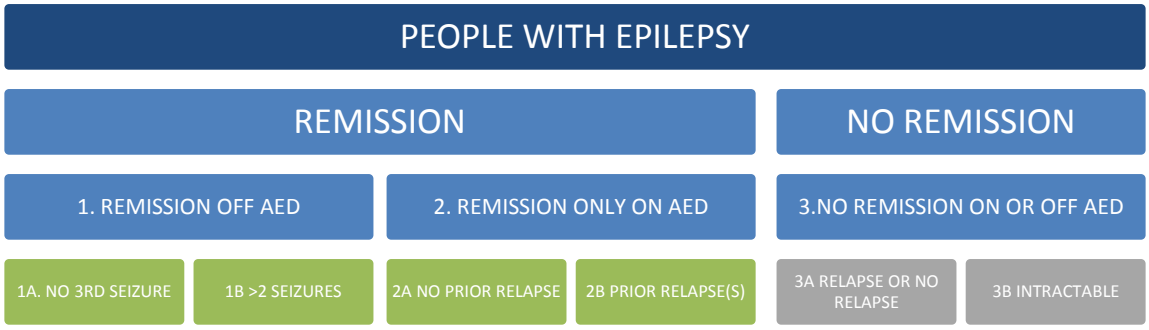


Figure 9 | Type III studies (Predicting Remission on or off AED)
The colour differences (lemon and grey) in the lowest set of boxes indicate comparison groups.

STUDIES PREDICTING INTRACTABILITY (TYPE IV)

These are studies predicting patients that will have medically intractable seizures. There are 2 kinds of ***Type IV Studies*** identified as eligible. There are those where patients satisfying the definition of medical intractability (*Sub-Group 3B*) are compared with all other patients who do not (*Group 1*, *Group 2 and Sub-Group 3A)*. These studies include all the patients within the entire cohort (72-74) as shown in Figure 10.

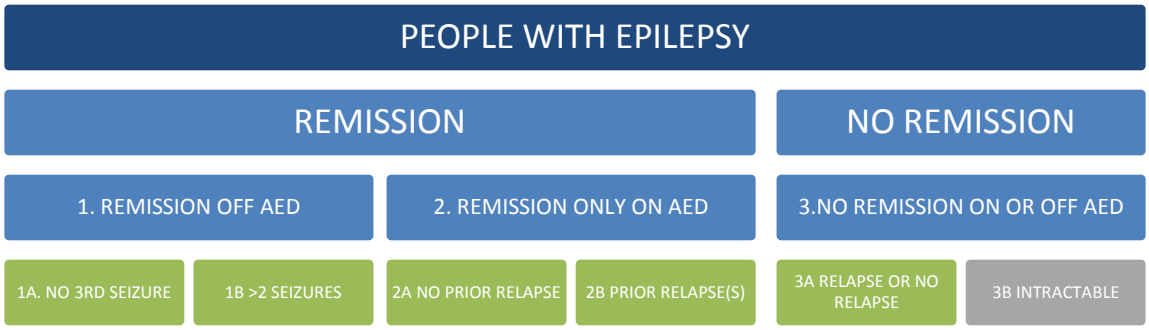


Figure 10 | Type IV studies (Predicting Intractability including the entire cohort)
The colour differences (lemon and grey) in the lowest set of boxes indicate comparison groups.

The other kind of study are case control studies nested within cohorts that compare only patients with remission on or off AED (*Group 1* and *Group 2*) being controls with patients satisfying the definition of intractability (*Sub-Group 3B*) as cases, leaving out those patients in *Sub-Group 3a* who are not in remission but also do not fulfil the criteria for medical intractability.(75, 76, 78, 79, 94) This is illustrated in Figure 11, with *Sub-Group 3A* taken off.

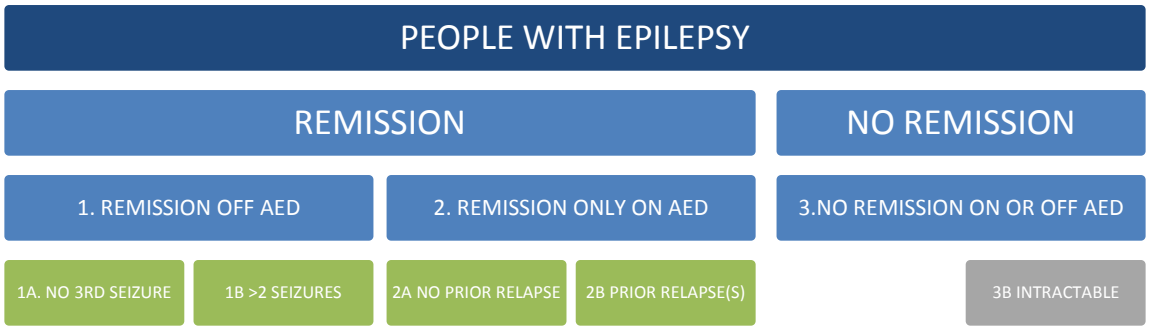


Figure 11 | Type IV studies (Predicting Intractability in nested case control studies)
The colour differences (lemon and grey) in the lowest set of boxes indicate comparison groups.

STUDIES PREDICTING NO REMISSION AFTER RELAPSE (TYPE V)

The last type of study, ***Type V Studies,*** has only 1 study within the category. This study reported by Sillanpaa and Schmidt 2006(25) considers the predictors of not achieving remission on or off AED after a patient's seizures have run a remitting-relapsing course. *Sub-Group 3A* represents patients without remission that do not satisfy the criteria for intractability. However, although there are also within the group those who have never experienced remission, Figure 12 assumes that *Sub-Group 3A* sufficiently represents those who have not achieved remission after a remitting-relapsing course.

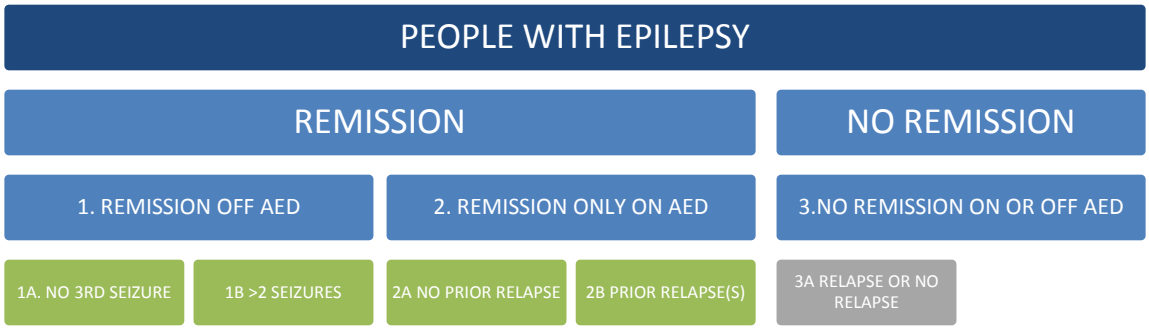


Figure 12 | Type V studies (Predicting no remission after relapse)
The colour differences (lemon and grey) in the lowest set of boxes indicate comparison groups.

4.6 REVIEW OF STUDIES BY OUTCOME CATEGORY

The studies are now reviewed within these categories, especially in relation to: 1) Understanding and explaining similarities and differences in results given each study's peculiar characteristics and potential for bias, 2) Identifying consistent independent predictors and non-predictors within each category, and 3.) Assessing the quality and performance of externally validated prognostic models within each outcome category.

PREDICTING EARLY/IMMEDIATE REMISSION (TYPE I)

Five studies investigated the predictors of early or immediate remission (Table 6).(24, 95, 96, 98, 99) One of the studies, Del Felice et al,(96) was a nested case control study with patients achieving remission after at least 2 years of antiepileptic drug therapy as cases(11% of the entire cohort), and having patients with immediate remission as controls, i.e. those without seizure recurrence once started on antiepileptic drugs, and who remained in remission for 2 years (33% of the entire cohort).

In the remaining 4 studies, the proportion of patients without seizure recurrence at 2 years of follow up (i.e. early or immediate remission) ranged from 37% in Shinnar et al,(24) (the only study with exclusively prospective case ascertainment) to between 42% and 57.5% in studies with mixed case ascertainment, including different proportions of first seizure, prospectively identified, and retrospectively ascertained cases.

Two of the studies, CGSE 1988 (95) and Del Felice 2010 (96), both in all age cohorts, had remarkably similar proportion of patients in each seizure category with the ratio of 1st seizure to 2-5 seizures and >5 seizures being roughly 4:9:7 in both studies. In spite of this similarity, the proportion of patients that achieved immediate remission at about 2 years of follow up varied widely: 48% in CGSE 1988,(95) and 33% in Del Felice 2010.

Table 6 presents potential predictors that were examined by at least 2 studies. Neither age nor gender was found to be significantly related to achieving early/immediate remission.

The number of seizures (as a continuous variable), was only significant in 2 studies in the univariate analysis. However, the 2 studies found having "2 or more" seizures before the index seizure or AED was retained in their multivariable models (Box 1):

Box 1 | Relative risk (RR) of achieving early remission in patients with two or more seizures before intake

Lindsten et al 2001	**RR 0.63 (95%CI 0.36-1.11)**
CGSEPI 1988	**(Not Stated)**

All 5 studies considered the early or intake Electro Encephalogram (EEG). In 3, EEG finding was not associated with early remission on univariate analysis. One found that EEG finding was associated, and in 1 study, having an abnormal EEG was retained in the multivariable model. Neither a family history of epilepsy nor a prior history of febrile seizures was found to be predictive of early or immediate remission.

The 5 studies included also considered having aetiological factors as potential predictors, with three of the 5 retaining the variable in their multivariable models:

Box 2 | Relative risk (RR) of achieving early remission in patients with remote symptomatic aetiology

Kim et al 2006	**RR 0.74 (95%CI 0.58-0.94)**
Shinnar et al 2000	**RR 0.59 (95%CI 0.41-0.86)**
Lindsten et al 2001	**RR 0.44 (95% CI 0.26-0.77)**

None of the models were externally validated.

Table 6 | Studies predicting immediate remission with information on potential for bias

Age* (Years)	Study (Ref)	Design Setting N	Study Participation	Study Attrition	Prognostic Factor	Outcome	Analysis	Remarks	Follow Up	Outcome Measure % with Outcome•	Independent Predictors	Risk Estimate (95%CI)
0 – 19	Shinnar, 2000(24)	Prospective Hospital N=182	Y	Y	Y	Y	Y	Excellent case ascertainment – NDE‡ (100%)	8.4yrs (Mean)	No 3rd Seizure (37% at 2 years, 28% at 5 years)	Remote Symptomatic Aetiology AED within 3mo of 2nd Seizure AED after 3mo of 2nd Seizure 2nd Seizure within 3months 2nd Seizure between 3-6months	HR: 1.69 (1.16-2.47) HR: 0.37 (0.22-0.63) HR: 1.28 (0.75-2.18) HR: 4.00 (2.28-7.00) HR: 0.86 (0.49-1.50)
2 – 81 (19)	CGSE, 1988(95)	Mixed† Hospital N=283	Y	Y	Y	Y	Y	Progressive neurological disorders excluded 1st Seizure (18%), 2-5 Seizures (46%), >5 Seizures 34%)	0.1-3.3yrs	Next seizure after Intake (48% at ≈2.5 years)	≥2 seizures before intake Mixed seizure types	NS NS
IQR (17.4-43.4)	Kim, 2006(98)	Mixed† Hospital N=1443	Y	Y	Y	Y	Y	RCT, therefore known poor prognosis excluded. 1st seizure (57%), 2nd seizure – NDE‡ (24%), and 3 or more seizures – retrospective case ascertainment (19%)	3.0-6.3yrs	Next seizure after Intake (57.5% at 2 years, 47% at 5 years, 43.5% at 8 years)	Log No seizures before intake Abnormal EEG Neurological Disorder	HR:1.56 (1.42-1.72) HR: 1.54 (1.27-1.86) HR: 1.35 (1.07-1.72)
17-83	Lindsten, 2001(99)	Mixed† Population N=107	Y	Y	N	Y	Y	1st seizure (29%), 2nd seizure – NDE‡ (15%), and 3 or more seizures – retrospective case ascertainment (56%)	8.8-13.5yrs	Next seizure after Index (42%at 2 years)	≥2 seizures before intake No AED Therapy Remote Symptomatic Aetiology	HR: 1.6 (0.9-2.8) HR: 0.29 (0.11-0.74) HR: 2.25 (1.3-3.9)
3-84 (31.5)	Del Felice, 2010(96)	Mixed† Hospital N=352 *Cases* 38 *Controls* 115	Y	Y	Y	Y	Y	1st Seizure (16%), 2-5 Seizures (46%), >5 Seizures 38%) This is a case control study nested within a cohort	6.9yrs (Mean)	*Cases* 2 year seizure-freedom begins at least 2 years after AED therapy starts *Controls* 2 year seizure-freedom begins with AED (33% at 2 years)	2–5 Partial Seizures before AED >5 Partial Seizures before AED	OR: 2.7 (1.0-6.8) OR: 6.7 (2.3-19.3)

*Age range in years (Mean ± Standard Deviation); •The proportion reported is of those who did not have a relapse following diagnosis (2nd seizure), recruitment or commencement of AED; †Mixed–Cohort combined prospective and retrospective identification of cases; ‡NDE – Newly Diagnosed Epilepsy i.e. cases that were ascertained on having the second seizure. Case ascertainment after 2nd seizure is considered retrospective; Y–Yes, N–No, CI-Confidence Interval, CI-Confidence Interval, IQR–Interquartile Range, RCT–Randomised Controlled Trial, AED–Antiepileptic Drug, EEG–Electro Encephalogram, No–Number, NS–Not Stated, OR–Odds Ratio, HR–Hazard Ratio

Table 7 | Consistent predictors and non-predictors of immediate remission

	Shinnar, 2000	CGSE, 1988	Kim, 2006	Lindsten, 2001	Del Felice, 2010
Demographic					
Age at Onset		✘			✘
Gender		✘		✘	✘
Epilepsy Before AED, Intake or Index					
Duration		✘	ϴ	✘	✘
≥2 seizures before Intake		✔		✔	
N of Seizures before Intake				✔	✔
EEG					
Intake/Early - EEG Abnormal	✘	✘	✔	✘	✔
Seizure Type					
Generalised Onset		✘			✔
Partial		✘			✔
Aetiology | Syndrome					
Remote Symptomatic Aetiology	✔	✘	✔	✔	✘
Neurological Signs					
Neurological Examination		✘			✘
Others					
Family History		✘	ϴ		✘
Febrile Seizure	✘	✘			

✔ *- Variable is significant or retained in multivariate model*

✔ *- Variable is only significant on univariate analysis*

✘ *- Variable is not significant on univariate analysis*

ϴ *– Variable is not reported in univariate analysis, but reported as not significant on multivariate analysis*

PREDICTING REMISSION OFF ANTIEPILEPTIC DRUGS (TYPE II)

Nine studies considered the predictors of remission off antiepileptic drugs. They were all conducted in childhood cohorts. Three were from the Nova Scotia cohort,(71, 106) 2 from each of the Turku,(32) and Montreal cohorts,(72) 1 from the Dutch cohort,(106) and the last one was an analysis of reconstituted and combined data from the Nova Scotia and Dutch cohorts.(106) (Tables 8 and 9)

The proportion of patients that remained in remission while successfully weaned off antiepileptic medication ranged from 52% in a retrospective cohort to between 47% and 55% in mixed cohorts and from 56% to 65% in prospective cohorts. It was 59% in the combined cohort of the reconstituted (after including patients with known poor prognosis and generalised absence seizures) Nova Scotia cohort (55%) and the Dutch DSEC cohort (65%).

The potential predictors considered for remission off antiepileptic drugs and found to be consistent predictors or non-predictors are presented in Table 10. Age at onset of seizures and gender were not found to be significantly related to remaining in remission while taken off antiepileptic medication. However, having more than 1 seizure in the period between 6 and 12 months while on AED was assessed in the 2 studies that considered onset variables in combination with variables assessed after 1 year of AED medication,(71, 72)and was found to consistently predict remission off AED. The relative risk was 0.24 (95% CI 0.10-0.60) from Oskoui et al,(72) while the relative risk is similar at 0.25 (95% confidence intervals not provided) from Camfield et al(71).

Box 3 | Relative risk (RR) of remission off AED in children having more than 1 seizure 6 to 12 months on AED

Oskoui et al 2005	**RR 0.24 (95%CI 0.10-0.60)**
Camfield et al 1993	**RR 0.25 (95% CI Not Stated)**

Cognitive impairment at onset or diagnosis of epilepsy was another consistent predictor of remission off AED, considered in all the 9 models. It was retained in 6 of the 9, and excluded in the remaining three studies, which however did not report the test of univariate association. The relative risk from 2 of the three studies using only intake variables, diverged widely, albeit with overlapping confidence intervals, at 0.77 (95% CI 0.61-0.94) from the combined Nova Scotia and Dutch cohort [Geelhoed et al(106)] and 0.23 (95%CI 0.07-0.74) from the Montreal cohort [Oskoui et al(72)]. The third study, Camfield et al,(71) did not report 95% confidence interval. The Geelhoed et al cohort(106) includes patients from the Camfield et al cohort.(71)

Box 4 | Relative risk (RR) of remission off AED in children with intellectual disability (models with only onset variables)

Oskoui et al 2005	**RR 0.23 (95%CI 0.07-0.74)**
Geelhoed et al 2005	**RR 0.77 (95%CI 0.61-0.94)**
Camfield et al 1993	**RR 0.25 (95%CI Not Stated)**

Table 8 | Studies predicting remission off AED (Nova Scotia and DSEC Cohort)

Age (Years)*	Study	Design Setting N	Study Participation	Study Attrition	Prognostic Factor	Outcome	Analysis	Remarks	Follow Up	Outcome Measure (% with Outcome)	Independent Predictors	Risk Estimate (95%CI)
0-16 (6.7±4.5)	Nova Scotia Camfield, 1993(71)	Mixed Population N=486	Y	Y	Y	Y	Y	Patients with known poor prognosis, generalised absence and progressive neurological disorders excluded Only intake variables	7.1yrs (Mean)	Off AEDs at Last Follow up (54%)	Age ≤ 1yr Age 1-12yrs Intellectual disability History of Neonatal Seizures 1-2 Seizures before AED ≥3 Seizures before AED	HR: 0.23 (NS) HR: 0.21 (NS) HR: 4.00 (NS) HR: 0.17 (NS) HR: 0.42 (NS) HR: 0.31 (NS)
0-16 (6.7±4.5)	Nova Scotia Camfield, 1993(71)	Mixed Population N=486	Y	Y	Y	Y	Y	Patients with known poor prognosis, generalised absence and progressive neurological disorders excluded Intake and 1yr variables	7.1yrs (Mean)	Off AEDs at Last Follow up (54%)	Age ≤ 1yr Age 1-12yrs Intellectual disability History of Neonatal Seizures 1-2 Seizures before AED ≥3 Seizures before AED ≤1 Seizure 6-12months on AED >1 Seizure 6-12months on AED	HR: 0.37 (NS) HR: 0.17 (NS) HR: 3.45 (NS) HR: 0.16 (NS) HR: 0.42 (NS) HR: 0.31 (NS) HR: 2.78 (NS) HR: 4.00 (NS)
0-16	Nova Scotia Geelhoed, 2005(106)	Mixed Population N=602	Y	Y	Y	Y	Y	Includes all epilepsy types from the Nova Scotia cohort	8.8yrs (Mean)	Off AEDs at Last Follow up (55%)	Idiopathic Partial Epilepsy Cryptogenic Partial Epilepsy Intellectual disability	NS NS NS
0-16 (5.9±4.2)	DSEC Cohort Geelhoed, 2005(106)	Prospective Hospital N=453	Y	Y	Y	Y	Y	Exact same cohort as reported in Arts et al, 2004	5yrs (Minimum)	Off AEDs at Last Follow up (65%)	Age >12yrs Symptomatic Gen. Epilepsy Cryptogenic Gen. Epilepsy Symptomatic Partial Epilepsy Cryptogenic Partial Epilepsy	NS NS NS NS NS
0-16	Nova Scotia & DSEC Cohort Geelhoed, 2005(106)	Combination Mixed (Hospital and Population) N=1055	Y	Y	Y	Y	Y	Includes all epilepsy types from Nova Scotia cohort merged with the Dutch DSEC cohort	5yrs (Minimum for >95%)	Off AEDs at Last Follow up (59%)	Age >12 yr N seizures before AED Neurologic Deficits Intellectual disability Absence Seizures Cryptogenic Gen. Epilepsy Symptomatic Partial Epilepsy Cryptogenic Partial Epilepsy + History of Febrile Seizures	OR: 2.04 (1.67, 2.63) OR: 1.02 (1.01, 1.04) OR: 1.61 (1.04, 2.5) OR: 1.81 (1.19, 2.28) OR: 0.57 (0.36, 0.95) OR: 2.17 (1.22, 3.85) OR: 2.94 (1.92, 4.34) OR: 1.75 (1.33, 2.38)

*Age range in years (Mean ± Standard Deviation); CI-Confidence Interval, Y-Yes, HR-Hazard Ratio, OR-Odds Ratio, AED-Antiepileptic Drug, NS-Not Stated

Table 9 | Studies predicting remission off AED (Montreal and Turku Cohort)

