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EPIDEMIOLOGY OF EPILEPSY IN TASMANIA

A thesis presented in partial fulfilment of the requirements

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Abstract

Background

Better understanding of the demographic distribution of epilepsy and the prevalence of ‘more specific forms of epilepsy’ in community-based settings would improve our understanding of this disorder at the population level. Although we now have good estimates of epilepsy prevalence for most countries, we still lack knowledge on its demographic distribution by age, ethnicity, region, and socioeconomic status. In addition, no studies to date have reported the prevalence of epilepsy syndromes using patient interview outside a hospital setting. This thesis provides the first community-based estimates of the prevalence of the most common clinical group of epilepsies presumed to have a genetic basis – The Idiopathic Generalised Epilepsies (IGE) - by patient and witness interview.

Methods

This thesis has involved conducting five pieces of new research: (i) a series of reviews and analyses of descriptive data on epilepsy prevalence, particularly focusing on the critical methodological issues of ascertainment, diagnosis and classification of epilepsy for epidemiological purposes; (ii) the validation of a modified diagnostic epilepsy questionnaire adapted for administration in population studies; (iii) recruitment of a community-based cohort – The Tasmanian Epilepsy Register (TER) - through the Australian national prescription database; (iv) estimation of the overall prevalence and distribution of self-reported treated epilepsy in Tasmania by imputation methods; (v)

estimation of the prevalence and distribution of IGE in Tasmania by telephone interviewing.

Results

My modified diagnostic questionnaire, administered by telephone interviewing and interpreted with standardized guidelines, demonstrated excellent agreement with an epilepsy specialist's clinical assessment in diagnosing the presence of epilepsy ($\kappa = 0.94$), seizure-onset types ($\kappa = 0.84$), simple or complex partial seizures ($\kappa=0.87$), any generalized non-convulsive seizure ($\kappa=0.82$), and IGE ($\kappa = 0.82$). Although still substantial, agreement was not as close for secondarily generalized seizures ($\kappa = 0.74$), and generalized tonic-clonic seizures ($\kappa = 0.79$).

7541 patients treated with antiepileptic drugs (AEDs) in the preceding year in Tasmania were eligible for recruitment through the Australian national prescription database. After three mail contacts, 54.0% responded, with 43.6% who indicated treatment for epilepsy representing 86.0% of total possible epilepsy cases by imputation ($n=2063$) in Tasmania. 1180 agreed to participate in the TER, 90.0% of participants received their AEDs either exclusively from their general practitioner (70.9%) or in combination with a medical specialist (19.1%) in the preceding twelve months. The adjusted treated epilepsy prevalence was 4.36 per 1000 (95% CI 4.34, 4.39); this was: lower in women (prevalence ratio 0.92 (95% CI 0.84, 1.00); greater with increasing age ($p < 0.001$); similar in the three main geographical regions; and similar by categories of socioeconomic status based on postcode of residence.

Following enrolment, 959/1083 (88.6%) eligible TER participants completed the diagnostic telephone interviewing, with partial epilepsy classified in two thirds, and generalised epilepsy in slightly more than one-fifth. IGE was observed in 20.3%, with tonic-clonic seizures (17.03%) and the absence epilepsies combined (11.01%) being the most common IGE seizure types and syndromes respectively. The estimated prevalence of IGE was 0.89 per 1000; is highest between the ages of 20-39 years and in females, but was similar between Tasmanian regions and socio-economic groups. IGE prevalence beyond childhood related to refractory childhood or adolescent disease rather than older-onset cases, and was characterised by the presence of myoclonic and tonic-clonic seizures. Generalised seizures, but not IGE, were less prevalent in southern Tasmania.

Conclusions

Utilising the design approach described in this thesis may provide an alternative to neurological assessment, and when coupled with case ascertainment through prescription data, can provide a valid estimate of the prevalence of 'more specific forms of epilepsy' in countries with high access to health services. The observed pattern of high elderly epilepsy prevalence, is similar to patterns in recent studies in other developed countries, and has important implications for future planning of health services in these countries. IGE represents a considerable proportion of community-treated disease with important aetiological and prognostic determinants occurring at the seizure rather than syndrome level of classification.