Age* (Years)	Study	Design Setting N	Study Participation	Study Attrition	Prognostic Factor	Outcome	Analysis	Remarks	Follow Up	Outcome Measure (% with Outcome)	Independent Predictors	Risk Estimate (95%CI)
0-15 (4.3)	Turku, Fin Sillanpaa, 1998(32)	Mixed Population N=176	Y	U	Y	Y	Y	Three seizures diagnosed epilepsy	23-39yrs	Off AEDs 5yrs before Last Follow up (47%)	75-100% reduction in seizures within 3months of AED Complex Partial Seizures Cryptogenic vs. R. Symptomatic Idiopathic vs. R. Symptomatic	HR: 0.09 (0.03, 0.31) HR: 3.03 (1.40, 6.67) HR: 0.33 (0.15, 0.71) HR: 0.32 (0.16, 0.65)
0-15	Turku, Fin Sillanpaa, 1998(32)	Prospective Population N=117	Y	Y	Y	Y	Y	Three seizures diagnosed epilepsy Only prospectively identified patients in Turku cohort	11-39yrs	Off AEDs 5yrs before Last Follow up (56%)	75-100% reduction in seizures within 3months of AED Complex Partial Seizures Atonic Seizures Cryptogenic vs. R. Symptomatic Idiopathic vs. R. Symptomatic	HR: 0.45 (0.25, 0.81) HR: 3.57 (1.70, 7.69) HR: 3.85 (0.83, 16.68) HR: 0.30 (0.14, 0.64) HR: 0.38 (0.18, 0.83)
2-17 (7.6±3.7)	Montréal, Ca Oskoui, 2005 (72)	Retrospective Hospital N=196	Y	P	Y	Y	Y	Only onset variables Data collection was remarkably good	2-13.6yrs	Off AEDs at Last Follow up (52%)	Intellectual disability Remote Symptomatic Epilepsy Mixed Seizure Types	HR: 4.35 (1.35, 14.29) HR: 2.17 (1.09, 4.35) HR: 2.94 (1.28, 6.67)
2-17 (7.6±3.7)	Montréal, Ca Oskoui, 2005(72)	Retrospective Hospital N=196	Y	P	Y	Y	Y	Onset and 1yr variables Data collection was remarkably good	2-13.6yrs	Off AEDs at Last Follow up (52%)	Intellectual disability >1 Seizure 6-12months on AED Mixed Seizure Types	HR: 5.26 (1.70, 16.68) HR: 4.17 (1.67, 10.0) HR: 2.5 (1.08, 5.56)

*Age range in years (Mean ± Standard Deviation); CI-Confidence Interval, Y-Yes, Unclear, P-Partly, HR-Hazard Ratio, OR-Odds Ratio, AED-Antiepileptic Drug

Table 10 | Consistent predictors and non-predictors of remission off AED

	Camfield, 1993	Camfield, 1993	Geelhoed, 2005N	Geelhoed, 2005D	Geelhoed, 2005ND	Sillanpaa, 1998	Sillanpaa, 1998†	Oskoui, 2005	Oskoui, 2005*
Demographics									
Age at Onset						ϴ	ϴ	ϴ	ϴ
Gender			ϴ	ϴ	ϴ			ϴ	ϴ
Epilepsy Before AED, Intake or Index									
N of Seizures before Intake or AED					✔	ϴ	ϴ	ϴ	ϴ
Early Epilepsy Characteristics									
>1 Seizure from 6 - 12months		✔							✔
EEG									
Intake/Early - EEG Abnormal	✔		ϴ	ϴ	ϴ			ϴ	ϴ
Aetiology | Syndrome									
Remote Symptomatic Aetiology	✔		ϴ					✔	ϴ
Cryptogenic Epilepsy			ϴ	✔	✔			ϴ	ϴ
ILAE Syndrome						ϴ	ϴ	ϴ	ϴ
Cognition									
Abnormal Cognitive Development	✔	✔	✔	ϴ	✔	ϴ	ϴ	✔	✔
Neurological Sign									
Neurological Examination	✔		ϴ	ϴ	✔	ϴ	ϴ	ϴ	ϴ

✔ *- Variable is significant or retained in multivariate model*

✔ *- Variable is only significant on univariate analysis*

✘ *- Variable is not significant on univariate analysis*

ϴ *– Variable is not reported in univariate analysis, but reported as not significant on multivariate analysis*

Intellectual disability was also retained in 2 studies (71, 72) that combined variables assessed at intake or onset with those only assessable at 1 year after onset/intake (e.g. number of seizures between 6-12 months while on AED):

Box 5 | Relative risk (RR) of remission off AED in children with intellectual disability (models combining onset and 1 year variables)

Oskoui et al 2005 | **RR 0.19 (95%CI 0.06, 0.59)**
Camfield et al 1993 | **RR 0.29 (95%CI Not Stated)**

None of the studies that considered abnormal EEG at intake or early in the course of epilepsy confirmed it as an independent predictor of remission off AED. However, 1 study (106) out of 5 found the number of seizures before intake to be an independent predictor. The same model (106)also retained deficit on neurological examination as an independent predictor out of 8 studies that considered signs on neurological examination.

Three of the models were externally validated. The results of the validation studies are presented in Table 11. Sillanpaa et al(105) externally validated the Nova Scotia model (developed using the intake variables only) on the Turku cohort, although this was to predict three years seizure-free status immediately before last follow up on or off medication instead of remission off AED. This was because physicians handling patients within the Turku cohort were reluctant to discontinue medication and as 75% of those with 3 year remission at last follow up had been in remission for at least 10 years, it was considered unlikely that these patients would relapse off medication.

Patients in the Turku cohort were selected with the same specific inclusion criteria in the Nova Scotia cohort for the validation study. The performance of the Nova Scotia intake model(105) had greater specificity (88% vs. 64%) and positive predictive value (84% vs. 71%) compared to the results of internal validation, but much poorer sensitivity (43% vs. 73%) and negative predictive value (51% vs. 67%), and fewer instances of correct prediction (61% vs. 67%)

The other 2 externally validated models were reported by Geelhoed et al(106), from the model derived from the reconstituted Nova Scotia cohort and from the DSEC cohort to predict remission off AED, externally validated in the other, with similar results on external and internal validation in both models.

Table 11 | Externally validated models predicting remission off AED

Predictors in Model	Derivation Cohort	Internal Validation: Performance of Model in Derivation Cohort	Validation Study	Validation Cohort	External Validation: Performance of Model in Validation Cohort	Score	Easy to Use	Important Variable	Probability or Action	Clinical Use Studied
Age at Onset -< 1 yr, -1-12 yrs, ->12 yrs *Intelligence* -Normal/-Retardation *Neonatal Seizure* No/Yes *Seizures before AED* -1 or 2, -3 to 20, ->20	Camfield 1993(71) Nova Scotia Patients with known poor prognosis, generalised absence and progressive neurological disorders excluded **Pre-Test Probability (54%)**	AUC (NS) **Best probability cut-off (NS)** Sensitivity (74% ± 4%) Specificity (64% ± 5%) PPV (71% ± 4%) NPV (67% ± 5%) Correct Prediction (68%)	**Sillanpaa 1995(105)**	Turku Cohort 141 patients with the same inclusion criteria as the Nova Scotia Cohort. The Turku cohort had significantly more patients with intellectual disability Validated predicting remission, and not remission off AED **Pre-Test Probability (60%)**	AUC (NS) **Probability cut-off (NS)** Sensitivity (43%) Specificity (88%) PPV (84%) NPV (51%) Correct Prediction (61%)	Y	Y	Y	Pr	N
Idiopathic Partial Epilepsy Cryptogenic Partial Epilepsy Intellectual disability	Geelhoed 2005(106) Reconstituted Nova Scotia Cohort to includes all epilepsy types **Pre-Test Probability (55%)**	AUC (NS) **Best probability cut-off (≈50%)** Sensitivity (69%) Specificity (69%) PPV (73%) NPV (35%) Correct Prediction (69%)	**Geelhoed 2005(106)**	Geelhoed 2005 DSEC Dutch Cohort Validation cohort similar to derivation cohort **Pre-Test Probability (65%)**	AUC (NS) **Probability cut-off (50%)** Sensitivity (71%) Specificity (58%) PPV (76%) NPV (53%) Correct Prediction (64%)	N	N	Y	Pr	N
Age >12yrs Symptomatic Gen. Epilepsy Cryptogenic Gen. Epilepsy Symptomatic Partial Epilepsy Cryptogenic Partial Epilepsy	Geelhoed 2005(106) DSEC Dutch Cohort **Pre-Test Probability (65%)**	AUC (NS) **Best probability cut-off (≈50%)** Sensitivity (70%) Specificity (66%) PPV (79%) NPV (55%) Correct Prediction (69%)	**Geelhoed 2005(106)**	Geelhoed 2005 Reconstituted Nova Scotia Cohort Validation cohort similar to derivation cohort **Pre-Test Probability (55%)**	AUC (NS) **Probability cut-off (50%)** Sensitivity (57%) Specificity (67%) PPV (67%) NPV (56%) Correct Prediction (61%)	N	N	N	Pr	N

AUC-Area Under Receiver Operator Characteristics (ROC) Curve, PPV-Positive Predictive Value, NPV-Negative Predictive Value, NS-Not Stated, Pr-Probability, N-No, Y-Yes, AED-Antiepileptic Drug

PREDICTING REMISSION ON OR OFF AED (TYPE III)

Twenty studies (Table 12 to 14) investigated the independent predictors of achieving remission irrespective of whether patients continue on antiepileptic medication or are taken off AEDs successfully. Eleven of the studies were analysed using logistic regression analysis with the odd ratio for developing refractory seizures (i.e. not entering remission on or off AED) as risk estimate, whereas studies using the Cox regression analysis, estimated the relative risk for achieving remission. However, the Nepalese study reported by Lohani et al(100)was not conducted among patients with newly diagnosed epilepsy as 50% had seizures for more than 1 year before intake into the cohort and antiepileptic medication.

The proportion of patients in remission ranged from as low as 50% in a retrospective cohort (93) to as high as 76% in 2 prospective studies (66, 70) and even higher at 80% in a mixed cohort (63) with the proportion of patients in remission varying widely within the same study design according to how remission was defined: studies that defined remission as “seizure-free period immediately before last assessment” (terminal remission) tend to have less proportion in remission than studies that defined remission simply as “seizure-free period during follow up.” For example, in 2 adult-onset epilepsy mixed cohorts with 1 year minimum follow up, the study that defined remission as 1 year terminal had 60% in remission,(97) while the study that defined remission as 1 year “seizure free period during follow up” had 80%. (63) However, in prospective studies more patients were in remission than in mixed or retrospective studies with the same outcome definition and minimum follow up period. (Tables 15 and 16)

Having mixed (multiple) seizure types at onset was found to predict remission in studies from 2 independent cohorts. The Italian CGSE cohort retained mixed seizure types in the model predicting remission as 2 years seizure-free status during follow up [relative risk 0.70 (95% CI 0.37-1.04)]and 3 years seizure-free status [relative risk 0.70 (95%CI 0.37-1.04)] by 5 years of follow up.(64) Banu et al (93) found that the odds of achieving remission (3 months terminal remission at I year minimum follow up) was about 0.23 (95% CI 0.10-0.48) times in patients with multiple seizure types at onset compared to those with single seizure types. However, Banu et al(93) did not provide sufficient data to assess the absolute risk of not achieving remission in patients without multiple seizure types in order to compute the relative risk from odds ratio.

Box 6 | Risk of achieving remission in patients with mixed seizure types at onset

CGSEPI 1992	**RR* 0.70 (95%CI 0.37-1.04)**
Banu et al 2002	**OR• 0.23 (95% CI 0.10-0.48)**

*RR-Relative Risk, •OR-Odds Ratio

Four studies from different cohorts found remote symptomatic aetiology to be an independent predictor of remission with similar risk estimates.(21, 24, 77, 104)

Box 7 | Relative risk (RR) of achieving remission in patients who have remote symptomatic aetiology

Shinnar et al 2000	**RR 0.47 (95% CI 0.27- 0.81)**
Berg et al 2001b	**RR 0.63 (95% CI 0.47-0.84)**
Sillanpaa 1993	**RR 0.44 (95% CI 0.25-0.92)**
Shafer et al 1988	**RR 0.44 (95% CI Not Stated)**

Banu et al(93) and Hui et al(97) also identified intellectual disability as an independent predictor of remission. However the outcome measure used in the cohort reported by Banu et al(93) [3 months terminal remission] is not comparable to that used by Hui et al(97) [1 year terminal remission]This difference in outcome measure, together with the disparity in the proportion of patients in remission – 50% (Banu et al) and 60% (Hui et al) – and possible difference in the definition of intellectual disability (Hui et al did not specify how this was defined), and the fact that Banu et al(93) was a childhood cohort while Hui et al (97) was in adults may be responsible, at least in part, for the wide disparity in the risk estimates:

Box 8 | Odds ratio (OR) of achieving remission in patients with intellectual disability

Banu et al 2003	**OR 0.40 (95%CI 0.18-0.90)**
Hui et al 2007	**OR 0.10 (95%CI 0.05-0.25)**

The frequency of seizures, before and after intake or AED, albeit defined differently in studies, was also found to be a consistent predictor of remission. The model fitted by Arts et al 1999(65) with only intake variables, retained the natural logarithm transformation of the number of seizures before intake as an independent predictor. The model reported by MacDonald et al(101)to predict 1 year seizure-free period during follow up also retained the log transformation of the number of seizures before intake. The estimate of the relative risk in Arts et al 1999 (predicting 6 months terminal remission) is compared with that from MacDonald et al (predicting experiencing 1 year free of seizures during follow up):

Box 9 | Relative risk (RR) of achieving remission in patients as a function of Log N of Seizures before index

Arts et al 1999	**RR 0.66 (95%CI 0.46-0.95)**
MacDonald et al 2000	**RR 0.81 (95%CI 0.66-0.99)**

Table 12 | Studies predicting remission on or off AED (the DSEC Cohort)

Age (Years)*	Study	Design Setting N	Study Participation	Study Attrition	Prognostic Factor	Outcome	Analysis	Remarks	Follow Up	Outcome Measure (% with Outcome)•	Independent Predictors	Risk Estimate (95%CI)‡
0-16 (6.7±4.5)	Arts, 1999	Prospective Hospital N=466	Y	Y	Y	Y	Y	Only intake variables Included 1 status epilepticus in epilepsy definition	2yrs (Minimum)	6 months seizure-free immediately before 2yrs follow up (68.7%)	Log N of Seizures before intake Simple Partial vs. GTCS Infantile Spasms, Myoclonic, Atonic vs. GTCS R. Symptomatic vs. Idiopathic Cryptogenic vs. Idiopathic	OR: 1.51 (1.05, 2.19) OR: 3.15 (1.32,7.51) OR: 3.01 (1.45, 6.23) OR: 1.90 (1.06, 3.39) OR: 2.20 (1.25, 3.87)
0-16 (6.7±4.5)	Arts, 1999	Prospective Hospital N=466	Y	Y	Y	Y	Y	Intake and 6 month variables Included 1 status epilepticus in epilepsy definition	2yrs (Minimum)	6 months seizure free immediately before 2yrs follow up (68.7%)	Simple Partial vs. GTCS Cryptogenic vs. Idiopathic Abnormal EEG at 6 months *During 1st 6 months after intake:* 3 months seizure free >25 Seizures Log N seizures	OR: 2.72 (1.07, 6.89) OR: 1.95 (1.05, 3.61) OR: 2.21 (1.12, 4.36) OR: 0.32 (0.18, 0.58) OR: 2.20 (1.06, 4.56) OR: 1.99 (1.39, 2.85)
0-16 (6.7±4.5)	Arts 2004	Prospective Hospital N=453	Y	Y	Y	Y	Y	Only intake variables Included 1 status epilepticus in epilepsy definition	5yrs (Minimum)	1 year seizure free immediately before 5yrs follow up (76%)	Age <6 years at intake Not Idiopathic Aetiology + No history of febrile seizures No history of febrile seizures + Idiopathic Aetiology	OR: 0.62 (0.39, 0.99) OR: 3.72 (2.20, 6.30) OR 4.37 (1.70, 11.26)
0-16 (6.7±4.5)	Arts, 2004	Prospective Hospital N=453	Y	Y	Y	Y	Y	Intake and 6 month variables Included 1 status epilepticus in epilepsy definition	5yrs (Minimum)	1 year seizure free immediately before 5yrs follow up (76%)	Female Post-ictal Signs Not Idiopathic Aetiology + No history of febrile seizures No history of febrile seizures + Idiopathic Aetiology ≤2 Seizure free months immediately before 6 month follow up	OR: 1.64 (1.00, 2.70) OR:2.23 (1.08, 4.63) OR:3.58 (2.05, 6.27) OR:5.28 (1.92, 14.51) OR: 4.47 (2.00, 9.99)

*Age range in years (Mean ± Standard Deviation); •The proportion reported is of those who achieved remission on or off AED; ‡Risk estimates for not achieving remission are presented; CI-Confidence Interval, Y-Yes, OR-Odds Ratio, GTCS-Generalised Tonic Clonic Seizures, EEG-Electroencephalogram, NS-Not Stated

Table 13 | Studies predicting remission on or off AED (Others 1)

Age (Years)*	Study	Design Setting N	Study Participation	Study Attrition	Prognostic Factor	Outcome	Analysis	Remarks	Follow Up	Outcome Measure (% with Outcome)•	Independent Predictors	Risk Estimate (95%CI)‡
0-15	Banu, 2003(93)	Retrospective Hospital N=151	Y	U	N	Y	Y		1yr (Minimum)	3 months seizure free immediately before last follow up (49.7%)	Multiple Seizure Types Intellectual disability Abnormal EEG	OR: 4.42 (2.07, 9.57) OR: 2.49 (1.11, 5.70) OR:4.09 (1.53, 12.11)
0-15	Berg, 2001b	Prospective Population N=594	Y	Y	Y	Y	Y		2-8yrs	2 year seizure free period during follow up (74%)	Log Initial Seizure Frequency Family History of Epilepsy Remote Symptomatic Aetiology Abnormal EEG Idiopathic Generalized Epilepsy Age 5–9 yrs at onset	HR: 0.90 (0.86, 0.95) HR: 0.58 (0.42, 0.81) HR: 0.63 (0.47, 0.84) HR: 0.71 (0.54, 0.93) HR: 1.65 (1.28, 2.12) HR: 1.23 (1.01, 1.50)
0-15 (4.8±1.6)	Sillanpaa, 1990	Mixed Population N=182	Y	U	Y	Y	Y	Three seizures diagnosed epilepsy	23-39yrs	3yrs seizure free immediately before last follow up (76.4%)	High initial Seizure Frequency Occurrence of Status Epilepticus Abnormal Fine Motor Status	OR: 8.5 (3.1, 25.8) OR: 3.2 (1.5, 6.9) OR: 9.6 (3.4, 27.1)
0-15 (4.8±1.6)	Sillanpaa, 1993	Mixed Population N=178	Y	U	Y	Y	Y	Three seizures diagnosed epilepsy	23-39yrs	12 seizure free months during last 10 years of follow up (77.5%)	Remote Symptomatic Aetiology High Initial Seizure Frequency Occurrence of Status Epilepticus No Seizure Freedom within 3 months of AED	OR: 2.9 (1.1, 8.2) OR: 4.6 (1.1, 19.3) OR: 11.4 (3.2, 41.0) OR: 3.6 (1.2-10.4)
0-15 (4.3)	Sillanpaa, 1998	Mixed Population N=176	Y	U	Y	Y	Y	Three seizures diagnosed epilepsy	23-39yrs	5yrs seizure free immediately before last follow up (64%)	75-100% reduction in seizures within 3months of AED Complex Partial Seizures Atonic Seizures	HR: 0.27 (0.15, 0.49) HR: 3.33 (2.04, 5.56) HR: 4.55 (1.37, 14.3)
0-15	Sillanpaa, 2009	Prospective Population N=102	Y	Y	Y	Y	Y	Three seizures diagnosed epilepsy Only prospectively identified patients St. Epilepticus excluded	11-40yrs	1yr seizure free immediately before last follow up (76%)	*< Weekly seizures:* Before AED During first year of AED	 HR: 0.37 (0.2, 0.67) HR: 0.59 (0.35, 0.96)
0 – 19	Shinnar, 2000	Prospective Hospital N=182	Y	Y	Y	Y	Y	Excellent identification. 10 recurrences defined refractoriness.	8.4yrs (Mean)	Not up to 10th seizure (71.4%)	Remote Symptomatic Aetiology 2nd Seizure within 1 year	HR: 2.13 (1.22, 3.71) HR: 6.94 (1.56, 30.7)

*Age range in years (Mean ± Standard Deviation); •The proportion reported is of those who achieved remission on or off AED; ‡Odds Ratio for not achieving remission are presented; CI-Confidence Interval, Y-Yes, U-Unsure, OR-Odds Ratio, HR-Hazard Ratio, AED-Antiepileptic Drug, EEG-Electroencephalogram, NS-Not Stated

Table 14 | Studies predicting remission on or off AED (Others 2)