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Abbreviations

AED	Anti-epileptic drug
BMEI	Benign Myoclonic Epilepsy of Infancy
CAE	Childhood Absence Epilepsy
CATI	Computer-assisted-telephone-interviewing
CDC	Centers for Disease Control
CTB	Computed Tomography of the Brain
EEG	Electroencephalogram
EMA	Epilepsy with Myoclonic Absences
FDG-PET	Fluoro-deoxyderibose glucose positron emission testing
SPECT	Single photon emission computerized tomography
FRACP	Fellow of the Royal Australasian College of Physicians
GEFS+	Generalised Epilepsy with Febrile Seizures Plus
GPRD	The General Practice Research Database
GTCS	Generalised tonic clonic seizures
HIC	Health Insurance Commission
ICEBERG	The International Community-based Research Group
IGE	Idiopathic Generalised Epilepsy
IGEUn	Idiopathic Generalised Epilepsy not otherwise specified
ILAE	International League Against Epilepsy
JAE	Juvenile Absence Epilepsy
JS	Jeavons's Syndrome
JME	Juvenile Myoclonic Epilepsy
MAE	Epilepsy with Myoclonic Astatic seizures
MRI	Magnetic resonance imaging
MRIB	Magnetic resonance imaging of the brain
NGPSE	National General Practice Study on Epilepsy
NHIS	National Health Interview Survey
NHMRC	National Health and Medical Research Council (Australia)
NHS	National Health Service
NHSCR	National Health Service Central Register
NHNN-GPLS	The National Hospital for Neurology and Neurosurgery General Practice Linkage Scheme
NPV	Negative Predictive Value
OREp	Osservatorio Regionale per l'Epilessia
PPV	Positive Predictive Value
SSCI	Semi-structured seizure classification interview
SEIFA	Socio-economic status index for postcode area
SENS	Sensitivity
SNES	The Sicilian Neuroepidemiology Study
SPEC	Specificity
TER	Tasmanian Epilepsy Register
UK	United Kingdom
WHO	World Health Organisation
YI	Youden's Index

Chapter One: Introduction

1.1 Background

Epilepsy is the most common serious neurological disorder, and is one of the world's most prevalent non-communicable diseases, affecting approximately 2-4% of individuals at some time in their lives (Scott et al. 2001). Epilepsy is not a single disease but rather a heterogeneous group of disorders encompassing more than forty clinical syndromes, consisting of biochemical, anatomic, and physiologic changes that lead to recurrent unprovoked seizures. Epilepsy classification combines information on seizure types, age at onset, aetiology, clinical course, electroencephalography (EEG) (a non invasive test of a person's brain wave activity) and structural and functional brain imaging to reach a diagnosis. This often necessitates a degree of investigation only available in a tertiary referral setting. Hence classifying epilepsy by less resource intense methods, without appreciable loss of validity to a tertiary-derived one, would have great benefit in population-based research (Everitt and Sander 1999).

It is now well established that the group of idiopathic epilepsy syndromes has a major genetic contribution (Ottman et al. 1998a). Evidence for a genetic contribution to the epilepsies is derived from studies demonstrating increased familial aggregation (Annegers and Hauser 1982, Annegers et al. 1982), higher concordance rates in monozygotic versus dizygotic twins (Berkovic et al. 1996), genetic linkage and gene identification studies in human epilepsies (Annegers et al. 1982), and studies of human Mendelian disorders with seizures as part of the phenotype (Berkovic et al. 1994).

Familial aggregation studies suggest a significant genetic contribution with the standardized morbidity ratio for epilepsy in relatives of index cases with epilepsy with onset prior to age 16 years being 2.5 in siblings (95% CI 1.3-4.4) and 6.7 in offspring (95% CI 1.8-17.1)(Ottman and Annegers 1998, Ottman et al. 1998b) .