Age (Years)*	Study	Design Setting N	Study Participation	Study Attrition	Prognostic Factor	Outcome	Analysis	Remarks	Follow Up	Outcome Measure (% with Outcome)•	Independent Predictors	Risk Estimate (95%CI)‡
2 – 81 (19)	CGSE, 1992	Mixed Hospital N=280	Y	Y	Y	Y	Y		0.1-7.25yrs	2 year seizure free period by 5 years follow up (67.5%)	≥2 Seizures before AED Mixed Seizure Types	HR: 1.49 (0.98-3.13) HR: 1.43 (0.96-2.70)
2 – 81 (19)	CGSE, 1992	Mixed Hospital N=280	Y	Y	Y	Y	Y		0.1-7.25yrs	3yrs seizure free period by 5 years follow up (51.1%)	≥2 Seizures before AED Mixed Seizure Types	HR: 1.52 (0.94, 5.0) HR: 1.61 (0.98-4.35)
2 – 68 (24)	Lohani, 2010	Retrospective Hospital N=284	Y	U	Y	Y	Y	Not a newly diagnosed epilepsy cohort. 50% had seizures for >1yr before AED and only6.5% <1mo	6mo on AED (Minimum)	6mo seizure free immediately before last follow up (73.2%)	Neurological Deficit Failure of first AED	OR:6.69 (1.37, 32.67) OR:71.82 (16.51, 312.44)
5->50	MacDonald, 2000	Prospective Population N=289	Y	Y	Y	Y	Y	Age < 5 excluded from analysis to avoid interactions	5.6-7.6yrs (IQR)	1 year seizure free period during follow up (NS)	Log N Seizures before index Log N Seizures (index - 6months) >10 Seizures before index	HR: 0.81 (0.66, 0.99) HR:0.59 (0.50, 0.70) HR: 1.89 (1.14, 3.13)
5->50	MacDonald, 2000	Prospective Population N=289	Y	Y	Y	Y	Y	Age < 5 excluded from analysis to avoid interactions	5.6-7.6yrs (IQR)	5 years seizure free period during follow up (NS)	Log N Seizures (index - 6months) >10 Seizures before index	HR: 0.64 (0.51, 0.81) HR: 1.80 (1.10, 2.92)
All ages (NS)	Shafer, 1988	Retrospective Population N=298	Y	U	N	Y	Y	Patients without EEG or information on GTC Seizure excluded	≈13-17yrs Mean (NS)	5 years seizure free period during follow up (NS)	Unknown Aetiology No Gen. Spike Waves on 1st EEG No Gen. Tonic Clonic Seizures	HR: 2.27 (NS) HR: 1.58 (NS) HR: 1.4 (NS)
12-85 (28.7±12.4)	Abduljabbar, 1998	Mixed Hospital N=826	Y	Y	Y	Y	Y		1yr (Minimum)	1 year seizure free period during follow up (80%)	≥2 AEDs Compliance Therapeutic Drug Level Short duration btw onset & AED	OR: 7.39 (NS) OR: 40.44 (NS) OR: 3.0004 (NS) OR: 1.003 (NS)
15-79 (34)	Hui, 2007	Mixed Hospital N=260	Y	Y	Y	Y	Y		1-17yrs 7years (Mean)	1yr seizure free immediately before last follow up (60%)	Intellectual disability Mesial Temporal Sclerosis	OR:9.39 (3.98, 22.12) OR: 7.6 (3.53, 16.4)
18-67 (44±12)	Lossius, 1999	Retrospective Population N=669	Y	Y	Y	Y	Y		NS	1yr seizure free immediately before last follow up (72.5%)	≥2 AEDs vs. No Treatment Age ≥ 50 years	OR: 5.6 (2.7, 11.9) OR: 1.7 (1.1, 2.6)

*Age range in years (Mean ± Standard Deviation); •The proportion reported is of those who achieved remission on or off AED; ‡Odds Ratio for not achieving remission are presented; CI-Confidence Interval, Y-Yes, U-Unsure, N-No, OR-Odds Ratio, HR-Hazard Ratio, AED-Antiepileptic Drug, EEG-Electroencephalogram, NS-Not Stated

Table 15 | Consistent predictors and non-predictors of remission on or off AED (1)

	Arts, 1999	Arts, 1999[6mo]	Arts, 2004	Arts, 2004[6mo]	Banu, 2003	Berg, 2001b	Sillanpaa, 1990	Sillanpaa, 1993	Sillanpaa, 1998	Sillanpaa, 2009	Shinnar, 2000	CGSE, 1992 [2]	CGSE, 1992[3]	Lohani, 2010	MacDonald, 2000[1]	MacDonald, 2000[3]	Shafer, 1988	Abduljabbar, 1998	Hui, 2007	Lossius, 1999
Demographics																				
Age at Onset	✘						✘		ϴ	✘		ϴ	ϴ	✘	✘	✘			✘	
Gender	✘		✘	✔*						✘		ϴ	ϴ	✘	✘	✘	✘		✘	✘
AED Therapy																				
≥2 AEDs														✔				✔		
Epilepsy Before AED, Intake or Index																				
Duration	✔											✘	✘	✘				✔		
N of Seizures before Intake						✘			ϴ			✔	✔							
Log N of Seizures before Intake	✔														✔	✔				
Seizure Frequency					✔	✔	✔	✔	ϴ	✔				✔				✔		
Early Epilepsy Characteristics																				
Log N (+1) of Seizures from 0 - 6mo		✔													✔	✔				
Status Epilepticus (SE)						✔	✔	✔	ϴ											
EEG																				
Intake/Early - EEG Abnormal	✘	✘			✔	✘					✘	✘	✘				✘			
Intake Epileptiform Abnormality		ϴ	✘			✘														
Gen (Epileptiform) Spike and Wave						✘											✔			
Focal																	✘			✘

✔ - *Variable is significant or retained in multivariate model,* ✔ - *Variable is only significant on univariate analysis,* ✘ - *Variable is not significant on univariate analysis*
ϴ – *Variable is not reported in univariate analysis, but reported as not significant on multivariate analysis*
*In this study, female was the gender retained in the model

Table 16 | Consistent predictors and non-predictors of remission on or off AED (2)

	Arts, 1999	Arts, 1999[6mo]	Arts, 2004	Arts, 2004[6mo]	Banu, 2003	Berg, 2001b	Sillanpaa, 1990	Sillanpaa, 1993	Sillanpaa, 1998	Sillanpaa, 2009	Shinnar, 2000	CGSE, 1992 [2]	CGSE, 1992[3]	Lohani, 2010	MacDonald, 2000[1]	MacDonald, 2000[3]	Shafer, 1988	Abduljabbar, 1998	Hui, 2007	Lossius, 1999
Seizure Type																				
Mixed Seizure Types					✔							✔	✔							
Seizure Type										✘							✘	✘		
Generalised Onset														✘	✘	✘				
Partial														✘	✘	✘				
Complex Partial							✘		✔											
Secondarily Generalised						✘	✘								✘	✘				
Atonic						✘			✔											
Generalised Tonic Clonic						✘	✘								✘	✘	✔			
Aetiology | Syndrome																				
Remote Symptomatic Aetiology						✔		✔		✔	✔	✘	✘		✘	✘	✔		✔	✔
Cryptogenic															✘	✘			✔	
West Syndrome							✔	✔												
Cognition																				
Abnormal Cognitive Development					✔		✔	✔	Θ										✔	
Neurological Sign																				
Neurological Examination	✔		✘						Θ			✘	✘	✔				✔		✔
Neuroimaging Findings	✔		✘											✘				✔		✘
Others																				
Family History	✘				✘	✔	✘					✘	✘				✘			
Perinatal Asphyxia					✘										✘	✘				
Neonatal Seizures					✘							✘	✘							
Febrile Seizure	✘		✘			✘					✘	✘	✘							
Tumour															✘	✘			✘	
Vascular Malformation															✘	✘			✘	

✔ - Variable is significant or retained in multivariate model, ✔ - Variable is only significant on univariate analysis, ✘ - Variable is not significant on univariate analysis
Θ – Variable is not reported in univariate analysis, but reported as not significant on multivariate analysis

The natural logarithm transformation of the number of seizures from intake to 6 months was also consistently identified as independent predictor of remission in Arts et al 1999(65) (in the model including 6 months variables) and MacDonald et al(101) (although it is also retained in the model predicting a 5 year seizure-free period, the model predicting I year free of seizures during follow up is used in this comparison owing to its greater similarity to the outcome measure in Arts et al 1999):

Box 10 | Relative risk of achieving remission in patients as a function of Log N of Seizures from index to 6 months

Arts et al 1999	**RR 0.50 (95%CI 0.35-0.72)**
MacDonald et al 2000	**RR 0.59 (95%CI 0.50-0.70)**

No demographic variable was found to consistently predict remission; only 1 study,(66) found gender to be an independent predictor on multivariate analysis, albeit with borderline statistical significance. Other variables not associated with remission include age at onset, abnormal EEG at intake and the range of seizure types considered, as were factors like family history of epilepsy, history of neonatal seizures and the specific aetiological factors considered.

The 2 models derived in Arts et al 1999(65) were externally validated in a temporal cohort from the same centre as the derivation cohort. (Table 17) The model derived from only variables assessed at intake showed poor discriminative ability (AUC, <0.70) in both internal and external validation. However, the model that was fitted with both intake and 6 month variables showed good discrimination (AUC, >0.70), with the AUC reducing from 0.78 in internal validation to 0.71 when externally validated. The proportion of patients with correct prediction (accuracy) also reduced from 73% to 63% in external validation.

The 2 models were calibrated, with a plot of 4 risk groups of unequal size, which suggest that the percentage of children correctly predicted not to achieve remission did increase with the predicted chance of not achieving remission. The calibration was however not assessed using a formal statistical test.

Table 17 | Externally validated models predicting remission on or off antiepileptic drugs

Predictors in Model	Derivation Cohort	Internal Validation: Performance of Model in Derivation Cohort	Validation Study	Validation Cohort	External Validation: Performance of Model in Validation Cohort	Score	Easy to Use	Important Variable	Probability or Action	Clinical Use Studied
Log N of Seizure before intake >/<25 Seizures before intake *Seizure Type* -Generalised Tonic Clonic -Complex Partial -Simple Partial -Absences -Other Types *Aetiology* -Remote symptomatic -Cryptogenic, -Idiopathic Yes/No Neurological signs	Arts 1999 Only intake variables Included 1 status epilepticus in epilepsy definition Remission defined by 6 months seizure free immediately before 2yrs follow up **Pre-Test Probability (31%)**	AUC 0.69 (0.64, 0.74) **Best probability cut-off (38%)** Sensitivity (61.6%) Specificity (69.1%) PPV (47.2%) NPV (20.0%) Correct Prediction (66.7%)	Geerts 2006	Temporal Validation N=273 2 years (Minimum Follow up) The 2 cohorts were similar except there were more children with normal EEG findings than in the derivation cohort. **Pre-Test Probability (34%)**	AUC 0.62 (0.55, 0.69) **Probability cut-off (38%)** Sensitivity (60.0%) Specificity (61.4%) PPV (44.5%) NPV (25.1%) Correct Prediction (59.9%)	Y	N	Y	Pr	N
Seizure Type -Generalised Tonic Clonic -Complex Partial -Simple Partial -Absences -Other Types *Aetiology* -Remote symptomatic -Cryptogenic, -Idiopathic *During 1st 6 mo after intake:* -Log N Seizures ->/<25 Seizures -Yes/No 3 month remission *EEG at Intake* -Normal, -Epileptiform,-Other *EEG 6 mo after intake* -Normal,-Epileptiform, -Other	Arts 1999 Intake and 6 month variables Included 1 status epilepticus in epilepsy definition Remission defined by 6 months seizure free immediately before 2yrs follow up **Pre-Test Probability (31%)**	AUC 0.78 (0.73, 0.82) **Best probability cut-off (34%)** Sensitivity (72.6%) Specificity (73.1%) PPV (54.8%) NPV (14.4%) Correct Prediction (73.0%)	Geerts 2006	Temporal Validation N=273 2 years (Minimum Follow up) The 2 cohorts were similar except there were more children with normal EEG findings than in the derivation cohort. **Pre-Test Probability (34%)**	AUC 0.71 (0.64, 0.78) **Probability cut-off (34%)** Sensitivity (67.4%) Specificity (60.2%) PPV (46.6%) NPV (21.8%) Correct Prediction (62.7%)	Y	N	Y	Pr	N

AUC-Area Under Receiver Operator Characteristics (ROC) Curve, PPV-Positive Predictive Value, NPV-Negative Predictive Value, NS-Not Stated, Pr-Probability, N-No, Y-Yes, AED-Antiepileptic Drug

PREDICTING INTRACTABILITY (TYPE IV)

Twelve studies, all conducted in childhood epilepsy cohorts, attempted to identify independent predictors of medically intractable seizures. Six of the analyses were conducted on the entire cohort, (Table 18) while the other 6 fitted their model with a case control analysis nested within cohorts. (Table 19 and 20)

The proportion of patients with intractable seizures in the cohorts varied among the studies depending on design and how medical intractability was defined and conceptualised in each study. Most of the studies defined intractability as having “at least 1” or “more than 1” seizure per month for about 1 year (ranged between at least 6 months and at least 2 years) after more than 2 antiepileptic drug trials singly or in combination, at the maximum tolerable dose.

The frequency of seizures that define medical intractability in each study influenced the proportion of patients that met the criteria. The studies that defined intractability as having “1 or more” seizures per month(72, 75, 76) had more patients who met the criteria for intractability (13% to 14%) compared to the studies(73, 74) that defined intractability as only “more than 1” seizure per month (9% to 10%). However, in a retrospective, hospital based study reported by Berg et al 1996(78), with the seizure frequency that defined epilepsy being “1 or more” seizures per month, one third (32.5%) of the patients met the criteria for medical intractability.

Two of the studies reported by Oskoui et al(72)and the report by Ko et al(79) included patients who required epilepsy surgery during follow up as medically intractable even when they did not meet the usual criteria for intractability. The same 2 studies by Oskoui et al(72) also included patients who required the use of the ketogenic diet to control seizures, and only patients who have had recurrent seizures in the last 6 months of follow up in a category designated as having “poor outcome.” 7% of the cohort was included in this category.

The age of children at the onset of seizures, kept as a continuous variable, was retained in the models predicting medical intractability in three different cohorts, with nested case control analysis (75, 78, 79):

Box 11 | Relative risk (RR) of having intractable seizures for each increasing year of age at onset of seizures

Casetta et al 1999	**RR 0.98 (95%CI 0.97-1.28)**
Ko et al 1999	**RR 0.86 (95%CI 0.75-0.97)**
Berg et al 1996	**RR 0.78 (95%CI 0.69-0.89)**

Table 18 | Studies predicting intractability (full cohort)

Age (Years)*	Study	Design Setting	Study Participation	Study Attrition	Prognostic Factor	Outcome	Analysis	Remarks	Follow Up	Outcome Measure (% with Outcome)	Independent Predictors	Risk Estimate (95%CI)
0-15	Berg, 2001a	Prospective Population	Y	Y	Y	Y	N		5yrs (Median)	>1 Seizure per month for ≥1.5yrs with >2AEDs (10%)	Cryptogenic and Symptomatic Generalized Syndrome Idiopathic Syndrome Log Initial Seizure Frequency Abnormal EEG (Focal Slowing) Age 5 to 9 at Onset Provoked, Non-Febrile and Neonatal Status Epilepticus Myoclonic Seizures + Log Initial Seizure Frequency	 HR: 3.01 (1.32, 6.85) HR: 0.23 (0.09, 0.63) HR: 1.41 (1.23, 1.62) HR: 2.31 (1.13, 4.74) HR: 0.42 (0.19, 0.92) HR: 5.96 (2.00, 17.71) HR: 0.73 (0.57, 0.95)
0-14 (4.8±3.8)	Ramos-Lizana, 2009	Mixed Hospital	Y	Y	Y	Y	Y	All variables measured at 6 months of follow up	2-11.6yrs	>1 Seizure per month for ≥1.5yrs with >2AEDs (8.7%)	Age <1 year at Onset Idiopathic Aetiology >1 Seizure (diagnosis -6 months)	HR: 2.6 (1.0, 6.9) HR: 0.2 (0.0, 0.8) HR: 4.8 (1.8, 13.0)
2-17 (7.6±3.7)	Oskoui, 2005	Retrospective Hospital	Y	P	Y	Y	Y	Only onset variables Data collection was remarkably good	2-13.6yrs	≥1 Seizure per month for >1yr with >2AEDs (12.8%)	Multiple Seizure Types	OR: 17.4 (4.8–63.1)
2-17 (7.6±3.7)	Oskoui, 2005	Retrospective Hospital	Y	P	Y	Y	N	Onset and 1yr variables Data collection was remarkably good	2-13.6yrs	≥1 Seizure per month for >1yr with >2AEDs (12.8%)	Multiple Seizure Types Intellectual disability Seizure 6 to 12 months on AED	OR: 6.5(1.9–35.4) OR: 7.2 (1.0–50.8) OR: 70.4 (7.5–661.4)
2-17 (7.6±3.7)	Oskoui, 2005	Retrospective Hospital	Y	P	Y	Y	N	Only onset variables Data collection was remarkably good Outcome included having required epilepsy surgery or ketogenic diet	2-13.6yrs	Recurrent seizures on adequate AED 6 months immediately before last follow up (6.9%)	Multiple Seizure Types Intellectual disability Idiopathic Epilepsy	OR: 14.7 (4.7–46.1) OR: 3.3 (1.1–10.2) OR: 0.13 (0.03–0.52)
2-17 (7.6±3.7)	Oskoui, 2005	Retrospective Hospital	Y	P	Y	Y	N	Onset and 1yr variables Data collection was remarkably good Outcome included having required epilepsy surgery or ketogenic diet	2-13.6yrs	Recurrent seizures on adequate AED 6 months immediately before last follow up (6.9%)	Multiple Seizure Types Intellectual disability Seizure 6 to 12 months on AED	OR: 8.9 (2.6–31.2) OR: 8.9 (2.4–32.7) OR: 21.6 (6.3–74.0)

*Age range in years (Mean ± Standard Deviation); CI-Confidence Interval, Y-Yes, P-partly, N-No, HR-Hazard Ratio, OR-Odds Ratio, AED-Antiepileptic Drug, EEG-Electroencephalogram

Table 19 | Studies predicting intractability (nested case control)

Age (Years)*	Study	Design Setting N	Study Participation	Study Attrition	Prognostic Factor	Outcome	Analysis	Remarks	Follow Up	Outcome Measure	Independent Predictors	Risk Estimate (95%CI)
0-19 *Cases* 3.3 *Controls* 6.4	Casetta, 1999	Prospective Population N=222 *Cases* 31 *Controls* 95	Y	Y	Y	Y	Y	Two models – I with age as continuous variable and II with age dichotomous 13.96% of patients in the cohort had intractable seizures	*Cases* 20.97yrs Controls 20.98yrs	*Cases* ≥1 Seizure per month for ≥2yrs with >2AEDs *Controls* 5 years seizure free period during follow up	*Model I* Age at Onset (in years) Remote Symptomatic Aetiology Weekly Seizures before AED *Model II* Age <1 year at Onset Remote Symptomatic Aetiology Weekly Seizures before AED	 OR: 0.98 (0.97, 1.28) OR: 8.6 (2.3, 32.2) OR: 4.5 (1.3, 16) OR: 3.9 (1.1, 14.25) OR: 8.6 (2.4, 26.1) OR: 4.1 (1.3-13.8)
0-15	Kwong, 2003	Mixed Population N=309 *Cases* 44 *Controls* 211	Y	Y	Y	Y	Y	14.24% of patients in the cohort had intractable seizures	3yrs (Minimum) Cases 5.88yrs Controls 4.67yrs	*Cases* ≥1 Seizure per month for ≥2yrs with ≥3AEDs *Controls* 2 year seizure free period during follow up	Daily Seizures before AED ≥3 Seizures 6-12 months on AED History of Febrile Seizure Abnormal Neurodevelopmental Status (Intellectual disability and/or Cerebral Palsy)	OR: 1.58 (1.0, 2.51) OR:21.86(7.35,65.01) OR:4.83 (1.31, 17.83) OR:18.16(5.19,63.61)
Cases 1.58±2.38 *Controls* 5.83±2.54	Chawla, 2002	Mixed Hospital N=(NS) *Cases* 50 *Controls* 50	U	U	N	U	Y	Equal number of cases and controls were selected from the cohort The total number of base population not presented	1yr (Minimum)	*Cases* ≥1 Seizure per month for ≥0.5yr with ≥2AEDs *Controls* 6 months seizure free immediately before last follow up	Age <1 year at Onset Remote Symptomatic Aetiology Neurological Impairment Initial Seizure Type (Myoclonic or Infantile Spasms)	OR: 11.7 (2.95,46.43) OR: 2.91 (1.14, 7.44) OR12.25 (3.58,41.89) OR: 10.36 (2.39, 44.94)
Cases 1.8 *Controls* 5.8	Berg, 1996	Retrospective Hospital N=234 *Cases* 76 *Controls* 96	N	Y	Y	Y	Y	Case control study nested in a cohort 32.5% of patients in the cohort had intractable seizures	*Cases* 6yrs *Controls* 5yrs	*Cases* ≥1 Seizure per month for ≥2yrs with >2AEDs *Controls* 2 year seizure free period during follow up	Age at Onset (in years) Remote Symptomatic Epilepsy Occurrence of Status Epilepticus Infantile Spasms	OR: 0.78 (0.69, 0.89) OR: 2.24, (1.05, 4.80) OR: 3.30 (1.06,10.28) OR: 10.42 (1.27, 85.39)

*Age range in years (Mean ± Standard Deviation); CI-Confidence Interval, Y-Yes, N-No, U-Unclear, OR-Odds Ratio, AED-Antiepileptic Drug, NS-Not Stated

Table 20 | Studies predicting intractability (nested case control by Ko et al)

Age (Years)*	Study	Design Setting N	Study Participation	Study Attrition	Prognostic Factor	Outcome	Analysis	Remarks	Follow Up	Outcome Measure	Independent Predictors	Risk Estimate (95%CI)
0-18 *Cases* 2.9 *Controls* 5.2	Ko, 1999	Retrospective Hospital N=(NS) *Cases* 144 *Controls* 39	N	Y	Y	U	N	Patients without EEG at intake were excluded Only clinical variables entered in this model The total number of base population not presented	2yrs (Minimum) *Cases* 5.3yrs *Controls* 4.9yrs	*Cases* "Continued Seizures" with ≥3AEDs or having required epilepsy surgery *Controls* 1 year seizure free period during follow up	Age at Onset (in years) Remote Symptomatic Aetiology Occurrence of Status Epilepticus Simple Partial Seizures Absence Seizures Tonic Seizures	OR: 0.86 (0.75, 0.97) OR: 4.41 (1.68, 13.0) OR: 7.7(1.42, 143.48) OR: 5.11(1.21, 36.08) OR: 0.92 (0.32, 2.70) OR:13.5(2.56,249.74)
0-18 *Cases* 2.9 *Controls* 5.2	Ko, 1999	Retrospective Hospital N=(NS) *Cases* 144 *Controls* 39	N	Y	Y	U	N	Patients without EEG at intake were excluded Only EEG variables entered in this model The total number of base population not presented	2yrs (Minimum) *Cases* 5.3yrs *Controls* 4.9yrs	*Cases* "Continued Seizures" with ≥3AEDs or having required epilepsy surgery *Controls* 1 year seizure free period during follow up	Photo-convulsive Response 3 Hz Spike and Wave Diffuse Slowing Focal Spike and Wave Frequent Sharp Wave/ Spike (>1/60 s)	OR: 0.10 (0.02, 0.51) OR: 0.21 (0.05, 0.74) OR: 2.59 (1.05, 6.84) OR: 5.21 (1.25,38.16) OR: 1.68 (0.67, 4.43)

*Age range in years (Mean ± Standard Deviation); CI-Confidence Interval, Y-Yes, P-partly, N-No, HR-Hazard Ratio, OR-Odds Ratio, AED-Antiepileptic Drug, NS-Not Stated

Table 21 | Consistent predictors and non-predictors of intractability

	Berg, 2001a	Ramos-Lizana, 2009	Oskoui, 2005 intractable	Oskoui, 2005 intractable*	Oskoui, 2005 poor	Oskoui, 2005 poor*	Casetta, 1999	Kwong, 2003	Chawla, 2002	Berg, 1996	Ko, 1999 CLI	Ko, 1999 EEG
Demographics												
Age at Onset (in years)*	✔		ϴ	ϴ	ϴ	ϴ	✔	✔		✔	✔	
Age at onset <1 year†	✔	✔					✔		✔			
Gender	✘	✘	ϴ	ϴ	ϴ	ϴ	✘					
Epilepsy Before AED, Intake or Index												
Seizure Frequency - Daily	✔							✔	✔		✔	
Early Epilepsy Characteristics												
Status Epilepticus (SE)	✔	✘					✔	✔	✘	✔	✘	
EEG												
Intake/Early - EEG Abnormal	✘	✘	ϴ	ϴ	ϴ	ϴ		✔		✘		
Focal Slowing	✔											✘
Seizure Type												
Mixed Seizure Types	✔	✘	✔	✔	✔	✔						
Generalised Onset	✘									✘		
Partial	✘						✔			✘		
Simple	✘										✔	
Complex	✘										✘	
Myoclonic	✔										✔	
Absence	✔									✔	✔	
Generalised Tonic Clonic										✘	✘	
Aetiology | Syndrome												
Remote Symptomatic Aetiology	✔	✔	ϴ	ϴ	ϴ	ϴ	✔	✔	✔	✔	✔	
Idiopathic	✔	✔	ϴ	ϴ	✔	ϴ						
West Syndrome		✔								✔	✔	
ILAE Syndrome	✔		ϴ	ϴ	ϴ	ϴ		✔				
Cognition												
Abnormal Cognitive Development		✔	ϴ	✔	✔	✔		✔			✔	
Neurological Sign												
Neurological Examination			ϴ	ϴ	ϴ	ϴ			✔			
Normal Neuroimaging Findings	✔	✔						✔			✔	
Others												
Motor disability		✘									✔	
Family History		✘	ϴ	ϴ	ϴ	ϴ	✘		✘		✘	
Neonatal Seizures	✔	✘					✘	✔	✔	✔	✘	
Febrile Seizure	✘	✘					✘	✔	✘	✘	✘	
Multiple Seizures within 24 Hours	✔	✔										
Microcephaly									✔	✔	✘	

✔ - Variable is significant or retained in multivariate model, ✔ - only significant on univariate analysis, ✘ - not significant on univariate analysis ϴ – not reported in univariate analysis, but reported as not significant on multivariate analysis

*Where "age in years" was retained, the risk of intractability reduces with each additional year increase in the age of onset.

†"Age at onset < 1 year" was retained as a variable which increases the risk of intractability.

Three studies also retained onset of seizures in infancy (age at onset < 1year) as an independent predictor of medically intractable seizures (74, 75, 94):

Box 12 | Relative risk (RR) of having intractable seizures with onset of seizures in infancy (age <1 year)

Ramos-Lizana et al 2009	**RR 2.6 (95%CI 1.0-6.9)**
Chawla et al 2002	**RR 3.1 (95%CI 2.0-3.6)**
Casetta et al 1999	**RR 2.6 (95%CI 1.1-4.3)**

The presence of remote symptomatic aetiology was also found to be a consistent predictor of a patient developing medically intractable seizures in 4 studies, all nested cohort studies, with the risk estimate from Casetta et al(75) being remarkably higher than the rest:

Box 13 | Relative risk (RR) of having intractable seizures in patients with remote symptomatic aetiology

Chawla et al 2002	**RR 2.06 (95%CI 1.11-3.10)**
Casetta et al 1999	**RR 5.48 (95%CI 2.10-9.64)**
Ko et al 1999	**RR 1.34 (95%CI 1.15-1.43)**
Berg et al 1996	**RR 1.67 (95%CI 1.04-2.36)**

Three studies also retained idiopathic aetiology/syndrome as an independent predictor of patients developing medically intractable seizures, with similar estimates although the study from Oskoui et al (72) was one in which "intractability" defined as "poor outcome" (patients who required epilepsy surgery and/or the use of ketogenic diet to control seizures, or who have had recurrent seizures in the last 6 months of follow up) was rather atypical:

Box 14 | Relative risk (RR) of having intractable seizures in patients with idiopathic aetiology

Ramos-Lizana et al 2009	**RR 0.20 (95%CI 0.0-0.80)**
Oskoui et al 2005	**RR 0.13 (95%CI 0.03-0.52)**
Berg et al 2001a	**RR 0.23 (95%CI 0.09-0.63)**

Intellectual disability was another consistent predictor of patients developing medically intractable seizures, with the variable retained in three of the 4 studies on intractability reported by Oskoui et al(72) and in the only study reported by Kwong et al(76). The result of the study from Oskoui et al(72) whose definition of medical intractability is most similar to that from Kwong et al(76) is presented for comparison. Kwong et al(76) includes patients with cerebral palsy, and the compared estimate from Oskoui et al(72) was assessed alongside variables collected at 1 year follow up.

However, as Oskoui et al(72) did not provide enough data (absolute risk of intractability in non-intellectually disabled patients) to compute the relative risk, the estimates are compared as odds ratio:

Box 15 | Odds ratio (OR) of having intractable seizures in patients with intellectual disability

Oskoui et al 2005	**OR 7.2 (95%CI 1.0-50.8)**
Kwong et al 2003	**OR 18.2 (95%CI 5.2-63.6)**

Having mixed seizure types was only found to be a predictor of intractability in studies reported by Oskoui et al(72). Other potential predictors related to seizure type were not confirmed to be consistently predictive of intractability, as were the occurrence of status epilepticus, family history of epilepsy or history of neonatal seizures, seizure frequency, and abnormal EEG.

None of the models were externally validated.

PREDICTING NO REMISSION AFTER RELAPSE (TYPE V)

Only 1 study, Sillanpaa and Schmidt 2006(25) investigated the predictors of not achieving remission after 1 or more relapses following initial remission. In the study, 14% of the cohort belonged in this category. The only independent predictor was having remote symptomatic aetiology with the odds 8 [8.2 (95%CI 2.7-24.8)] times as high compared to those without remote symptomatic aetiology. Intellectual disability, localisation related epilepsy and temporal lobe epilepsy were not included in the model. The model was not externally validated.

Table 22 | Studies predicting no remission after relapse

Age (Years)*	Study	Design Setting N	Study Participation	Study Attrition	Prognostic Factor	Outcome	Analysis	Remarks	Follow Up	Outcome Measure	Independent Predictors	Risk Estimate (95%CI)
0-15	Sillanpaa, 2009	Prospective Population N=144 *Cases* 20 *Controls* 97	Y	Y	Y	Y	Y	Three seizures diagnosed epilepsy Cases and controls nested within a selection of only prospectively identified patients in Turku cohort	11-42yrs	*Cases* Patients who after relapse, did not achieve 5 years seizure free status immediately before last follow up *Controls* 5 years seizure free immediately before last follow up	Remote Symptomatic Aetiology	OR: 8.2 (2.7–24.8)

*Age range in years (Mean ± Standard Deviation); CI-Confidence Interval, Y-Yes, HR-Hazard Ratio, OR-Odds Ratio

Table 23 | Predictors and non-predictors of no remission after relapse

	Sillanpaa, 2006
Aetiology | Syndrome	
Remote Symptomatic Aetiology	✔
Cognition	
Abnormal Cognitive Development	ϴ
Others	
Localisation Related Epilepsy	ϴ
Temporal Lobe Epilepsy	ϴ

✔ *- Variable is significant or retained in multivariate model,*

ϴ – not reported in univariate analysis, but reported as not significant on multivariate analysis

5 CHAPTER FIVE: DISCUSSSION

This chapter presents a general discussion and reflection on the results of the review. The chapter is presented according to recommendations that advocate structured discussion of the results of scientific research.(38) The principal findings of 1) the literature search; 2) the quality appraisal of studies and reporting characteristics of publications; 3) the study classification; and 4) the studies within each category, were stated and interpreted. Thereafter, possible explanations for the results are presented and their implications for clinical practice are stated where applicable. There are also suggestions for future studies and the direction of future research for each set of results. The strengths of the study are highlighted, and the weaknesses are also discussed also with a view to making recommendations for future studies.

5.1 THE LITERATURE SEARCH

MEDLINE alone retrieved 91% of all eligible publications, with an overlap of 42% (14 out of 33 publications) between MEDLINE and EMBASE. This distribution of search results mirrors that of the study by Royle et al(240) which sought to ascertain how many databases were necessary for a comprehensive coverage of observational studies of diabetes published in English language. MEDLINE alone accounted for 94% of all the articles retrieved and the rest were from EMBASE. No additional English language publication was retrieved beyond these 2 databases. This suggests that the search in this thesis was likely exhaustive; a notion further reinforced by the fact that the screening of reference lists of eligible publications did not yield any eligible study. These findings further confirm that the 2 databases are generally complimentary.(241, 285-288)

The 3 eligible publications unique to EMBASE(96, 97, 100) were all published in journals indexed on MEDLINE.(289) That 2 of the 3 publications were published in 2010 may support the claim that EMBASE is much more current than MEDLINE.(242) The fact that all the articles were published in the last 15 (1988 to 2010) years may reflect the period when multivariate analysis became popular due to proliferation of computer software packages that made the statistical technique much easier to conduct, beginning in the late 1980s.(263)

One journal, *Epilepsia*, accounted for about a third of the 33 eligible publications. Future systematic reviews of observational studies in epilepsy may therefore also benefit from hand-searching *Epilepsia*. Evidence from the search and systematic reviews of intervention studies suggest that hand searching of selected high impact journals may be necessary to ensure comprehensive search as the processes associated with indexing and electronic search are not infallible. (290, 291) The greatest value of hand searching has been found to be in identifying publications in supplement editions and abstract sections of journals.(291) This is particularly the case in MEDLINE search(291) and in this review, as 1 (292) of the 4 EMBASE unique publications (although not eligible) was published in the abstract section of a supplement edition of *Epilepsia,* a MEDLINE-indexed relatively high impact journal.

Notwithstanding that the care of patients with newly diagnosed epilepsy is often initiated and followed up in primary care,(293, 294) only 1 out of the 33 publications was in a non-specialist journal. This may have implications for the uptake of research findings, as the category of physicians who often have first contact with patients may not be specialists and they may be the physicians with the responsibility to assess prognosis and plan further care or referral.(295)

5.2 QUALITY AND REPORTING CHARACTERISTICS

The report of important study items in the eligible publications was generally poor, which impacted negatively on the ability to conduct a detailed critical appraisal of the quality of some studies, this being so despite seeking out referenced publications for further information on the studies.

No study gave a power calculation to justify their sample size. However, the more important issue, which affects the stability and reliability of risk estimates from multivariate models is the number of patients with the outcome under consideration in relation to the number of independent variables in the model.(263, 296) Nine out of the 47 studies with multivariate analysis failed to meet the criterion that there must be at least 10 times the number of patients with the less frequent outcome per prognostic variable in the model. Two (66, 77) of the 9 studies had more than 9 events per variable. The overall small sample size may also be a major source of unreliability, especially with the use of a stepwise algorithm for selecting the variables to retain in the model, if continuous markers are dichotomized, (an act that effectively reduces the sample size by 30% or more) and when interactions between variables is investigated.(45, 296)

Eight of 31 publications reported testing for interaction terms, 16 reported the use of stepwise selection of variables and only 4 handled continuous variables appropriately. However, Altman and Lyman suggested, rather arbitrarily, that studies that use stepwise algorithm, dichotomise continuous variables and investigate interaction terms should be based on at least 250 to 500 patients with outcome. In this review, only 2 publications (reporting 4 studies) had such rate of outcome. The 2 studies were reports of international collaborative studies. The sample size of the cohorts included in this review ranged from 102 to 1443 (median 287, mean 390).

The practice in 2 previous systematic reviews of prognosis studies, as in this review, was to have 100 participants in a study as minimum requirement for inclusion.(234, 235) However, to ensure robustness of results of multivariate analyses, future prognosis studies of seizure outcome in newly diagnosed patients with epilepsy may benefit from international collaborations and the meta-analysis or reanalysis of individual patient data from different cohorts. Having a large sample size can only improve the precision and stability of models, but will not necessarily make up for inherent weaknesses in study design and execution.(45, 296)Therefore, these

international collaboration studies will also ensure that other quality measures such as prospective case ascertainment and long follow up to allow patients to be reliably grouped into appropriate outcome categories.

Less than 60% of the publications reported the statistical package or software used to conduct the multivariate analysis, a practice which Concato et al(263) described as "analogous to a laboratory researcher [not] indicating the particular experimental protocol used for physiologic measurements." The reporting of issues directly related to multivariate analysis was also deficient. The test for collinearity was reported in only 1 publication; model assumptions were tested in 2, missing data was mentioned in 8, and the statistical criteria for including variables in models were stated in only 50% of the 31 papers reporting studies with multivariable models. However, all but 1 paper(68) reported a measure of follow up, while all but 2 (101, 104) reported the proportion with outcome.

The poor reporting of studies is not unique to prognosis studies; it affects observational studies in general.(297) Therefore in 2007, the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist was produced in order to serve as guidelines for reporting observational studies.(298) The checklist consists of a flexible 22-item checklist which provides reporting recommendations for all sections of manuscripts of the 3 types of observational study design (cohort, case control and cross-sectional) while allowing authors to utilize their preferences and creativity when selecting the order and format of presenting the details.(298) Eighteen of the items are applicable to all the 3 study designs. Four are design-specific: information in the methods section regarding participants (item 6) and statistical methods (item 12); information in the results section regarding descriptive data (item 14) and outcome data (item 15).(40) The checklist is presented in Appendix V

However only 2 journals (*Lancet Neurology* and *Neurology*, containing 1 publication each) out of the total 17 journals where the papers in the review were published have endorsed the STROBE statement by way of referring to it in their Instructions for Authors.(299) The 2 articles in the STROBE-endorsing journals were published before the STROBE statement was produced, therefore it was not possible to compare the reporting characteristics of the publications with the others published in journals that are yet to endorse the STROBE guidelines.

5.3 THE CLASSIFICATION OF STUDIES

The task of developing a method for classification of studies to assist quality assessment and to guide the present and also future systematic reviews and meta-analyses is an important role for systematic reviews. This is especially important for observational studies, given the range of differences in quality, methods and potential for heterogeneity.(300) This thesis developed a classification system for studies of prognosis of seizure outcome in epilepsy. The classification is based on: 1) the potential seizure outcome category where a newly diagnosed patient could

belong e.g. immediate remission, remission off medication, remission on or off medication or medical intractability; and 2) how in the analysis to identify independent predictors of each outcome, patients belonging to different outcome groups are compared to identify exposure or epilepsy characteristics that are significantly different between the groups. The studies included in this review were classified into 5 types and systematically reviewed within the categories.

5.4 EARLY/IMMEDIATE REMISSION

PROPORTION WITH EARLY/IMMEDIATE REMISSION

The rate of recurrence after a second seizure is not influenced by antiepileptic drug therapy,(24, 175) although randomised trials have suggested that this may only be a long term outcome and that medication may suppress seizures in the short term.(98, 108-111) The studies predicting immediate remission employed different approaches to antiepileptic drug therapy: 2 studies(95, 96) had all the patients in the cohort placed initially on antiepileptic monotherapy; 1 study(98) randomised treatment; the other 2 studies treatment did not randomise patient allocation to medication (80% on medication in 1,(99) and 44% in the other(24)) with choice of therapy at the discretion of the physician. These different approaches to treatment in the cohorts were not reflected in the proportion of patients that achieved immediate remission. However, 3 factors were important in influencing the proportion of patients that entered immediate remission: case ascertainment, inclusion criteria, and the age of patients within the cohort.

Box 16 | Proportion of patients in immediate remission at 2 years by the proportion of patients on AED

33% in immediate remission at 2 years | 100% on AED | Del Felice et al 2010
37% in immediate remission at 2 years | 44% on AED | Shinnar et al 2000
42% in immediate remission at 2 years | 80% on AED | Lindsten et al 2001
48% in immediate remission at 2 years | 100% on AED |CGSEPI 1988
58% in immediate remission at 2 years | 50% on AED | Kim et al 2006

Where there was exclusive prospective case ascertainment i.e. all the patients in the study were identified at the exact point of their second seizure, fewer patients (37%) did not experience a next seizure after 2 years(24) compared to between 42% and 57.5% in 3 of the 4 studies with mixed case ascertainment,(95, 98, 99)especially including different proportions of first seizure, prospectively identified and retrospectively ascertained patients. The proportion of the cohort without immediate remission was highest (57.5%) where more than half of the patients were single seizure patients.(98) In the other 2 cohorts, single seizure cases were less than a third of the cohort. This supports previous evidence that for most patients, the rate of seizure recurrence reduces with increasing number of seizures.(119, 301, 302)

However, among the cohorts with mixed retrospective and prospective case identification, 2 hospital based studies with similar proportions of patients in each seizure category (the ratio of 1st seizure to 2-5 seizures and >5 seizures being roughly 4:9:7 in both studies) had widely

different proportion of patients in immediate remission at about 2 years of follow up: it was as high as 48% in 1 (95) and only 33% in the other.(96) The hypothesised explanations for this difference were:

1) The age difference between the cohorts. The cohort with 48% in immediate remission at 2 years after intake had a mean age of 19 years while the cohort with 33% had a mean age of about 32 years suggesting that younger/childhood-onset epilepsy may have a better prognosis than adult onset epilepsy,(48) which may be due to more symptomatic epilepsy occurring in adult-onset epilepsy(303, 304) and benign syndromes occurring more in childhood(305).

2) Inclusion criteria in the cohorts. The study with 48% of the cohort in immediate remission at 2 years excluded patients with progressive neurological disorders associated with increased risk of seizures e.g. brain tumour, while the other cohort included every patient with newly diagnosed epilepsy.

The 2 studies (95, 98) that excluded patients with known poor prognosis compared to the other 3, had a higher proportion of patients in immediate remission at 2 years after intake (57.5% and 48%) at 2 years follow up. The study from a randomised controlled trial(98) (with 57.5%) excluded all the patients for whom indication for antiepileptic drug therapy was certain, while the other study(95) only excluded the patients with progressive neurological disorder. This finding also suggests that patients with known poor prognosis, or "for whom indication to commence treatment was not clear" are more likely to have a recurrence after diagnosis.

PREDICTORS AND NON PREDICTORS

There were 2 consistent independent predictors of early/immediate remission in people with newly diagnosed epilepsy: having 2 or more seizures before intake and a patient having remote symptomatic epilepsy.