Idiopathic Generalised Epilepsy (IGE) is a common group of epilepsies accounting for about 20-40% of all epilepsies (Loiseau et al. 1991, Osservatorio Regionale per l'Epilessia (OREp) 1996). This syndrome is clinically characterized by the presence of particular generalized seizure types (absence, myoclonic and tonic-clonic seizures) and the EEG pattern of bilateral, synchronous, and symmetrical spike and wave or polyspike and wave discharges. On the basis of the predominant seizure type, seizure pattern and age of onset, the International League Against Epilepsy now recognises seven main IGE sub-syndromes: Benign Myoclonic Epilepsy of Infancy (BMEI), Epilepsy with Myoclonic Absences (EMA), Epilepsy with Myoclonic Astatic seizures (MAE) Childhood Absence Epilepsy (CAE), Juvenile Absence Epilepsy (JAE), Juvenile Myoclonic Epilepsy (JME), and Idiopathic Generalised Epilepsy not otherwise specified (IGEU) (Engel 2001, ILAE 1989). Although phenotypic concordance of these IGE sub-syndromes among first degree relatives is about one third (Group 1993, Ottman et al. 1998b), these studies all show overlap of sub-syndromes within families, suggesting that the IGEs are genetically closely related, with the absence epilepsies more closely related than the myoclonic epilepsies (Winawer et al. 2003). This is not surprising, as the presence of specific seizure types and their expression drives both the diagnosis of IGE and its sub-syndromes and underlines the importance of better genotype-phenotype

understanding in dissecting the genetics of IGE (Loiseau et al. 2002, Malafosse et al. 1994).

The prevalence of epilepsy was chosen as the focus for study in this thesis as the major contribution of epidemiology to the study of chronic disease has been the focus on the population level, including analyses of patterns of disease prevalence across demographic groups and geographic areas and across time (Pearce 1998). In particular, many of the epidemiological hypotheses concerning the cause of chronic disease have arisen, at least in part, from geographical comparisons. For example, many of the recent discoveries on the causes of cancer have their origins, directly or indirectly, in the systematic international comparisons of cancer conducted in the 1950s and 1960s (Doll et al 1966). Therefore, although the primary purpose of this thesis was to highlight the burden of disease from IGE, by also describing its demographic distribution (age, gender, region and socioeconomic status) it was also hoped that new insights into the aetiology of IGE would be gained.

The modern epidemiologic study of epilepsy probably dates from 1923 when Davenport, using a variety of sources, compared the frequency of epilepsy in different countries, geographic regions and ethnic groups (Davenport 1923). This study highlights some of the early problems in epilepsy epidemiology (Sander and Shorvon 1987). Firstly, cases were ascertained from various settings (army draftees, army sick reports, 'agricultural' areas, American Indian reservations, hospital outpatients, hospital inpatients and private

specialists). Secondly, the measurement and comparison of population groups was performed by non-validated, non-standardized diagnostic and classification methods.

The issues which hinder comparisons between different populations in this study have largely been addressed in the studies which followed over the next eighty years (Le et al. 2007). These have demonstrated that measuring epilepsy prevalence by household survey is time-consuming, resource intensive and, given the relative low prevalence of epilepsy, inevitably insufficiently powered to study the demographic distribution of epilepsy (age, gender, region, socioeconomic status) or ‘more specific forms of epilepsy’ e.g. IGE. However, if we are to better understand the major etiological factors of epilepsy at the population level, further knowledge needs to be gained about ‘more specific forms of epilepsy’ which will require newer population-based solutions to be developed for these challenges (D'Souza 2006).

1.2 Objectives

The main intention of this thesis is to measure how common the idiopathic generalized epilepsies (IGE) are in a community-based population survey. This ‘more specific form of epilepsy’ was chosen as there are no community-based prevalence estimates of IGE outside hospital settings, and this group of epilepsies is generally considered to represent the most common epilepsy syndrome with a genetic basis. Therefore, the measurement of the prevalence of IGE in a representative community-based population cohort should lead to a better understanding of the contribution of the commonest genetic epilepsy syndrome to the epilepsies as a whole. However, to effectively measure IGE in a

community setting requires the development of methods that are valid and practical for recruitment, diagnosis and classification of epilepsy on a large scale.

1.3 Thesis Organisation

This thesis is presented in two parts. Part One (Chapters Two, Three and Four) provides the background information to the thesis presenting an overview of the prevalence of epilepsy and epilepsy syndromes, and some of the key methodological issues relating to case ascertainment, case diagnosis and case classification. Part Two (Chapters Five, Six, Seven and Eight) presents the new research conducted for this thesis.

Chapter Two outlines the issues of epilepsy case ascertainment. The first part of the chapter provides some background to the context of seizures and epilepsy particularly with reference to its profound stigma which dates back to ancient civilisation (Manyam 1992). The second part of the chapter illustrates the problems of epilepsy case ascertainment progressing through institutional, medical, community setting and multiple recruitment sources, with an analysis of the strengths and limitations from these various settings.

Chapter Three outlines the issues of epilepsy case classification and diagnosis. The first part of the chapter deals with the emergence of clinical and operational definitions for epilepsy, epileptic seizures and syndromes and their widespread acceptance and adoption (ILAE 1981, ILAE 1989). The second part of the chapter deals with diagnosis in epilepsy prevalence studies from its progression, based on secondary medical records of

patients, to primary community sources without disease. This has involved the use of clinical impression, screening questionnaires and diagnostic instruments, all dependent on an epilepsy specialist's interpretation of symptoms.

Chapter Four provides a summary of our current knowledge of the prevalence and distribution of epilepsy, seizures and 'more specific forms of epilepsy'. The first part of the chapter addresses the overall prevalence of epilepsy and its distribution by age, gender, region, ethnicity and socioeconomic status. The second part of the chapter deals with the prevalence of seizures, seizure-onset types, and 'more specific forms of epilepsy', with specific reference to the IGE syndrome.

Chapter Five presents the results of a validation study of a modified diagnostic epilepsy questionnaire conducted by computer-assisted-telephone-interviewing (CATI) and interpreted with newly developed standardized epilepsy diagnostic guidelines validated against an epilepsy specialist's clinical assessment (D'Souza et al. 2007a). Chapter Six describes the recruitment methodology used to establish a large community-based epilepsy cohort in the Australian island state of Tasmania from the Australian national prescription database and discusses its relative strengths and limitations (D'Souza et al. 2007c).

This is followed by Chapter Seven which utilises the recruitment design involved in Chapter Six to estimate the prevalence of treated epilepsy in Tasmania, and its distribution by age-group, gender, region and socio-economic status by imputation

methods (D'Souza et al. 2007d). Chapter Eight finally brings together the community-based epilepsy cohort described in Chapter Six, and the diagnostic epilepsy questionnaire validated in Chapter Five, to estimate the prevalence and distribution of the IGEs and their seizures in Tasmania (D'Souza et al. 2007b).

The thesis concludes with Chapter nine which summaries the major findings and discusses the implications of this work in relation to health service provision, broader public health considerations and suggestions for future research.

Chapter Two: Methodological issues in measuring the prevalence of epilepsy I: Case ascertainment

2.1 Introduction

This chapter discusses the problems of epilepsy case ascertainment and the strengths and limitations of prevalence estimates when recruitment is conducted from these different settings. I start by presenting a brief overview of stigma both as historical background but also because it has direct consequences for measuring epilepsy prevalence, irrespective of ascertainment source.

The systematic review of the epilepsy prevalence literature commences with Davenport's original 'modern' epidemiological study (Davenport 1923) and discusses subsequent research up until the end of June 2007 (Noronha et al. 2007). This provides the historical development and contemporary critical appraisal of our knowledge relating to the methodological problems that have been encountered, and the design solutions that have been used, in measuring the prevalence of epilepsy. The review involved a systematic MEDLINE search for all English language published articles, not focusing exclusively on particular age groups, for the key words epilepsy, epidemiology, prevalence, and incidence along with any articles cited from these studies. 115 studies fulfilled these criteria.

2.2 Stigma

The ancient Indian medical system, Ayurveda, meaning science of life, is the oldest system of medicine in the world. In this system, epilepsy is defined as Apasmara: apa, meaning negation or loss of; smara, meaning recollection or consciousness (Manyam 1992). Hence, during the early stages of civilization, epilepsy was attributed to the temporary loss of the soul from the body. In most regions this led to a negative connotation, attributing this loss of soul to possession of the body by some demon or other malignant spirit. The later concept of epilepsy as a contagious disease, which was common during the middle ages, is thought to have sprung from this ancient belief that the disorder was due to seizure by demons. Patients were strictly isolated and as late as the middle of the fifteenth century, isolation hospitals for victims of epilepsy were still in existence.

'Kifafa', a Swahili word used for seizures, denotes "being half-dead and rigid", and signified that a family is cursed by ancestral spirits for past infringements (Jilek-Aall 1965, Jilek-Aall 1979). Although it was also said that poisoning, head injuries, and spinning around might also lead to this disorder in certain people, it was generally accepted that such attacks were due to the wrath of ancestral spirits for past infringements, and that later generations had to suffer because of parental conflicts, infidelity, and witchcraft. Furthermore, it was believed that during 'Kifafa' attacks the evil spirit could leap from the patient into bystanders, who would also be at risk of contracting the malady through physical contact with the convulsive patient or the patient's saliva, urine or faeces. Such beliefs explain the crippling burns, often seen as

the presenting problem in affected individuals, acquired by falling into the open domestic fire as everybody ran away in panic rather than risk contagion by trying to pull the unconscious patient out of the fire.