The patients with adult-onset epilepsy with 2 or more pre-intake seizures are 37% (95%CI -11% to 64%) more likely than people with a single seizure before diagnosis to have a recurrence, again showing that the risk of having a subsequent seizure may depend on the number of previous seizures. However, the 95% confidence interval crosses unity for this estimate and is therefore not particularly reliable. The second study that retained "having 2 or more pre-intake seizures" was from an all age cohort with mostly young (mean age 19 years) patients. The study however did not report the risk estimates. This predictor would anyway not have been available in an ideal prognosis study of epilepsy, especially one that is predicting early remission, a category in which the number of seizures being only 2 at intake into the cohort is particularly important to limit potential for bias.

The children with remote symptomatic aetiology are 41% (95%CI 14% to 59%) more likely than children with idiopathic/cryptogenic aetiology to have a recurrence.(24) The estimates from 2

other studies,(98, 99) while similar, may be fraught with the bias that the inclusion criteria of the studies might introduce. The estimate from Kim et al,(98) an all age cohort which excluded patients “for whom indication to commence treatment was not clear” and which also included single seizure cases and people with more than 2 seizures prior to intake was: 26% (95%CI 6% to 42%). Lindsten et al,(99)also a mixed cohort, but of patients with adult-onset epilepsy, found that adults with remote symptomatic aetiology are 66% (95%CI 23% to 74%) more likely than people with idiopathic/cryptogenic aetiology to have a recurrence. These estimates suggest that while remote symptomatic aetiology is a predictor of seizure recurrence in patients with newly diagnosed epilepsy, it may be a more important predictor in adult-onset epilepsy.

The other variables – gender, age at onset of seizures, duration of epilepsy before intake into cohort, abnormal EEG, seizure focus, family history and history of febrile seizures – assessed in more than 1 study, were not found to be consistent independent predictors of early/immediate remission in newly diagnosed epilepsy. That the age at onset of seizures is not associated with recurrence suggests that the age difference in the proportion of people that achieve immediate remission is accounted for by the fact that a higher proportion of patients with adult-onset epilepsy have symptomatic aetiology (303, 304) and that benign epilepsy syndromes are more common in childhood-onset epilepsy.(305)

5.5 REMISSION OFF ANTIEPILEPTIC MEDICATION

PROPORTION WITH REMISSION OFF ANTIEPILEPTIC MEDICATION

Three study factors were important in explaining the variation in the proportion of patients that were successfully weaned off antiepileptic medication: the study setting, the method of case ascertainment, and the readiness of the treating physician to wean patients off medication. If the proportions of patients in remission off medication at last follow up in the respective studies are arranged according to the hypothesis that prospective, population based studies are the least likely to be biased, and retrospective, hospital based studies are the most likely to be biased,(20) the progression of the proportion of patients off AED is largely linear. (Box 17) The less biased studies have a higher proportion of patients in remission off AED, except for 2 data points from the Turku cohort (32) where the definition of remission off AED was such that the patient had to have continued in remission off medication for at least 5 years. The relatively lower proportion of patients in remission off AED may have been further accentuated by the fact that 3 seizures instead of 2 diagnosed epilepsy in the Turku cohort and that the physicians responsible for patients in the cohort were more reluctant to discontinue AED(105). This finding however suggests that in childhood-onset epilepsy, more than two thirds of patients may be successfully taken off antiepileptic medication.

Box 17 | Proportion of patients in remission off AED arranged according to potential for bias

52% Retrospective | Hospital | off AED at last follow up | Oskoui et al 2005
47% Mixed | Population |5 years off AED at last follow up | Sillanpaa et al 1998*
54% Mixed | Population |off AED at last follow up | Camfield et al 1993
55% Mixed | Population |off AED at last follow up| Geelhoed et al 2005
59% Mixed/Prospective | Population/Hospital |off AED at last follow up | Geelhoed et al 2005
65% Prospective | Hospital |off AED at last follow up | Geelhoed et al 2005
56% Prospective | Population |5 years off AED at last follow up | Sillanpaa et al 1998*

*(Physicians were reluctant to discontinue AED)

The progression was not significantly affected by the fact that patients with generalised absence seizures and known poor prognosis, including progressive neurological disorders were excluded from the cohort with 54% in remission off medication(71) compared to 55% when the previously excluded patients were included.(106) It is possible that the poor prognosis and the good prognosis of generalised absence seizures balance each other in such a way that it did not reflect in the proportions.

PREDICTORS AND NON PREDICTORS

Two factors consistently predicted achieving remission off antiepileptic medication: intellectual disability and having more than 1 seizure in the period between 6 and 12 months on antiepileptic medication. Two types of model retained intellectual disability as independent predictor of seizure-free status off medication: models that included only variables assessed at intake/onset, and models that combined variables assessed at intake/onset with those only assessable after 1 year of follow up such as having more than 1 seizure in the period between 6 and 12 months on antiepileptic medication.

The risk estimates from models with only intake/onset variables vary widely, but with overlapping 95% confidence intervals. The model from the combined Dutch and reconstituted Nova Scotia cohorts estimated that children with intellectual disability are 23% (95%CI 6% to 39%) less likely to achieve remission off medication than intellectually normal children.(106) The estimate was much higher in the other 2 studies which were more prone to bias: 75% (95%CI not stated) in Camfield et al(71) with generalised absence seizures and known poor prognosis excluded, and 77% (95%CI 26% to 93%) in Oskoui et al,(72) a retrospectively ascertained, hospital based cohort.

The risk estimates from models with both intake/onset and 1 year variables are also from these 2 more biased cohorts, showing that children with intellectual disability are 81% (95%CI 41% to 94%) less likely than intellectually normal children to achieve remission off medication in Oskoui et al(72) and 71% (95%CI not stated) in Camfield et al. (71) However, the fact that the 4 estimates from 2 possibly biased studies are similar may be due to the fact that the true

estimate of the risk of not achieving remission off medication may be closer to the estimate from the study(106) that is less likely to be biased.

These same 2 potentially biased studies had models with both intake/onset and 1 year variables which show that children with more than 1 seizure in the period between 6 and 12 months while on antiepileptic medication are: 75% (95%CI not stated) and 76% (95%CI 40% to 90%) less likely to achieve remission off medication compared with children who have 1 or no seizure 6 to 12 months on medication.

None of the other variables such as gender, age at onset, number of seizures before intake into cohort, abnormal EEG, epilepsy syndrome and abnormal sign on neurological examination that were assessed in more than 1 study, were consistently retained as an independent predictor of remission off AED in children with newly diagnosed epilepsy.

EXTERNALLY VALIDATED MODELS

Three models were externally validated and of the 3 models, 1 was derived with Cox regression and 2 were derived by logistic regression. Neither of the logistic regression-derived models reported the area under the receiver operating characteristics (ROC) curve, AUC, an important measure of discrimination. However, the 2 logistic regression models reported the best probability cut off (≈50%) at which the accuracy of the model was assessed and reported. None of the 3 models was assessed for calibration.

The model that was derived using the reconstituted Nova Scotia cohort performed slightly worse in the external validation study in the Dutch cohort.(106) Specificity reduced from 69% to 58% in external validation, while sensitivity increased marginally from 69% to 71%. This shows that the model's ability to detect negative outcome (no remission off AED) was poorer compared to its ability to detect patients with remission off AED. The positive and negative predictive values show that positive prediction was right 73% of the time, whereas negative prediction was right in only 35% of the instances when it was made. However, the PPV and NPV were expectedly higher in the validation study (PPV rises from 73% to 76%, NPV from 35% to 53%) owing to the fact that the pre-test probability (i.e. proportion of cohort with outcome, being in remission off AED) was higher in the validation sample at 65% compared to 55% in the derivation cohort.(279) This means that in the validation cohort, just knowing that a child has epilepsy allows the prediction of remission off AED to be right 65% of the time. However, if the prediction were to be based on the model and not prevalence, the positive predictive gain only improves by 11%, compared to the negative predictive gain that rises by 18%. However, in spite of these predictive gains, the model predicts wrongly in about 1 out of 3 children, although worse in the external validation cohort (36% vs. 31%).

The second externally validated model that was derived using logistic regression was developed on the Dutch cohort and validated on the reconstituted Nova Scotia cohort.(106) Specificity was

remarkably worse (reduced from 70% to 57%) in external validation with a marginal increase in specificity (66% to 67%), showing that the model's ability to detect negative outcome (no remission off AED) was better compared to its ability to detect patients with remission off AED in external validation. In spite of lower pre-test probability in the validation cohort (55% vs. 65%), the NPV slightly increases from 55% in derivation cohort to 56%. The PPV however reduces from 79% to 67%. Therefore, in external validation, the positive predictive gain was 12% while the negative predictive gain was 11% above pre-test probability. However, in spite of these predictive gains, the model predicts wrongly in about 1 out of 3 children, although worse in the external validation cohort (39% vs. 31%).

The model derived from the Nova Scotia cohort by Camfield et al(71) using Cox regression had a marked loss in sensitivity when externally validated in the Turku cohort (74% to 47%), although the specificity increased from 64% to 88%. However, owing largely to the pre-test probability being higher in the validation cohort, (60% vs. 54%) the PPV increases from 71% to 84%, although the NPV decreases to 51% from 67%. Therefore from a pre-test probability of 60% in the validation cohort, the model increases the accuracy of positive prediction by 24% and of negative prediction by 11%. The increase in positive prediction over pre-test probability may however be due to the fact that instead of predicting remission off AED in external validation, the model was used to predict remission on or off AED, a decision that was justified by the argument that the physicians handling patients within the Turku cohort were reluctant to discontinue medication and as 75% of those with 3 year remission at last follow up had been in remission for at least 10 years, it was considered unlikely that these patients would relapse off medication. However, the model predicts wrongly in about 1 out of 3 children, and worse in the external validation cohort (39% vs. 32%).

The 3 externally validated models have not been evaluated prospectively in a randomised clinical trial to assess their effect in clinical practice, possibly owing to their poor performance and the fact that they only reported probabilities, which did not necessarily recommend any particular course of action that may be assessed in a trial. Only the model from the Nova Scotia cohort presented scores and the scores may be easy to use for physicians, as well as patients. The other 2 models did not present scores for their models, and with the variables included, (mostly of syndromic diagnosis) may not be quite as easy to assess for physicians and patients. Finally, 2 of the 3 models (Nova Scotia intake and Nova Scotia reconstituted) had the most consistent predictor variable, intellectual disability, in their model.

5.6 REMISSION ON OR OFF MEDICATION

PROPORTION WITH REMISSION ON OR OFF ANTIEPILEPTIC MEDICATION

Four study factors were important in explaining the variation in the proportion of patients that was reported to have achieved remission on or off medication among the cohorts and studies:

the definition of remission, the length of follow up, the study design, and the age of patients within the cohort.

In studies that described their outcome as terminal remission (number of seizure-free months or years immediately before the last follow up) the proportion of the cohort in remission varied according to the length of seizure-free period that defined terminal remission: the proportion in remission rises with length of follow up and falls with the length of terminal remission. When it was 3 month terminal remission with 1 year minimum follow up, the proportion in remission is as low as 50%.(93) It rises to between 73% and 76%, with 1 to 3 years terminal remission when the minimum follow up ranged from 5 years to 20 years,(66, 68-70) and drops to 64% when 5 years seizure-free period defined terminal remission, even though the minimum follow up was 20 years.(32) For 2 largely prospective studies that defined terminal remission as 1 year seizure-free period,(66, 70) the proportion of patients in remission remained at 76% in spite of doubling (5 and 10 years) of minimum length of follow up between the 2 studies. (Box 18) These findings show that it does take time for people with newly diagnosed epilepsy to enter terminal remission; however, after a time period, possibly 5 years, patients who will ultimately enter remission would already have achieved the outcome.

However, the result from Hui et al(97) a study of an adult cohort, had a lower proportion of patients in remission relative to all the other comparable studies conducted in childhood onset epilepsy. The proportion in remission for prospective studies was also higher than in comparable cohorts with mixed and retrospective case ascertainment. This is in keeping with the evidence that retrospective studies introduces bias to estimates of proportion of patients in remission(20) and that childhood onset epilepsy may have a better prognosis than adult-onset epilepsy. (48, 303-305)

Box 18 |Remission as seizure-free period immediately before last assessment i.e. Terminal Remission (TR)

50% - 3 month TR with 1 year minimum follow up | Banu et al (Retrospective)
69% - 6 month TR with 2 years minimum follow up | Arts et al 1999 (Prospective)
60% - 1 year TR with 1 year minimum follow up | Hui et al 2007 (Mixed)
73% - 1 year TR (length of follow up not stated) | Lossius 1999 (Retrospective)
76% - 1 year TR with 5 years minimum follow up | Arts et al 2004 (Prospective)
76% - 1 year TR with > 10 years minimum follow up | Sillanpaa et al 2009 (Prospective)
76% - 3 year TR with > 20 years minimum follow up | Sillanpaa 1990 (Mixed)
64% - 5 year TR with > 20 years minimum follow up | Sillanpaa et al 1998 (Mixed)

Eight studies defined remission by the seizure-free period during follow up, which may or may not be terminal. Three (101, 104)of the 8 studies did not present the proportion of patients in remission. Of the 5 that presented the proportion with outcome, as expected, the percentage of patients in remission decreased as the number of seizure-free years that defined remission increased. In these studies, the proportion of patients in remission was higher for the same number of years when compared with those that entered terminal remission for the same

number of years and with comparable length of follow up. This is also an expected pattern as relapses may occur at any time to truncate terminal remission, whereas what is needed to satisfy the definition “seizure-free period during follow up” is 1 stretch of the designated seizure-free year(s) at any point during follow up.

Box 19 | Remission (R) as seizure-free period during follow up

80% - 1 year R with 1 year minimum follow up | Abduljabbar et al 1998 (Mixed)
78% - 1 year R (during the last 10 of min. 20 years) follow up | Sillanpaa 1993 (Mixed)
74% - 2 year R with 2 years minimum follow up | Berg et al 2001b (Prospective)
68% - 2 year R by 5 years of follow up | CGSEPI 1992 (Mixed)
51% - 3 year R by 5 years of follow up | CGSEPI 1992 (Mixed)

One study (24)had a different measure for refractoriness (not achieving remission) which was defined as having multiple recurrences of up to 10 seizures within about 8 years. In their cohort, patients were initially identified at the point of first seizure, and the diagnosis of epilepsy prospectively was confirmed with the second seizure. Of the patients with epilepsy 71% did not have 10 recurrences after a mean follow up of about 8 years. Therefore the predictors considered in this study included pre-diagnosis variables such as having the second seizure (which confirms the diagnosis of epilepsy) within 1 year of the first.

PREDICTORS AND NON PREDICTORS

There were 5 consistent predictors of achieving remission on or off antiepileptic medication: having mixed seizure types at onset, symptomatic aetiology, intellectual disability, number of seizures before index and the number of seizures in the first 6 months of follow up.

The finding from an all age cohort was that patients with mixed seizure types at onset are 30% (95%CI -4% to 63%) less likely than patients with a single seizure type to achieve remission on or off medication, although the 95% confidence interval crosses zero for this estimate and so may not be reliable.(64) However, in childhood onset epilepsy, the odds of achieving remission are about 1 in 4 [0.23 (95%CI 0.10 to 0.48)] for patients with multiple seizure types at onset compared to those with a single seizure type at onset.(93) However, this estimate may also not be reliable as it was from the study (93) that defined remission as 3 month terminal remission, rather than much longer (e.g. 6 months to up to 5 years) as in the other studies that defined remission as terminal remission.

None of the 4 studies (21, 24, 77, 104) that retained remote symptomatic aetiology in their model defined remission as terminal remission. Three defined remission as “seizure-free period during follow up” and 1 defined remission as not having up to 10 recurrences in an average of 8 years. However, the estimates from the 4 studies were similar. Of the 3 studies that defined remission more conventionally, (as “seizure-free period during follow up”), 2 were in childhood-onset epilepsy cohorts and of the 2, Berg et al(21) was the study with the less likelihood for bias as it is a population based prospective study. Berg et al(21) estimate that it was 37% (95%CI 16%

to 53%) less likely for children with remote symptomatic aetiology to achieve remission compared to children with idiopathic/cryptogenic aetiology. The other study(77) was from a mixed population based cohort, and the estimate was higher and with wider 95% confidence interval at 56% (95%CI 8% to 75%). The adult-onset epilepsy study(104) also estimated that it was 56% less likely for people with remote symptomatic aetiology to achieve remission compared to those with idiopathic and cryptogenic aetiology, but without reporting the 95% confidence interval. These estimates, particularly the similarity between the estimate from the childhood-onset epilepsy study with mixed case ascertainment and a retrospective adult-onset study suggest that the bias of the childhood-onset study may be towards a poorer prognosis for achieving remission.

Intellectual disability was retained in 2 models: The odds of achieving remission are 4 in 10 [0.40 (95%CI 0.18 to 0.90) in children with intellectual disability compared to those with normal cognitive development.(93) However, for adults-onset epilepsy, the odds are 1 in 10 [0.10 (95%CI 0.05 to 0.25)].(97) These results suggest that intellectual disability may be a more important predictor of not achieving remission in adult-onset epilepsy compared to patients who are diagnosed in childhood.

Two studies from different cohorts retained the natural logarithm of the number of seizures before index in their models. For Arts et al(65)the risk of achieving remission reduced by 34% (95%CI 5% to 54%) for every unit increase in the natural logarithm of the number of seizures a child has before the index seizure at presentation, and for MacDonald et al(101) by 19% (95%CI 1% to 34%) for every unit increase in the natural logarithm of the number (plus 1) of seizures a child has before the index seizure at presentation. This finding further suggests that “seizures beget seizures”(49) could be true in that increasing number of seizures a child experiences before intake/medication reduces the probability of achieving remission on or off medication.

The same studies also retained the natural logarithm of the number of seizures from the index seizure to 6 months after intake/medication in their models, showing that early response to antiepileptic medication is a predictor of eventual remission: For Arts et al(65)the risk of achieving remission reduced by 50% (95%CI 28% to 65%) for every unit increase in the natural log of the number (plus 1) of seizures a child has from the index seizure to 6 months after intake/medication, and for MacDonald et al(101) by 41% (95%CI 30% to 50%) for every unit increase in the natural log of the number (plus 1) of seizures a child has from the index seizure to 6 months after intake/medication.

The other variables not consistently predictive of remission on or off medication include age at onset, gender abnormal EEG at intake and the range of seizure types considered as were factors like family history of epilepsy, history of neonatal seizures and the specific aetiological factors considered.

EXTERNALLY VALIDATED MODELS

Two models were derived in Arts et al 1999 by logistic regression(65) (one with only intake variables, and the other including both intake and 6 month variables) were temporally validated. (107)

The model with only intake variables was calibrated, with a plot of 4 risk groups of unequal size. The calibration plot suggests that the model was well calibrated with the percentage of children correctly predicted not to achieve remission increasing with the predicted chance of not achieving remission, although calibration was not assessed using a formal statistical test. The model however had poor discriminative ability (AUC <0.70) on both internal and external validation. For the model, the chosen best probability cut-off was 38%: i.e. probability value greater than 38% indicates not achieving 6 month terminal remission.(107)

The model performed slightly worse on external validation with sensitivity reducing from 62% to 60% in external validation, and specificity from 69% to 61%. This shows that the model's ability to detect poor outcome (no 6 month terminal remission at 2 years) was similar to its ability to detect positive outcome (6 month terminal remission at 2 years) in the external validation population.(107) However, the NPV increases as expected from 20% to 25%, but the PPV reduces marginally from 47% to 45% in spite of the fact that the pre-test probability (i.e. proportion of cohort with outcome, not achieving 6 month terminal remission) was higher in the validation sample at 34% compared to 31% in the derivation cohort. Therefore, in the validation cohort, the knowledge that a child is within that cohort allows for a prediction of a child not entering remission to be correct 34% of the time (pre-test probability). However, if the prediction is based on the model and not prevalence, the positive prediction improves by 11%, compared to a loss of 9% in negative prediction. The model also predicts wrongly in more than 1 out of 3 children in internal and external validation. The negative predictive loss may be due to the fact that the cut-off model was particularly set to enhance sensitivity at the expense of specificity, thereby allowing for better prediction of not achieving 6 month terminal remission at 2 years.

The model with intake and 6 month variables was also calibrated, with a plot of 4 risk groups of unequal size. The calibration plot suggests that the model was well calibrated with the percentage of children correctly predicted not to achieve remission increasing with the predicted chance of not achieving remission, although calibration was not assessed using a formal statistical test. The model however had a fairly good discriminative ability (AUC >0.70) on both internal and external validation. The best probability cut-off for the model was 34%: i.e. probability value greater than 34% indicates not achieving 6 month terminal remission.(107)

The model performed worse on external validation with sensitivity reducing from 73% to 67% in external validation, and specificity from 73% to 60%. This shows that the model's ability to detect poor outcome (no 6 month terminal remission at 2 years) was better than its ability to

detect positive outcome (6 month terminal remission at 2 years) in the external validation population.(107) However, the NPV increases as expected from 14% to 22%, but the PPV reduces from 55% to 47% in spite of the fact that the pre-test probability (i.e. proportion of cohort with outcome, not achieving 6 month terminal remission) was higher in the validation sample at 34% compared to 31% in the derivation cohort. Therefore, in the validation cohort, the knowledge that a child is within that cohort allows for a prediction of a child not entering remission to be correct 34% of the time (pre-test probability). However, if the prediction is based on the model and not prevalence, the positive prediction improves by 13%, compared to a loss of 12% in negative prediction. In spite of its positive predictive gain over pre-test probability, the model also predicts wrongly in more than 1 out of 3 children in internal and external validation. The negative predictive loss, as in the first model may be due to the fact that the cut-off model was particularly set to enhance sensitivity at the expense of specificity, thereby allowing for better prediction of not achieving 6 month terminal remission at 2 years.

Each of the models contained 2 of the 5 factors found to be consistent predictors of remission: model with intake only variables (natural logarithm of the number of seizures before intake, and remote symptomatic aetiology) and model with intake and 6 month variables (natural logarithm of the number of seizures in the first 6 months after intake, and remote symptomatic aetiology). They both presented scores for the assessment of risk, although the scores were complex, the predictors many and the models may not be easily used by physicians and patients. The models however have not been assessed in a randomised study to confirm their usefulness in a clinical setting.

5.7 INTRACTABILITY

PROPORTION WITH MEDICALLY INTRACTABLE SEIZURES

Two factors explained the differences in the proportion of patients with medically intractable seizures in individual studies: how intractability was defined and the study design/setting. Medically intractable seizures is usually defined as having “at least 1” or “more than 1” seizure per month for about 1 year (ranged between at least 6 months and at least 2 years) after more than 2 antiepileptic drug trials singly or in combination, at their maximum tolerable dose.(78)

However, studies that defined intractability as having “1 or more” seizures per month (72, 75, 76) had more patients who met the criteria for intractability (13% to 14%) compared to the studies(73, 74) that defined intractability as only “more than 1” seizure per month (9% to 10%). The were 2 outliers, both from retrospective hospital based cohorts: the one that defined intractability as having recurrent seizures in the 6 months immediately before last follow up had 7% while the other, even though it defined intractability as having “at least 1” or more seizures per month, one third (32.5%) of the cohort met the criteria for intractability. (78)

Box 20 | Influence of definition and study design/setting on the proportion of patients with intractable seizures

07% - “6 months recurrent” | Retrospective, Hospital | Oskoui et al 2005
09% - “At least 1 Seizure” | Mixed, Hospital | Ramos-Lizana et al
10% - “At least 1 Seizure” | Prospective, Population | Berg et al 2001a
13% - “More than 1 Seizure” | Retrospective, Hospital | Oskoui et al 2005
14% - “More than 1 Seizure” | Prospective, Population | Casetta et al 1999
14% - “More than 1 Seizure” | Mixed, Population | Kwong et al 2003
33% - “At least 1 Seizure” | Retrospective, Hospital | Berg et al 1996

PREDICTORS AND NON PREDICTORS

Five variables were consistently retained in models as independent predictors of having medically intractable seizures: age at onset (continuous variable), onset of seizures in infancy (age < I year), remote symptomatic aetiology, idiopathic aetiology and intellectual disability.

Three studies had models that retained age at the onset of epilepsy (as a continuous variable) as an independent predictor of medical intractability. One of the studies(78) was a remarkably biased retrospective hospital based study with about a third of the cohort having intractable seizures. The second study (75) has an estimate that was not significant as the confidence interval that crosses unity, hence unreliable. The third study(79) is also likely to be biased in terms of study participation as there was also an over-representation of patients with intractable seizures (being about 4 times as many as patients who are in remission).

However, when onset of seizures at less than 1 year was considered, 3 studies retained it in their model. Ramos-Lizana et al(74)estimated that people with onset of seizures at infancy were 2.6 (95%CI 1.0 to 6.9) times more likely to have medically intractable seizures compared to children whose seizures begin after the age of 1. The estimate is remarkably similar at 2.6 (95%CI 1.1 to 4.30) in Casetta et al(75). The third estimate is however different from the other 2, possibly because the study by Chawla et al(94) may be particularly prone to bias. In the quality appraisal for potential for bias, it was unlikely to be biased in only 1 area of potential bias (multivariate analysis) out of 5 (others being study participation, study attrition, prognostic factor measurement and outcome measurement). For the study,(94) the estimate was that people with onset of seizures at infancy were 3 (95%CI 2.0 to 3.6) times more likely to have medically intractable seizures than children whose seizures begin after the age of 1.

Of the 4 models that identified remote symptomatic aetiology as an independent predictor of medically intractable seizures, 3 were particularly prone to bias. Two (78, 79) of the 3 were estimates from cohorts within which patients with intractable seizures were significantly over-represented. The third study was Chawla et al(94) which was unlikely to be biased in only 1 out of 5 areas of potential bias assessed in the studies included in this review. The 3 estimates from bias prone studies were similar with relative risk between 1.34 and 2.06 and largely overlapping confidence intervals. However, Casetta et al(75) estimates that it is about 5.48 (95%CI 2.10-

9.64), indicating that children with remote symptomatic aetiology are 5.5 times more likely to have medically intractable seizures than those with idiopathic/cryptogenic aetiology.

Three studies identified idiopathic aetiology as an independent predictor of intractable seizures in that children with idiopathic aetiology are less likely than those with symptomatic aetiology and cryptogenic aetiology to develop intractable seizures. However, 1 of the studies had an atypical definition of intractability (recurrent seizures in the 6 months before last follow up or requiring surgery or ketogenic diet to control seizures); the study estimates that it is 87% (95%CI 48% to 97%) less likely for a patient with idiopathic epilepsy to develop intractable seizures compared to children with symptomatic/cryptogenic aetiology. Estimates from the other 2 studies estimate are similar: 80% (95%CI 20% to 100%) less likely and 77% (95%CI 37% to 91%) less likely to develop intractable seizures with idiopathic aetiology than children with symptomatic/cryptogenic aetiology.

Intellectual disability was also shown to consistently predict medically intractable seizures. The odds of having intractable seizures are 7 times [7.2 (95%CI 1.0-50.8)] in 1 study,(72) albeit with EPV less than 10, and much higher in the other study which is less likely to be biased(76) at 18 times [18.2 (95%CI 5.2-63.6)] greater for children who have intellectual disability and/or cerebral palsy relative to those with normal cognitive development and without cerebral palsy. However, the confidence interval is remarkably wide for both estimates, which is probably due to few children in both studies having intellectual disability.

However, other potential predictors such as mixed seizure types, specific seizure types, seizure frequency, abnormal EEG, occurrence of status epilepticus, and family history of epilepsy or history of neonatal seizures, and were not found to be a predictor of intractability.

5.8 REMISSION AFTER RELAPSE

There was only 1 study(25) in this category. This fact precludes much further discussion. However, the study showed that the odds of not achieving remission after a relapse are about 8 times as high in children with remote symptomatic aetiology compared to those without symptomatic aetiology.

5.9 IMPLICATIONS FOR CLINICAL PRACTICE

The results of this review suggest that in deciding whether to initiate antiepileptic drug therapy in patients with newly diagnosed epilepsy, particular consideration should be given to whether the newly diagnosed patient is a child or an adult, if the epilepsy has asymptomatic aetiology and also possibly the occurrence of more than 1 seizure before the index seizure.

In making the decision, or in advising patients already in remission on whether to discontinue antiepileptic drug therapy, it may be important for physicians to be more reluctant or more

careful in patients with intellectual disability and those who had more than 1 seizure during the period between 6 and 12 months while on medication.

Patients with mixed seizure types at onset, remote symptomatic aetiology, intellectual disability, high number of seizures before diagnosis and poor early response to medication indicated by more than 1 seizure in the first 6 months of antiepileptic medication may require a more aggressive treatment strategy to prevent their seizures from becoming refractory to antiepileptic medication.

The children with onset of seizures in infancy (age < I year), with remote symptomatic aetiology, and intellectual disability, unlike children with idiopathic aetiology may require a more aggressive treatment strategy to prevent their seizures from becoming medically intractable and to also be managed with a view to early consideration of epilepsy surgery within 2 years of diagnosis. The parents and relatives of the children with these risk factors, especially when they occur together in the same child may need to be informed early on in the course of the illness regarding the possibility of intractability and the management strategies that may be necessary in addition to pharmacological intervention in case of intractability.

In all, there are at present no satisfactory prediction models for any of the outcome categories. It may suffice however to inform and advise patients and their relatives based on the proportion of patients that achieve each outcome. These predictors may be all that is presently available for the purpose of devising management strategy early in the course of the disease and for advising patients.

5.10 DIRECTIONS FOR FUTURE RESEARCH

This segment presents the suggested directions and recommendations for future studies related to this systematic review. These issues are discussed under the sub-headings based on the key areas of this review: the literature search, reporting characteristics and quality appraisal of studies, the classification of studies included in this review and the results of the review of prognostic factor studies in newly diagnosed epilepsy.

THE LITERATURE SEARCH

Four recommendations are made based on findings from the literature search: 1) There is need for more evidence on the number and exact databases that would be necessary to search in order to identify observational studies. Previous research on this issue has focused on identifying randomised trials. 2) Future systematic reviews of studies containing multivariate analysis may benefit from concentrating their search period to say the last 20 years. 3) Future systematic reviews of observational studies in epilepsy may benefit from hand-searching recent editions of *Epilepsia* especially where the resources are available, and the search does not include EMBASE as the 4 publications unique to EMBASE were actually published in 2009 and

2010 in MEDLINE-indexed journals. 4) The clinical uptake of the results of future studies of prognosis in newly diagnosed patients with epilepsy may benefit from authors and journal editors choosing to publish some of those studies in non-specialist and primary care journals.

QUALITY AND REPORTING CHARACTERISTICS

Four recommendations are made based on findings from quality appraisal and reporting characteristics of included studies: 1) To enhance the robustness of multivariate analyses, it may be necessary to engage in international collaboration studies in order to boost the number of patients included in analyses. This may have the added advantage of rare syndromes being better represented in multivariate analyses to better ascertain their prognostic significance, and for including studies based in Africa and Australasia as none of the studies in the review included patients from the 2 continents. 2) It would be beneficial in assessing the quality of future observational studies and for future systematic reviews if authors and journals adhered to the STROBE checklist as minimum standard for reporting observational studies. 3) It may also be possible therefore for a future systematic review to compare the reporting characteristics of publications in STROBE-endorsing journals with journals that leave the reporting of observational studies to the discretion of authors. 4) The review, especially of studies predicting medical intractability, shows that studies with a higher potential for bias according to the quality items used in this review have risk estimates that differ in most cases remarkably from studies with a lower potential for bias. There is need for further research into ways of adapting the Hayden et al criteria to reviews of prognosis studies in other subject areas.

THE CLASSIFICATION OF STUDIES

The classification scheme developed in this thesis has a potential advantage for future studies because study categories were presented with the prognostic sub-groups (i.e. potential seizure outcome categories) used to define and delineate comparison groups. It would be a task of future studies of seizure outcome of newly diagnosed epilepsy to determine the proportion of patients in each sub-group. To ease and facilitate subsequent systematic reviews and meta-analyses, authors of future studies of seizure outcome in patients with newly diagnosed epilepsy may locate their study within this classification scheme or its extension and label them as such. This will also allow results of the studies to be interpreted more easily and readily within the context of previous studies in the same category.

PROGNOSTIC FACTOR STUDIES IN NEWLY DIAGNOSED EPILEPSY

Further studies of immediate remission in newly diagnosed epilepsy will benefit from ensuring prospective case ascertainment at the point of a second seizure as this is the most important factor determining the proportion with outcome in this category of studies of seizure outcome in newly diagnosed patients with epilepsy.

The deliberate inclusion of the consistent predictors of outcome across seizure outcome categories, especially remote symptomatic aetiology and intellectual disability and of 1 year

variables, especially of the occurrence of seizures within the first year after diagnosis or while on medication may also be important in studies predicting remission off medication, and remission on or off medication.

The fact that intractability is a rare outcome, occurring in less than 15% of cohorts makes it particularly important for future studies to ensure that sample size is adequate to build the model with at least 10 events per independent variable entered into the model.

There should also be studies investigating predictors of seizure outcome in patients with adult-onset epilepsy as most the studies eligible for this review were in childhood-onset epilepsy.

The distinguishing characteristic of the only study that investigated remission after relapse is that it is a cohort with long follow up, ranging from 11 to 42 years.(25) It would require such long follow up to determine patients who will relapse, and then following relapse achieve terminal remission or not achieve terminal remission. Therefore, it is hoped that presently existing cohorts will continue to be followed so that we can better understand the characteristics that influence achieving remission after relapse(s) and of other seizure outcome categories.

5.11 STRENGTHS AND WEAKNESSES OF THE REVIEW

This review of prognosis studies in unselected populations of patients with newly diagnosed epilepsy has accomplished its aim of classifying studies, exploring heterogeneity, and identifying consistent predictors of seizure outcome in patients with newly diagnosed epilepsy. The main strengths of this thesis are its thorough examination of studies included for their potential for bias and exploration of sources of heterogeneity. The review was focussed specifically on studies with multivariate regression analysis because they are best suited to control for possible confounding bias(23). The thesis has also explored other potential sources of bias, using objectively identified and clearly defined criteria.

The studies included in the review were also classified such that like was compared to like within the study categories. The study also fills an important gap in the literature as there has been no previous review of the methods and results of prognosis studies that identified independent predictors of seizure outcome in newly diagnosed epilepsy. The quality appraisal items for systematic reviews of prognosis studies developed by Hayden et al(39) and adapted for use in this review have not been tested for validity and reliability. This review provides an instance where the quality items have been adapted for use in a specific subject area.

However, the work has several limitations and future discussion on the methods of identifying and handling consistent independent predictors in systematic reviews and meta-analysis is needed. There is a potential drawback to predictors identified by multivariate analysis, especially when it is in studies not aimed at investigating the predictive value of a particular

prognostic variable, and when a stepwise algorithm is used in selecting variables to include in the model.(45) It has been demonstrated through multiple bootstrap and split-sample analyses that the models so derived have low reproducibility within the same study sample.(306) However, the strategy this review employed to mitigate potentially spuriously identified predictors was to stipulate from the outset that only predictors identified in more than 1 study conducted by different groups on different cohorts will be considered to be consistent predictors of a particular outcome.

The discussions particularly relating to exploring factors that may explain the variations in the proportion of patients with seizure outcome in each category of studies is limited by the fact that only studies with multivariate analysis were included in the review. There are more studies in the literature that may have determined these proportions and might have thus provided more material for the discussions. However, the sample of studies in each category provides a heterogeneous sample of studies. Therefore there were enough studies on which to base the exploration and discussions in order to understand the characteristics that explain biases in the studies in each category.

The Zhang-Yu equation(266) was used where possible to convert the odds ratios from logistic regression analyses in order to approximate relative risk. The equation allowed for comparison of odds ratio with the risk estimates (hazard ratios) from Cox regression analyses, which was assumed to be a good approximation of relative risk. However, the conversion of odds ratio to relative risk is in itself only an approximation. (307, 308) The formula has been shown to account for only 85% of the required adjustment of odds ratio towards the relative risk. The 95% confidence intervals calculated using the formula are also much narrower, with the results from the formula being only about two thirds (67%) of the appropriately determined 95% confidence interval of the relative risk.(308) However, the Zhang-Yu equation provides a useful approach to interpreting risk estimates from logistic regression in a way that enhances comparison with the relative risk which is more intuitive to understand. There is a need to use alternatives to the odds ratio because of the limitations(308) of the Zhang-Yu equation.(266) Results of simulation studies have shown that there are viable alternative models to the logistic regression model.(309, 310) These models (Poisson regression and log-binomial regression) better approximate the relative risk and could be used on longitudinal data with binary outcomes.(309)

There is a possibility of selection bias in this systematic review. The prognosis studies that did conduct multivariate analysis to identify independent predictors may be of higher quality. There may be publication bias as studies with significant results (i.e. that identified independent predictors) may be more likely to get published. The search strategy yielded reviews published in English-language, peer-reviewed, MEDLINE- and EMBASE-indexed journals with adequate keywords and Medical Subject Heading (MeSH) or Emtree terms. There was no search of the grey literature. The methods used to identify publications may have missed some eligible, likely lower quality publications. However, given time and budget constraints, it was not feasible to search the grey literature or to translate non–English-language publications. Indeed, given that

the search is likely exhaustive within its limited framework, these factors are unlikely to have had much impact on the results and recommendations of this review.

For the same purpose of time and budget constraints, the data extraction, quality appraisal and calculations were conducted by 1 reviewer. This is a potential source of error and bias in the systematic review. However, the reviewer (MPhil candidate) extracted the data directly from the relevant publications 3 times while checking against the previous extraction at each stage to ensure accuracy. The quality appraisal was also conducted transparently and the information upon which quality appraisal was based was explicitly reported in the review such that researchers and practitioners can independently assess the quality of the studies included in the review. There was also limitation due to incomplete reporting by authors as only published data was used and the MPhil candidate did not contact authors to obtain additional information due to time constraints. However, the candidate searched referenced papers and also publications from the same group or cohorts for additional information where such information may be important for the quality appraisal.

Indeed, this work has several limitations. Future research should continue to discuss, debate and explore bias in prognosis studies and how to identify independent predictors of outcomes from studies conducted by multivariate analysis. This will further develop, expand and establish this burgeoning area of interest.

6 CHAPTER SIX: CONCLUSION

This thesis has shown that although a wide range of variables have been considered across the different seizure outcome categories, only a few have been consistently confirmed as being statistically significant independent predictors in multivariate analysis. The study demonstrates the feasibility of systematic review with thorough quality appraisal as a means of identifying the consistent predictors of an outcome in studies that do not specifically investigate one particular prognostic variable. Table 24 summarises the independent predictors and presents the least biased estimate for childhood-onset and adult-onset epilepsy from each study category:

1.) Having more than 1 seizure before intake and remote symptomatic aetiology were positive predictors of recurrence of seizure after intake (i.e. no immediate/early remission) in childhood-onset and adult-onset epilepsy.

2.) Having more than 1 seizure in the period between 6 and 12 months on medication and intellectual disability were negative predictors of achieving remission off medication in childhood-onset epilepsy. None of the studies in this category considered adult-onset epilepsy.

3.) Having more than 1 seizure before intake, having seizures in the first 6 months after the index seizure, mixed seizure types at onset of epilepsy, intellectual disability and remote symptomatic aetiology were negative predictors of achieving remission on or off medication in both childhood-onset and adult-onset epilepsy.

4.) Having onset of seizures in infancy, intellectual disability, and remote symptomatic aetiology were positive predictors of medical intractability, while idiopathic aetiology was a negative predictor of intractability in childhood-onset epilepsy. None of the studies in this category considered adult-onset epilepsy.

The neurobiology of epilepsy is heterogeneous. Therefore the aetiological classification, number of seizures, mixed seizure types, and comorbidity with intellectual disability that feature among independent predictors of seizure outcome may not fully capture the details of the biology, and possibly the prognosis of epilepsy. Important as the independent predictors are, they may not be important in the consideration of treatment and interventions in individual patients. For example, some types of seizure manifestation (e.g. focal seizures without impaired consciousness, absence seizures or seizures occurring only during sleep), and the benefits of treatment may not outweigh the potential adverse effects of medication. When seizures occur infrequently, even when the seizures are of a more severe form, the benefits of treatment over adverse effects also have to be weighed on a case by case basis.(8) Therefore these predictors can only serve as flexible guides to treatment and overall management strategy.

Table 24 | Consistent early predictors of seizure outcome in newly diagnosed epilepsy

	IMMEDIATE REMISSION	REMISSION OFF MEDICATION	REMISSION ON OR OFF MEDICATION (REMISSION)	MEDICAL INTRACTABILITY
ONSET OF SEIZURES IN INFANCY (AGE < 1YEAR)				RR 5.48 (95%CI 2.10-9.64) **C**
MORE THAN 1 SEIZURE BEFORE INTAKE	RR NOT STATED **CA** RR 0.63 (95%CI 0.36-1.11) **A**		RR 0.66 (95%CI 0.46-0.95)* **C** RR 0.81 (95%CI 0.66-0.99)* **CA**	
NUMBER OF SEIZURES FROM INTAKE TO 6 MONTHS			RR 0.50 (95%CI 0.35-0.72)‡ **C** RR 0.59 (95%CI 0.50-0.70)‡ **CA**	
NUMBER OF SEIZURES, 6 TO 12 MONTHS ON MEDICATION		RR 0.24 (95%CI 0.10-0.60) **C**		
MIXED SEIZURE TYPES AT ONSET			RR 0.70 (95%CI 0.37-1.04) **CA** OR 0.23 (95% CI 0.10-0.48) **A**	
INTELLECTUAL DISABILITY		RR 0.77 (95%CI 0.61-0.94) **C**	OR 0.40 (95%CI 0.18-0.90) **C** OR 0.10 (95%CI 0.05-0.25) **A**	OR 18.2 (95%CI 5.2-63.6) **C**
REMOTE SYMPTOMATIC AETIOLOGY	RR 0.59 (95%CI 0.41-0.86) **C** RR 0.44 (95% CI 0.26-0.77) **A**		RR 0.63 (95% CI 0.47-0.84) **C** RR 0.44 (95% CI NOT STATED) **A**	RR 5.48 (95%CI 2.10-9.64) **C**
IDIOPATHIC AETIOLOGY				RR 0.20 (95%CI 0.0-0.80) **C**

RR-Relative Risk, OR-Odds Ratio, C-Estimate from childhood-onset epilepsy, A-Estimate from adult-onset epilepsy, CA-Estimate from cohort with both childhood-onset and adult-onset epilepsy

*Relative risk of the natural logarithm of every additional seizure before intake

‡Relative risk of the natural logarithm of every additional seizure in the first 6 months of follow up.