The stigma related to 'Kifafa' is more marked than leprosy, because the community views the sufferers as contagious and demon-ridden resulting in the afflicted person being despised by their community group. Consequently the bridal price for even a healthy girl from an affected family was much lower than that from an unaffected group, making the prospects of marrying into a healthy family practically negligible. Therefore, the condition limited intermarriage with neighbouring tribes, and the families resorted to marrying likewise stigmatised partners. This intermarriage, together with the isolation of the tribe, and a traditional preference encouraging marital unions within the kin group (even between first cousins), might well explain the unusually high familial prevalence of 200 persons among a population of 10,000 persons described in the Wapogoro tribe in Tanzania (Jilek-Aall 1965, Jilek-Aall 1979). Negative marital consequences also affect women with the condition in Libya (Sridharan et al. 1986). In Ethiopia, without curative treatments people with epilepsy soon became outcasts in society, expelled from their homes and the community (Giel 1970).

In Benin, as elsewhere in West Africa, because epilepsy is believed to be a supernatural happening, patients initially consult village healers in order to receive a traditional treatment and to be exorcised. Late presentation at orthodox medical centres reflects a strong belief in evil spirits or 'juju' (black magic) as the cause of epilepsy. Accordingly it

is usually believed that the unorthodox medical practitioners (native doctors) are best able to treat epilepsy. Superstitions and certain taboos are also seen among some Bantu tribes, who regard epilepsy as something supernatural (Bird et al. 1962). This may result in disease non-disclosure, with lodgers in Nigeria ejected from the household and completely ostracised because epilepsy is thought to be infectious (Dada 1970).

In Uganda, epilepsy is thought to be the spoiling of the brain (“like butter melting in the sun”) so that the epileptic becomes foolish or violent and unable to learn, work, or take responsibility. The Baganda considered epilepsy to be a disease of the brain “sent” through an external agency such as witchcraft. A full convulsive epileptic fit ‘ensimbu’ may be provoked, so it is thought, by the movements within the head of a lizard either present since birth or “sent” through the agency of witchcraft (Billinghurst et al. 1973). Traditional treatments may thus be used in an attempt to induce a lizard to leave the head of the victim. The disease is considered indigenous, and therefore one unlikely to be killed by Western medicine.

Although maybe now not as extreme, the beliefs surrounding the causes of epilepsy, and guilt surrounding the condition are not restricted to developing countries. Parents in the United Kingdom (UK) attributed having caused epilepsy in their child to “the use of oral contraceptives and abortifacients, the practice of masturbation in pre-marital life, intercourse after over-indulgence in alcohol, and past venereal infection” (Cohen 1958). Even in more modern times, participants of an epilepsy survey when asked what others think of epilepsy suggested it to be: “a black mark against you”, “a bit of a disgrace” “a

taboo subject”, “terrible, disgusting” with some not even willing to discuss the topic (Lloyd Jones 1980).

The diagnosis is potentially disastrous for seamen and drivers (de Graaf 1974), and military recruits have been shown to keep their epilepsy hidden at induction time (Cornaggia et al. 1990). In a Sicilian study, the lower age-specific prevalence among women aged 15 to 19 years was felt to be possibly due to teenage girls concealing their epilepsy by providing misleading and inaccurate statements, or by opting out of the survey completely because of concerns that the condition might adversely affect their marriage prospects (Rocca et al. 2001). Most recently, the authors of the National Household Survey in the United States (CDC 1994) and a study in general practice in the United Kingdom (Cockerell et al. 1995) both acknowledge possible reporting bias because of social stigma making those surveyed reluctant to report the condition (Jacoby 1994).