The findings of this systematic review, especially of lack of association of several factors with seizure outcome, is in keeping with a dated systematic review by Berg and Shinnar in 1991(44) which identified factors associated with recurrence after first seizure, although mostly in studies with univariate analysis. They found, as in this thesis, that age at onset, gender, abnormal EEG, family history of epilepsy, history of neonatal seizures, status epilepticus or febrile seizures, antiepileptic medication were not consistently predictive of seizure outcome (recurrence after a first seizure). However, they also found that aetiology (remote symptomatic increasing the risk for recurrence and idiopathic with lower risk), was a consistent predictor of recurrence as was seizure type (focal seizures tend to recur after a first).

For Berg and Shinnar(44) as well, the method of case ascertainment was an important source of discrepancy in the proportion of patients with outcome as retrospective and mixed case ascertainment tend to result in biased estimates. In this thesis, the exploration of potential reasons for discrepancies in the proportion of patients with seizure outcome in each category was an illuminating exercise which yielded much information in assessing potential of individual studies for bias, and the differences in outcome between studies of childhood-onset epilepsy and those of adult-onset epilepsy. The adoption of this strategy in further systematic reviews of outcome in epilepsy is recommended.

Part of the sources of discrepancies in proportion of patients within cohorts with particular outcomes was the specific details of how seizure outcome measure was defined in each study. For example, studies that defined remission as terminal remission had fewer patients in remission relative to comparable studies that defined remission as seizure-free period during follow up. Therefore it is important to qualify estimates specifically by how they were defined in the study, the design of the study, the setting of the study, and the patient population in the study when quoting proportion of patients with any seizure outcome in epilepsy. It is also recommended that a future task for ILAE (International League Against Epilepsy) in updating the guidelines for epidemiological research in epilepsy(1, 2) will be to define to the specific details, the outcome measures (e.g. remission and intractability) that studies within the categories identified in this thesis will have to adhere.

The current models for predicting seizure outcome in newly diagnosed patients with epilepsy are neither accurate, nor have been rigorously developed and externally validated. The predictors identified in this thesis may therefore be the only reliable data currently available to allow the easy identification of those patients at the greatest risk of experiencing poor seizure outcome when newly diagnosed with epilepsy. Further research in this area would be of considerable importance not only in terms of increasing the understanding risk factors for poor outcome in epilepsy, but also in advancing health care delivery to improve patient care and reduce the burden of seizures on quality of life.

As challenging as they are to conduct, population based studies with prospective case identification at the point of second seizure remain the ideal study design for seizure outcome in epilepsy. More of these studies will need to be conducted, especially among the 3 populations that were not well represented in the cohorts on which the studies that made up this thesis were based: populations of people with adult-onset epilepsy, people in Australasia and people in developing countries, especially of Africa, as about 80% of epilepsy patients live in developing countries(3).

7 APPENDICES

7.1 Appendix I: PROTOCOL

EARLY PREDICTORS OF SEIZURE OUTCOME IN NEWLY DIAGNOSED EPILEPSY – SYSTEMATIC REVIEW OF PROGNOSIS STUDIES

INTRODUCTION

Prognosis studies investigate the relationship between occurrences of outcomes and predictors in defined populations of people with disease.(1, 2) The importance of prognostic research in epilepsy as in other chronic illnesses/diseases is overwhelming. They help to improve the understanding of the disease process, to guide treatment decision making (if and when to commence antiepileptic medication, if and when to have epilepsy surgery and other non-pharmacological interventions), and to predict the outcome of epilepsy more accurately for the purpose of patient information and counselling. (3)

However, in spite of the methodological demands, prognostic studies are usually not protocol driven, small sized, widely heterogeneous in characteristics of patients, choice and number of predictor variables, outcome and follow up measures, and often prognostic analyses are improvised as icing on the cake of studies designed for quite another purpose. For these reasons, the results of prognostic research are largely fraught with limitations, with attendant uncertainty about the reliability of conclusions of their synthesis/meta-analyses. (1)

This has led to the creation of a new Cochrane Prognosis Methods Group in 2008 aimed at providing support and a forum for discussion to facilitate and improve the quality of systematic reviews of prognosis research.(4) Systematic review of prognosis studies with particular focus on methodology is therefore a burgeoning field of interest, and there have been efforts at ensuring the quality of such reviews. Hayden et al have developed a set of criteria for quality assessment through a meta-review of systematic reviews of prognosis studies. (5)

There have only been systematic reviews in the literature of epidemiological studies that focus on incidence and prevalence of epilepsy generally(6) and with regional focus - Asia(7), Latin America(8), Middle East and North Africa(9), Europe(10) and sub-Saharan Africa(11). However, these studies, when they do, only make passing reference to the methodology and/or results of prognosis studies. Ross et al also systematically reviewed the literature, but on management issues in epilepsy from 1980 to 1999.(12) The studies on prognosis were therefore only partly considered and only in passing, without methodological rigour.

Parenthetically, also no systematic review has considered other outcomes in prognosis studies, important as they are: psychopathology outcomes (depression, anxiety, et cetera), neurodevelopmental outcomes (especially IQ in children), mortality, and quality of life measures. This will be the focus of future systematic review(s) following completion of the present one that is being proposed.

However, an epidemiological synthesis of the natural history of epilepsy by Kwan and Sander(13) suggest that there are three prognostic groups: group 1 (20–30%) comprises patients with excellent prognosis, as there is long term remission after a period of seizure activity, with or without antiepileptic drug treatment and the primary aim of antiepileptic drug treatment in this group of patients is to suppress seizures until 'spontaneous' remission occurs, and patients can be successfully withdrawn after

a period of seizure freedom; for group 2 (20–30%) seizure remission occurs only with treatment and patients only remain seizure-free with continuing antiepileptic drug treatment; and in group 3 (30–40%) there is continuing seizures despite antiepileptic drug treatment with some patients having frequent debilitating seizures qualifying them as having 'refractory' epilepsy.

Significance

Seizure outcome in epilepsy is varied. Epilepsy itself is a multi-aetiological and diverse disorder. The first seizure brings with it the opening of a fresh chapter in the life of the patient, with tough decisions to be made for the patient and for clinicians especially of when or whether to start medication as they carry risks of acute idiosyncratic reactions, dose-related and chronic toxic effects, and teratogenicity.

However, for most patients diagnosed with epilepsy, the benefits of treatment will far outweigh the risks associated with treatment, but for those who have had a single seizure and for those who have seizures with minor symptoms, this risk to benefit ratio is more finely balanced.(14) There is also the group of patients (Kwan & Sander's Group 3)(13) that may be candidates for epilepsy surgery as they will develop debilitating drug-resistant epilepsy; as seizures themselves are not benign events, there is the consequent considerable clinical and psychosocial distress or even mortality.

There is thus the need for studies that attempt to identify independent predictors of these seizure outcomes and also therefore useful to review the methodology and possibly synthesise the results of studies that have identified the factors which best predict clinically relevant seizure outcomes in patients that have been newly diagnosed with epilepsy.

There is a greater tendency for publication bias in observational studies compared to randomised clinical trials (15) and prognosis studies particularly so, as it is probable that studies showing a strong, statistically significant prognostic ability are more likely to be published and this can lead to invalid results and incorrect inferences.(16) The proposed review will therefore thoroughly assess for quality based on indices that reflect how prone the studies are to bias.

Objectives

This thesis aims to answer the following questions:

1.) What is the quality of prognosis studies that have attempted to identify independent predictors of seizure outcome among unselected population patients with newly diagnosed epilepsy?
2.) What is the effect of study quality, especially potential risk for bias, on the results of the prognosis studies?
3.) Which factors have been consistently identified as independent predictors of seizure outcome and which factors have been consistently identified as non-predictors?
4.) Do satisfactory seizure outcome prediction models already exist?

The review also proposes to assess the state of evidence of the prognosis of seizure outcomes in epilepsy with the view towards a possible synthesis of the results. A systematic review of methodology may also help in identifying areas of potential limitation and specific actions that may improve future investigations of prognosis in epilepsy.

METHODS

The guidelines for the design, performance and reporting for meta-analyses of observational studies published by the MOOSE group (17) will be followed in this systematic review.

Eligibility Criteria

The review will seek for inclusion, published cohort, nested case control and case control studies of unselected population of people with epilepsy that assess the independent effect of 3 (an arbitrary decision, following the example of Counsell and Dennis(18), based on the fact that 2 variables will be too few to give significant information about their independent effect) or more predictor variables on a range of measures of seizure outcome in patients with epilepsy collected within the first year of onset, diagnosis, or presentation, with patients followed up for at least 1 year. Only studies published in English will be included in the review.

There is no consensus on sample size estimations for multivariable models. However the standard rule of thumb is 10 or more events per variable entered into the model to allow a robust estimation of the coefficients (19), although a recent study showed that this number could be lower (20). Since about 30-40%(13) of patients with epilepsy do not achieve seizure remission despite continued AED treatment, a study of association of 3 predictor variables with this outcome will require at least 100 patients to achieve an EPV of 10 or more. Therefore we will also be seeking studies that include at least 100 patients. Studies with fewer than 100 patients will only be included if they have an EPV greater than 10 or have been validated on other data sets.

Seizure outcome has been assessed using different concepts of measure. However, the review will not be limited to outcomes assessed in these forms only: Terminal Remission (length of seizure-free period immediately before last follow up evaluation); Longest Remission (longest seizure-free period during follow up); Time to Remission (time from diagnosis to the commencement of remission); Time to Recurrence (time from diagnosis to recurrence of seizures); Seizure Frequency (number of seizures per specified period of time); Refractoriness (lack of response to antiepileptic medication); and Intractability (lack of response to seizures with debilitating frequency of seizures).

Search Strategy

There is probably no widely acknowledged optimal strategy for searching the literature for prognostic studies.(3) Wilczynski et al (21)have developed search strategies that optimise the yield for prognostic studies in MEDLINE(21) with good sensitivity (the proportion of high quality articles that are retrieved for a particular topic) and specificity (the proportion of low quality articles not retrieved), although understandably low precision (proportion of retrieved articles that are of high quality) as searches were not limited by clinical content terms. The most sensitive search strategy is recommended for those interested in all articles reporting studies on prognosis and who are willing to sort out less relevant articles. The search strategy developed using Ovid's search engine syntax for combination of terms with the best sensitivity was:

Incidence (MeSH) OR explode mortality OR follow-up studies (MeSH) OR prognos* (text word)
OR predict* (text word) OR course (text word)

These results will serve as a guide in deciding the search strategy for the review. These results were from searches not limited by specific clinical/disease terms and the authors suggest rather guardedly that it may be possible to increase the performance measures by combining search strategies with content specific terms using the Boolean 'AND'. Therefore MEDLINE was searched (from inception to March 2010) using “epilepsy” or “seizure” or “seizure disorders” with the explode feature where applicable, in combination with the search terms for prognostic studies developed by Wilczynski et al (21).

Furlan et al(22) identified terms in EMBASE related to study design and analysis that could reverse identify non-randomized studies in 4 systematic reviews across 4 different clinical areas. They found that text word "multivariate" was 1 of 2 terms which limit topic only searches in all 4 clinical areas. The text word "regression" (Cox regression and logistic regression) was among others common to 2 of the 4 clinical areas. These terms identified by Furlan et al(22) focusing on terms related to study design and statistical analysis will be used for the EMBASE search. The terms "multivariate" and "regression" are common to the inclusion criteria for studies to be included in the review. The terms were thus selected, and they will be used in addition to "multivariable" to limit an "epilepsy" topic search [explode epilepsy (Emtree) OR epilepsy (text word)]. The search will also be from inception to March 2010, and will not be limited to EMBASE-specific records alone.

The results of the MEDLINE and EMBASE search will be screened after they have been exported to the EndNote citation manager. There will be a three-step selection process to identify eligible studies. In the first step, the title and abstracts will be screened to identify all studies that are neither about prognosis nor epilepsy and do not meet any of the inclusion criteria, duplication or redundant studies, papers that are review, editorial, commentary or letter, studies with non-seizure outcomes, studies with population restricted to a particular epilepsy subtype or patient population (e.g. surgical cohort, drug withdrawal cohort et cetera), studies with epilepsy or seizures as an outcome of or in relation to another pathological process and exclusively first seizure studies. These publications will be excluded, and will then be left with only the potentially eligible papers. In the second step, after reading the full text versions of the remaining studies, those without multivariate analysis of predictor variables for seizure outcomes in unselected cohort of people with epilepsy will again be excluded. Then in the third step, there will be a manual search the reference lists of all eligible publications.

Data Extraction

The data will first be extracted from each paper directly into a form, then from the paper also directly onto an Excel spread sheet database; results of the 2 rounds of data extraction will be compared for accuracy, and where there are discrepancies, the paper will be consulted for clarification. The extracted data will include authors and title of study, year of publication, study design, study size, age range and sex of the participants, predictor variables assessed, investigated seizure outcome measures, and the independent predictors with their risk estimates and corresponding 95% confidence intervals. All data will be extracted from the published studies and their authors will not be contacted for further information.

REVIEW OF METHODS OF STUDIES

In a meta-review of systematic reviews of prognosis studies, Hayden et al (5) developed extensive guidelines for assessing quality in prognosis studies on the basis of a framework of potential biases. Hayden and colleagues set out by identifying quality items in systematic reviews of prognosis studies, and subsequently pooling the items identified into 6 areas of potential bias (Study Participation, Study Attrition, Prognostic Factor Measurement, Confounding Measurement, Outcome Measurement and Analysis) all of which are relevant to the purpose and question of the present systematic review and will therefore be adapted in the analysis of methodology of the studies being reviewed. (Appendix IV)

Studies with Externally Validated Models

For studies with externally validated prognostic models, further analysis will be done with particular reference to the models. Laupacis et al(23) suggested additional criteria specific to prognostic models in their 1997 paper which was an addition to previous criteria suggested by Wasson et al (24) in 1985,

many of which were again identified in the more recent work Hayden et al(5). The factors peculiar to prognostic models from Laupacis et al that are not present in Hayden et al are:

Internal validation: Although not explicitly stated and only implied by Laupacis et al, internal validation is important in assessing the performance of the model, although it does not provide information about the model's performance in another population. This is usually done by splitting the dataset randomly into 2 parts (often 2:1). The model is developed using the first portion and its predictive accuracy is assessed on the second portion. If the available data are limited, the model can be developed on the whole dataset and techniques of data re-use, such as cross validation and bootstrapping, applied to assess performance. (25)

External validation: It is important to prospectively validate the model in a group of patients different from the group in which it was derived, and preferably with different clinicians. This examines the generalisability of the model. (25)

Sensibility: The evaluation of sensibility relies on judgment rather than statistical methods: **Is the model clinically sensible?** Clinicians should think that the items in the model are clinically sensible and that no important items are missing. It is difficult to determine which factors are important in the prognosis of seizure outcomes in epilepsy, but this will be determined retrospectively following the systematic review, and then it will subsequently be documented whether these variables were entered into the analysis.(18) **Is the model easy to use?** This includes factors like time needed to apply the model, and how simple it is to use. Models that require extensive calculations may be less likely to be used than models with simpler scoring schemes. However, this may change as part of a cultural shift involving the increasing surrender of clinical information to the computer and statistical analysis, and this may further facilitate the use of prognostic scores. (26) **Probability of outcome vs. Course of action:** Laupacis et al(23) are of the opinion that prognostic models that recommend a course of action are more likely to be used compared with those that simply describe the probability of an outcome. Both indices of sensibility will be assessed.

Effects of use on clinical practice: This refers to the prospective evaluation of the effect on clinical practice of using the prognostic model in a patient population other than the one in which it was developed and validated to show if physicians and patients are willing to use the model and how its use affect patient behaviour and clinical outcomes. This is best done in randomised controlled trials.(27)

REPORT AND SYNTHESIS OF RESULTS / META-ANALYSIS

For each study, data will be collected on all of the variables shown to be independently predictive of seizure outcome. The variables included in the prognosis studies will be analysed and reported. Predictive variables consistently found to be independent predictors of an outcome in a range of studies will also be reported.

The results of quality assessment will incorporated into the review's synthesis of the evidence. Information on each of the areas of bias in prognosis studies as identified by Hayden et al(5) will be included in the review synthesis. For example, the evidence of effect would be presented on the basis of studies with low risk for bias associated with study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and analysis. The review synthesis will also include an assessment of evidence of effect based on studies with an overall low risk for any important bias. Therefore studies of acceptable quality for inclusion in the synthesis

would at least partly satisfy each of the areas of potential bias i.e. studies from the analysis that are at high risk for any important bias would be omitted from synthesis of results.

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7.2 Appendix II: LIST OF CITATIONS

This is the list of citations from screening endnote library (MEDLINE & EMBASE) and references of eligible publications

LEGENDS

From MEDLINE Only

From EMBASE Only

From EMBASE & MEDLINE

From References

Yes - Eligible | No - Not Eligible | MVA - Multivariate Analysis | RO - Relevant Outcome | NMA - No Multivariate Analysis | NRO - No Relevant Outcome
EVS - External Validation Study | CC - Case Control Study | R - Restricted Epilepsy Population | <100 - Fewer than 100 Patients

CITATIONS	ELIGIBILITY
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Suzuki N, Seki T, Yamawaki H, Kimiya S, Maezawa M, Tachibana Y, et al. Long-term prognosis of childhood epilepsy--follow-up until adulthood . Jpn J Psychiatry Neurol1987 Sep;41(3):437-9.	No (NMA)
Thapar A, Roland M, Harold G, Thapar A, Roland M, Harold G. Do depression symptoms predict seizure frequency--or vice versa? J Psychosom Res2005 Nov;59(5):269-74.	No (NRO)
Tsuboi T. Seizures of childhood. A population-based and clinic-based study. Acta Neurologica Scandinavica Supplementum. 1986;110:1-237.	No (NMA)
Udani VP, Dharnidharka V, Nair A, Oka M. Difficult to control epilepsy in childhood--a long term study of 123 cases. Indian Pediatr1993 Oct;30(10):1199-206.	No (NRO)
Vanderlinden L, Lagae LG, Vanderlinden L, Lagae LG. Clinical predictors for outcome in infants with epilepsy. Pediatr Neurol2004 Jul;31(1):52-5.	No (NMA)
Wada K, Kiryu K, Kawata Y, Chiba T, Mizuno K, Okada M, et al. Prognosis and clinical features of intractable epilepsy: a prospective study. Psychiatry Clin Neurosci1997 Aug;51(4):233-5.	No (NRO)
Wakamoto H, Nagao H, Hayashi M, Morimoto T. Long-term medical, educational, and social prognoses of childhood-onset epilepsy. Brain Dev2000 Jun;22(4):246-55.	No (NMA)
Watts AE. The natural history of untreated epilepsy in a rural community in Africa. Epilepsia1992 May-Jun;33(3):464-8.	No (NRO)
Williamsen R, Ranheim B, Dietrichson P. Prognosis in epilepsy. Preliminary report of an investigation. Acta Neurologica Scandinavica Supplementum1963;39(4):SUPPL4:349-63.	No (NMA)
Wilson WP, Stewart LF, Parker JB, Jr. Epilepsy: some factors influencing the prognosis and treatment. Tex State J Med1960 Jan;56:31-3.	No (NRO)
Wu LW, Kugimiya S, Numata Y, Wada T. Prognostic factors of primary generalized epilepsy: a reappraisal of 96 cases in terminal remission. Folia Psychiatr Neurol Jpn. 1985;39(2):139-45.	No (NMA)
Yamada H, Yoshida H, Ninomiya H. A five-year follow-up study of 66 epileptics. Folia Psychiatr Neurol Jpn1977;31(3):339-45.	No (NMA)
Yamada H, Yoshida H, Ninomiya H, Kato Y. A comparison of follow-up studies on epilepsy--five year and ten-year prognoses. Folia Psychiatr Neurol Jpn. 1978;32(3):451-2.	No (NMA)
Yamada H, Yoshida H, Ninomiya H, Kato Y. A 10-year follow-up study of 97 epileptics. Folia Psychiatr Neurol Jpn1979;33(2):172-82.	No (NMA)
Yamada H, Yoshida H, Ninomiya H, Kato Y. The social prognosis of epileptics--a 10-year follow-up study. Folia Psychiatr Neurol Jpn1980;34(3):306-7.	No (NRO)
Yamamoto Y, Kuwahara H, Miyauchi T, Hosaka H, Yokoi S. Follow-up survey on 131 dropout cases of epilepsy. Folia Psychiatr Neurol Jpn1980;34(3):299.	No (NRO)

7.3 Appendix III: DATA EXTRACTION AND QUALITY APPRAISAL FORM

This contains the three versions of the data extraction and quality appraisal form, from the first two pilots (Versions 1 and 2) to the final version (Version 3)

Data Extraction and Quality Appraisal Form Version 1

Data Extraction

First Author, Year, Title & Journal: _____

Study Design ☐ Prospective ☐ Retrospective ☐ Mixed ☐ Unclear

Type of Study ☐ Randomised Controlled Trial ☐ Cohort Study ☐ Nested Case Control Study ☐ Case Control Study

Study Population Characteristics
Gender ☐ Male ☐ Female ☐ Both

Age
Bracket _____
Remark ☐ Children ☐ Adolescents ☐ Adults

Setting ☐ Hospital ☐ Population ☐ Both

Follow up
Population
Initial_____, Final_____, %_____ ☐ Not Stated/ Unclear

Length of Reported Follow up
Minimal_____, Average_____, Median_____, Maximum_____ ☐ Not Stated/ Unclear

Outcome Measure
Seizure
☐ Remission – terminal remission, longest remission
☐ Seizure status at specified points within follow-up timeline
☐ Time to event – remission, recurrence of seizures, intractability
☐ Time to recurrence of seizures
☐ Intractability
☐ Refractoriness

Epilepsy Subtypes Included/Excluded
☐ All Included/ Unselected
☐ Undetermined/ Not stated / Not sure
Method of Multivariate Analysis
☐ Logistic Regression Model
☐ Cox Proportional Hazards Model

Treatment Details of Cohort _____

Independent Predictors
(with Regression Coefficient, Odds Ratio or Hazard Ratio and 95% CI)

Quality Appraisal for All Studies

Study participation

The source population or population of interest is adequately described for key characteristics	☐ Yes	☐ Partly	☐ No	☐ Unsure
The sampling frame and recruitment are adequately described	☐ Yes	☐ Partly	☐ No	☐ Unsure
Inclusion and exclusion criteria are adequately described	☐ Yes	☐ Partly	☐ No	☐ Unsure
There is adequate participation in the study by eligible individuals	☐ Yes	☐ Partly	☐ No	☐ Unsure
The baseline study sample (or cohort) is adequately described for key characteristics	☐ Yes	☐ Partly	☐ No	☐ Unsure

Study attrition

Response rate (proportion of study sample completing the study and providing outcome data) is adequate (>90%)	☐ Yes	☐ Partly	☐ No	☐ Unsure
Information on participants who dropped out of the study are described	☐ Yes	☐ Partly	☐ No	☐ Unsure
Reasons for loss to follow-up are provided	☐ Yes	☐ Partly	☐ No	☐ Unsure
Participants lost to follow-up are adequately described for key characteristics	☐ Yes	☐ Partly	☐ No	☐ Unsure
There are no important differences between those who completed the study and those who did not	☐ Yes	☐ Partly	☐ No	☐ Unsure

Prognostic factor measurement

The prognostic factors measured are clearly defined or described where necessary	☐ Yes	☐ Partly	☐ No	☐ Unsure
Continuous variables are reported or appropriate (i.e. not data-dependent) cut-points are used	☐ Yes	☐ Partly	☐ No	☐ Unsure
The prognostic factor measure and method are adequately valid and reliable to limit misclassification bias	☐ Yes	☐ Partly	☐ No	☐ Unsure
The method and setting of measurement are the same or similar for all study participants	☐ Yes	☐ Partly	☐ No	☐ Unsure
Adequate proportion of the study sample has complete data for prognostic factors	☐ Yes	☐ Partly	☐ No	☐ Unsure
Appropriate methods are used if imputation is used for missing prognostic factor data	☐ Yes	☐ Partly	☐ No	☐ Unsure

Outcome measurement

A clear definition of the outcome of interest is provided, including duration of follow-up and level and extent of the outcome construct	☐ Yes	☐ Partly	☐ No	☐ Unsure
The outcome measure and method used are adequately valid and reliable to limit misclassification bias	☐ Yes	☐ Partly	☐ No	☐ Unsure
The method and setting of measurement are the same or similar for all study participants	☐ Yes	☐ Partly	☐ No	☐ Unsure

Confounding measurement and account

Important confounders are measured	☐ Yes	☐ Partly	☐ No	☐ Unsure
Clear definitions of the important confounders measured are provided	☐ Yes	☐ Partly	☐ No	☐ Unsure
Measurement of important confounders is adequately valid and reliable	☐ Yes	☐ Partly	☐ No	☐ Unsure
The method and setting of confounding measurement are the same for all study participants.	☐ Yes	☐ Partly	☐ No	☐ Unsure
Appropriate methods are used if imputation is used for missing confounder data	☐ Yes	☐ Partly	☐ No	☐ Unsure
Important potential confounders are accounted for in the study design (e.g. matching, stratification, or initial assembly of comparable groups)	☐ Yes	☐ Partly	☐ No	☐ Unsure
Important potential confounders are accounted/adjusted for in the analysis	☐ Yes	☐ Partly	☐ No	☐ Unsure

Analysis

There is sufficient presentation of data to assess the adequacy of the analysis	☐ Yes	☐ Partly	☐ No	☐ Unsure
The strategy for model building (i.e. inclusion of variables) is appropriate and is based on a conceptual framework or model	☐ Yes	☐ Partly	☐ No	☐ Unsure
The selected model is adequate for the design of the study	☐ Yes	☐ Partly	☐ No	☐ Unsure
There is no selective reporting of results	☐ Yes	☐ Partly	☐ No	☐ Unsure

Data Extraction and Quality Appraisal Form Version 2

Data Extraction

First Author, Year, Title & Journal: _____

Study Design

☐ Prospective ☐ Retrospective ☐ Mixed ☐ Unclear

Type of Study

☐ Randomised Controlled Trial ☐ Non-Randomised Controlled Trial ☐ Cohort Study ☐ Nested Case Control Study ☐ Case Control Study

Study Setting

☐ Hospital ☐ Population

Study Recruitment Period

From_____ To_____ (n=_____)

Age

Bracket _____, Mean _____ ± _____SD

Follow up

Initial Population _____, Final_____, %_____ ☐ Not Stated/ Unclear

Length of Reported Follow up

Minimal_____, Mean_____, Median_____, Maximum_____ ☐ Not Stated/ Unclear

Outcome More Information

Seizure Outcome Measure

☐ Remission
☐ Time to Event
☐ Intractability/ Refractoriness
☐ Status at specified points within follow-up timeline
☐ Others _____

Proportion of Patients with Outcome _____%_____☐ Not Stated/ Unclear

Independent Predictors of Seizure Outcome

(with Regression Coefficient, Odds Ratio or Hazard Ratio and 95% CI)

1.
2.
3.
4.
5.
6.

Epilepsy Subtypes Included/Excluded More Information

☐ All Included - Unselected
☐ Not stated - Not sure
☐ Selected

Method of Multivariate Analysis More Information

☐ Logistic Regression Model
☐ Cox Proportional Hazards Model
Number of Predictor Variables entered into Model_____☐ Not Stated/ Unclear

ILAE Reference Standards More Information

Definition of Epilepsy	☐ Yes	☐ Partly	☐ No	☐ Unsure
Classification of Seizures	☐ Yes	☐ Partly	☐ No	☐ Unsure
Classification by Aetiology	☐ Yes	☐ Partly	☐ No	☐ Unsure
Classification by Syndromes	☐ Yes	☐ Partly	☐ No	☐ Unsure

AED Treatment & Withdrawal Details in Cohort More Information

☐ According to a published or newly developed protocol
☐ At the discretion of treating physician
☐ Every participant on the same regimen
☐ Randomised
☐ Not Stated/ Unclear

Quality Appraisal for All Studies

Study participation

The source population or population of interest is adequately described for key characteristics	☐ Yes	☐ Partly	☐ Unsure	☐ No
There is adequate participation in the study by eligible individuals	☐ Yes	☐ Partly	☐ Unsure	☐ No
Inclusion and exclusion criteria are adequately described	☐ Yes	☐ Partly	☐ Unsure	☐ No
The baseline study sample (or cohort) is adequately described for key characteristics	☐ Yes	☐ Partly	☐ Unsure	☐ No

Study attrition

Response rate (proportion of study sample completing the study and providing outcome data) is adequate (>80%)	☐ Yes	☐ Partly	☐ Unsure	☐ No
Information on participants who dropped out of the study are described	☐ Yes	☐ Partly	☐ Unsure	☐ No
Reasons for loss to follow-up are provided and participants lost to follow-up are adequately described for key characteristics	☐ Yes	☐ Partly	☐ Unsure	☐ No
There are no important differences between those who completed the study and those who did not	☐ Yes	☐ Partly	☐ Unsure	☐ No

Prognostic factor measurement

The prognostic factors measured are clearly defined or described where necessary	☐ Yes	☐ Partly	☐ Unsure	☐ No
The prognostic factor measure and method are adequately valid and reliable to limit misclassification bias	☐ Yes	☐ Partly	☐ Unsure	☐ No
The method and setting of measurement are the same or similar for all study participants	☐ Yes	☐ Partly	☐ Unsure	☐ No
Adequate proportion of the study sample has complete data for prognostic factors	☐ Yes	☐ Partly	☐ Unsure	☐ No

Outcome measurement

A clear definition of the outcome of interest is provided, including duration of follow-up and level and extent of the outcome construct	☐ Yes	☐ Partly	☐ Unsure	☐ No
The outcome measure and method used are adequately valid and reliable to limit misclassification bias	☐ Yes	☐ Partly	☐ Unsure	☐ No
The method and setting of measurement are the same or similar for all study participants	☐ Yes	☐ Partly	☐ Unsure	☐ No
The outcome measurement was blinded to prognostic factor measure or vice versa	☐ Yes	☐ Partly	☐ Unsure	☐ No

Analysis

There is sufficient presentation of data to assess the adequacy of the analysis	☐ Yes	☐ Partly	☐ Unsure	☐ No
The strategy for model building (i.e. inclusion of variables) is appropriate and is based on a conceptual framework or model	☐ Yes	☐ Partly	☐ Unsure	☐ No
The selected model is adequate for the design of the study	☐ Yes	☐ Partly	☐ Unsure	☐ No
There is no selective reporting of results	☐ Yes	☐ Partly	☐ Unsure	☐ No

Quality Appraisal for Models

Statistical validity

The mathematical technique used to derive the model is adequately justified	☐ Yes	☐ Partly	☐ Unsure	☐ No
There is no over-fitting the data with too few outcome events per predictor variable (i.e. EPV at least 10)	☐ Yes	☐ Partly	☐ Unsure	☐ No
There is an account of how predictor variables were selected (i.e. univariate association, stepwise analysis, and assessment for colinearity)	☐ Yes	☐ Partly	☐ Unsure	☐ No
There is the use of appropriate imputation methods for missing data	☐ Yes	☐ Partly	☐ Unsure	☐ No

Internal validation & Reproducibility of predictive variables

The method of ensuring/verifying interobserver reliability of predictor variables is described	☐ Yes	☐ Partly	☐ Unsure	☐ No
The final model was validated on the data that was used to generate it to assess its performance	☐ Yes	☐ Partly	☐ Unsure	☐ No
The method used for internal validation of the model is adequately described	☐ Yes	☐ Partly	☐ Unsure	☐ No
The model produced accurate predictions on the patients that were used to generate it	☐ Yes	☐ Partly	☐ Unsure	☐ No

External validation & Effects of use on clinical practice

The final model was/has been prospectively validated on new cohort(s) of patients, producing accurate results	☐ Yes	☐ Partly	☐ Unsure	☐ No
The prospective validation study was conducted by different clinicians from those who were used to develop the model	☐ Yes	☐ Partly	☐ Unsure	☐ No
The model produced accurate predictions on the patients other than those used to generate it	☐ Yes	☐ Partly	☐ Unsure	☐ No
RCTs have shown that physicians and patients are willing to use the model based on its effect on clinical outcomes	☐ Yes	☐ Partly	☐ Unsure	☐ No

Sensibility

The model is clinically sensible as no obviously clinically important items are missing	☐ Yes	☐ Partly	☐ Unsure	☐ No
The variables included in the model are easily assessable clinically	☐ Yes	☐ Partly	☐ Unsure	☐ No
The model is easy and simple to use arithmetically as it does not require much time and extensive calculations	☐ Yes	☐ Partly	☐ Unsure	☐ No
The model prescribes a course of action to be taken following certain probability of outcome	☐ Yes	☐ Partly	☐ Unsure	☐ No

ROC Curve ☐ Yes ☐ No

Predictive Performance – Development Data

Sensitivity -
Specificity -
Positive Predictive Value -
Negative Predictive Value -
Correct Prediction –

Predictive Performance – External Validation

Sensitivity -
Specificity -
Positive Predictive Value -
Negative Predictive Value -
Correct Prediction –

Data Extraction and Quality Appraisal Form Version 3 (Final)
Data Extraction

First Author, Year, Title & Journal: _____

Study Design
☐ Prospective ☐ Retrospective ☐ Mixed ☐ Unclear

Type of Study
☐ Randomised Controlled Trial ☐ Non-Randomised Controlled Trial ☐ Cohort Study ☐ Nested Cohort Study ☐ Case Control Study

Study Setting
☐ Hospital ☐ Community

Study Recruitment Period
From_____ To_____ (n=_____)

Age
Bracket _____, Mean _____ ± _____SD

Follow up
Initial Population _____, Final_____, %_____ ☐ Not Stated/ Unclear

Length of Reported Follow up
Minimal_____, Mean_____, Median_____, Maximum_____ ☐ Not Stated/ Unclear

Outcome More Information
Seizure Outcome Measure
☐ Remission
☐ Time to Event
☐ Intractability/ Refractoriness
☐ Status at specified points within follow-up timeline
☐ Others _____

Proportion of Patients with Outcome _____%_____☐ Not Stated/ Unclear

Independent Predictors of Seizure Outcome
(with Regression Coefficient, Odds Ratio or Hazard Ratio and 95% CI)

1.
2.
3.
4.
5.
6.

Epilepsy Subtypes Included/Excluded More Information

☐ All Included - Unselected
☐ Not stated - Not sure
☐ Selected

Method of Multivariate Analysis More Information

☐ Logistic Regression Model
☐ Cox Proportional Hazards Model

ILAE Reference Standards More Information

Definition of Epilepsy ☐ Yes ☐ Partly ☐ No ☐ Unsure
Classification of Seizures ☐ Yes ☐ Partly ☐ No ☐ Unsure
Classification by Aetiology ☐ Yes ☐ Partly ☐ No ☐ Unsure
Classification by Syndromes ☐ Yes ☐ Partly ☐ No ☐ Unsure

AED Treatment & Withdrawal Details in Cohort More Information

☐ According to a published protocol
☐ At the discretion of treating physician
☐ Every participant on the same regimen
☐ Randomised
☐ Not Stated/ Unclear

Reporting Characteristics of Studies

Justification of sample size ☐ Yes ☐ No
Report of test for colinearity ☐ Yes ☐ No
Report of test for interactions ☐ Yes ☐ No
Model assumptions tested ☐ Yes ☐ No
Mention of missing data ☐ Yes ☐ No
Criteria for Variable in Model ☐ Yes ☐ No
Report on loss to follow up ☐ Yes ☐ No
Statistical Package Stated ☐ Yes ☐ No
Type of stepwise analysis ☐ Yes ☐ No

How continuous variables were treated ☐ None Considered ☐ Kept continuous ☐Categorised _____

Quality Appraisal for All Studies

Study participation

The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results

The source population is adequately described for key characteristics ☐ Yes ☐ Partly ☐ Unsure ☐ No
Inclusion criteria and baseline cohort described ☐ Yes ☐ Partly ☐ Unsure ☐ No
There is adequate participation in the study by eligible individuals ☐ Yes ☐ Partly ☐ Unsure ☐ No

Study attrition

Loss to follow-up is not associated with key characteristics (i.e., the study data adequately represent the sample)

Response rate (proportion of study sample completing the study and providing outcome data) is adequate ☐ Yes ☐ Partly ☐ Unsure ☐ No
Reasons for loss to follow-up are provided and those lost to follow-up are adequately described ☐ Yes ☐ Partly ☐ Unsure ☐ No
There are no important differences between those who completed the study and those who did not ☐ Yes ☐ Partly ☐ Unsure ☐ No

Prognostic factor measurement

The prognostic factor of interest is adequately measured in study participants

The prognostic factors measured are clearly defined ☐ Yes ☐ Partly ☐ Unsure ☐ No
The measure methods adequately limit misclassification bias ☐ Yes ☐ Partly ☐ Unsure ☐ No
Adequate proportion of the study sample has complete data ☐ Yes ☐ Partly ☐ Unsure ☐ No
The continuous variables were handled appropriately ☐ Yes ☐ Partly ☐ Unsure ☐ No

Outcome measurement
The outcome of interest is adequately measured in study participants

A clear definition of the outcome is provided ☐ Yes ☐ Partly ☐ Unsure ☐ No
The measure method adequately limit misclassification bias ☐ Yes ☐ Partly ☐ Unsure ☐ No
The outcome was blinded to prognostic factor or vice versa ☐ Yes ☐ Partly ☐ Unsure ☐ No

Analysis
The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results

There is sufficient presentation of data to assess the adequacy of the analysis ☐ Yes ☐ Partly ☐ Unsure ☐ No
The strategy for model building (i.e. inclusion of variables) is described ☐ Yes ☐ Partly ☐ Unsure ☐ No
There is no over-fitting the data ☐ Yes ☐ Partly ☐ Unsure ☐ No

Quality Appraisal for Externally Validated Models

Validation
The final model was validated on the data that was used to generate it to assess its performance ☐ Yes ☐ No
The final model was/has been prospectively validated on new cohort(s) of patients, producing accurate results ☐ Yes ☐ No
RCTs have shown that physicians and patients are willing to use the model based on its effect on clinical outcomes ☐ Yes ☐ No

Sensibility
The model is clinically sensible (no important items are missing) ☐ Yes ☐ No
The variables included in the model are easily assessable clinically ☐ Yes ☐ No
The model is easy and simple to use arithmetically ☐ Yes ☐ No
The model prescribes a course of action to be taken ☐ Yes ☐ No

ROC Curve Characteristics Presented ☐ Yes ☐ No

Predictive Performance – Development Data
Sensitivity -
Specificity -
Positive Predictive Value -
Negative Predictive Value -
Correct Prediction –

Predictive Performance – External Validation
Sensitivity -
Specificity -
Positive Predictive Value -
Negative Predictive Value -
Correct Prediction -

7.4 Appendix IV: ITEMS FOR THE ASSESSSMENT OF BIAS IN PROGNOSIS STUDIES*

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias
Study participation	
The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results. Yes Partly No Unsure	The source population or population of interest is adequately described for key characteristics. The sampling frame and recruitment are adequately described, possibly including methods to identify the sample (number and type used, e.g., referral patterns in health care), period of recruitment, and place of recruitment (setting and geographic location) Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description). There is adequate participation in the study by eligible individuals. The baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics.
Study attrition	
Loss to follow-up (from sample to study population) is not associated with key characteristics (i.e., the study data adequately represent the sample), sufficient to limit potential bias. Yes Partly No Unsure	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate. Attempts to collect information on participants who dropped out of the study are described. Reasons for loss to follow-up are provided. Participants lost to follow-up are adequately described for key characteristics. There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not.
Prognostic factor measurement	
The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias. Yes Partly No Unsure	A clear definition or description of the prognostic factor measured is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement). Continuous variables are reported or appropriate (i.e., not data-dependent) cut-points are used. The prognostic factor measure and method are adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall). Adequate proportion of the study sample has complete data for prognostic factors. The method and setting of measurement are the same for all study participants. Appropriate methods are used if imputation is used for missing prognostic factor data.
Outcome measurement	
The outcome of interest is adequately measured in study participants to sufficiently limit potential bias. Yes Partly No Unsure	A clear definition of the outcome of interest is provided, including duration of follow-up and level and extent of the outcome construct. The outcome measure and method used are adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test). The method and setting of measurement are the same for all study participants.
Confounding measurement and account	
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. Yes Partly No Unsure	All important confounders, including treatments (key variables in conceptual model), are measured. Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures). Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall). The method and setting of confounding measurement are the same for all study participants. Appropriate methods are used if imputation is used for missing confounder data. Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups). Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).
Analysis	
The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results. Yes Partly No Unsure	There is sufficient presentation of data to assess the adequacy of the analysis. The strategy for model building (i.e., inclusion of variables) is appropriate and is based on a conceptual framework or model. The selected model is adequate for the design of the study. There is no selective reporting of results.

* Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine2006 Mar 21;144(6):427-37.

7.5 Appendix V: ITEMS TO BE CONSIDERED IN REPORTING OBSERVATIONAL STUDIES*

Item	Item Number	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.
Introduction		
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported.
Objectives	3	State specific objectives, including any prespecified hypotheses.
Methods		
Study design	4	Present key elements of study design early in the paper.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.
Participants	6	(a) Cohort study: Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. Case–control study: Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. Cross-sectional study: Give the eligibility criteria, and the sources and methods of selection of participants. (b) Cohort study: For matched studies, give matching criteria and number of exposed and unexposed. Case–control study: For matched studies, give matching criteria and the number of controls per case.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.
Bias	9	Describe any efforts to address potential sources of bias.
Study size	10	Explain how the study size was arrived at.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) Cohort study: If applicable, explain how loss to follow-up was addressed. Case–control study: If applicable, explain how matching of cases and controls was addressed. Cross-sectional study: If applicable, describe analytical methods taking account of sampling strategy. (e) Describe any sensitivity analyses.
Results		
Participants	13*	(a) Report the numbers of individuals at each stage of the study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed. (b) Give reasons for nonparticipation at each stage. (c) Consider use of a flow diagram.
Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate the number of participants with missing data for each variable of interest. (c) Cohort study: Summarize follow-up time—e.g., average and total amount.
Outcome data	15*	Cohort study: Report numbers of outcome events or summary measures over time. Case–control study: Report numbers in each exposure category or summary measures of exposure. Cross-sectional study: Report numbers of outcome events or summary measures.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence intervals). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions and sensitivity analyses.
Discussion		
Key results	18	Summarize key results with reference to study objectives.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.
Generalizability	21	Discuss the generalizability (external validity) of the study results.
Other Information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.

*Give such information separately for cases and controls in case–control studies, and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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