Therefore, although epilepsy may be considered a positive condition of religious significance (Garcia-Noval et al. 2001) and in the Mariana Islands authors suggest no stigma towards epilepsy (Lessell et al. 1962, Mathai et al. 1968), the majority of cultures report a stigmatising effect of being given the label of epilepsy (Wang et al. 2003). This may have considerable negative social and economic consequences leading to disease concealment (Birbeck and Kalichi 2004, Rwiza et al. 1992), refusal to participate in surveys because of a fear of exposure to modern medical practice (Debrock et al. 2000). Although the negative occupational consequences of epilepsy have been known to result in false disease disclosure to avoid military recruitment (Sridharan et al. 1986), stigma is

most likely to lead to active denial of diagnosis with underreporting of epilepsy in about a quarter of cases (Beran et al. 1985b, Rowan and Hyman 1976), leading to underestimation rather than overestimation of epilepsy prevalence when disease ascertainment is based on patient or family experience reports.

2.3 Institutionalised residents

Most of the first studies of epilepsy prevalence focused on chronically intellectually, physically, psychiatrically and criminally institutionalised persons (see Table 2.1 and Figure 2.1) (Anderson CL 1936, Brewis et al. 1966, Epileptics 1928, Tylor Fox 1937, Tylor Fox 1939) to include the ‘epileptic, spastic and educationally subnormal’ (Brewis et al. 1966). The language and focus of this earlier period reflects the stigmatised image of epilepsy and its care in society at the time which has often lead to non-disclosure and denial of the condition, affecting its complete enumeration (Beran et al. 1985b).

However, with an increasing proportion of elderly in developed countries, ‘institutionalised’ nursing home residents should not be discounted as an important source population for epilepsy case ascertainment (Forsgren and Nystrom 1990, Keranen et al. 1989, Rocca et al. 2001).

Table 2.1: Case ascertainment methods in epilepsy prevalence studies from English-language publications from 1923-2007 (n=115)

Region	Country	Ascertainment method										
		1	2	3	4	5	6	7	8	9	10	11
Africa												
(Rwiza et al. 1992)	Tanzania	√										
(Osuntokun et al. 1982)	Nigeria	√										
(Tekle-Haimanot et al. 1990b)	Ethiopia	√										
(Giel 1970)	Ethiopia	√										
(Tekle-Haimanot et al. 1990a)	Ethiopia	√										
(Orley 1970)	Uganda	√					√		√			
(Kaamugisha and Feksi 1988)	Kenya	√	√									
(Goudsmit et al. 1983)	Liberia	√										
(Birbeck and Kalichi 2004)	Zambia	√										
(Sridharan et al. 1986)	Libya							√	√	√		
(Levy 1970)	Rhodesia	√										
(Coleman et al. 2002)	Gambia	√										
(Debrock et al. 2000)	Republic of Benin	√	√		√			√	√			
(Haddock 1967)	Ghana							√	√			
(Bird et al. 1962)	Southern Africa				√							
(Osuntokun et al. 1987)	Nigeria	√										
(Dada 1970)	Nigeria	√										
(Snow and al 1994)	Kenya	√										
(Bondestam et al. 1990)	United Republic of Tanzania	√										
(Jilek and Jilek-Aall 1970)	Tanzania						√		√			
(Gerrits 1983)	Liberia	√										

Region	Country	Ascertainment method										
		1	2	3	4	5	6	7	8	9	10	11
(Hurst et al. 1961)	South Africa								√			
Asia & Oceania												
(Li et al. 1985)	People's republic of China	√										
(Wang et al. 2003)	People's republic of China	√										
(Bharucha et al. 1988)	India	√										
(Kaoul et al 1988)	India	√										
(Mani et al. 1998)	India	√										
(Pal et al. 1998)	India	√	√									
(Fong et al. 2003)	Hong Kong	√										
(Loh et al. 1997)	Singapore				√							
(Asawavichienjinda et al. 2002)	Thailand	√										
(Puvanendran 1997)	Singapore				√			√		√		
(Rajbhandari 2003)	Nepal	√										
(Tran et al. 2006)	PDR	√	√									
(Beran et al. 1982)	Australia	√										
(Lambie et al. 1981)	New Zealand											√
(Crombie et al. 1960)	Australia						√					
(Mathai et al. 1968)	Mariana, Islands	√										
(Chen et al. 1968)	Mariana, Islands							√	√			
(Lessell et al. 1962)	Mariana, Islands	√										
(Stanhope et al. 1972)	Mariana, Islands	√						√	√		√	
Eastern Mediterranean												
(Attia-Romdhane et al. 1993)	Tunisia	√										
(Onal et al. 2002)	Turkey	√										
(Aziz et al. 1994)	Pakistan	√										

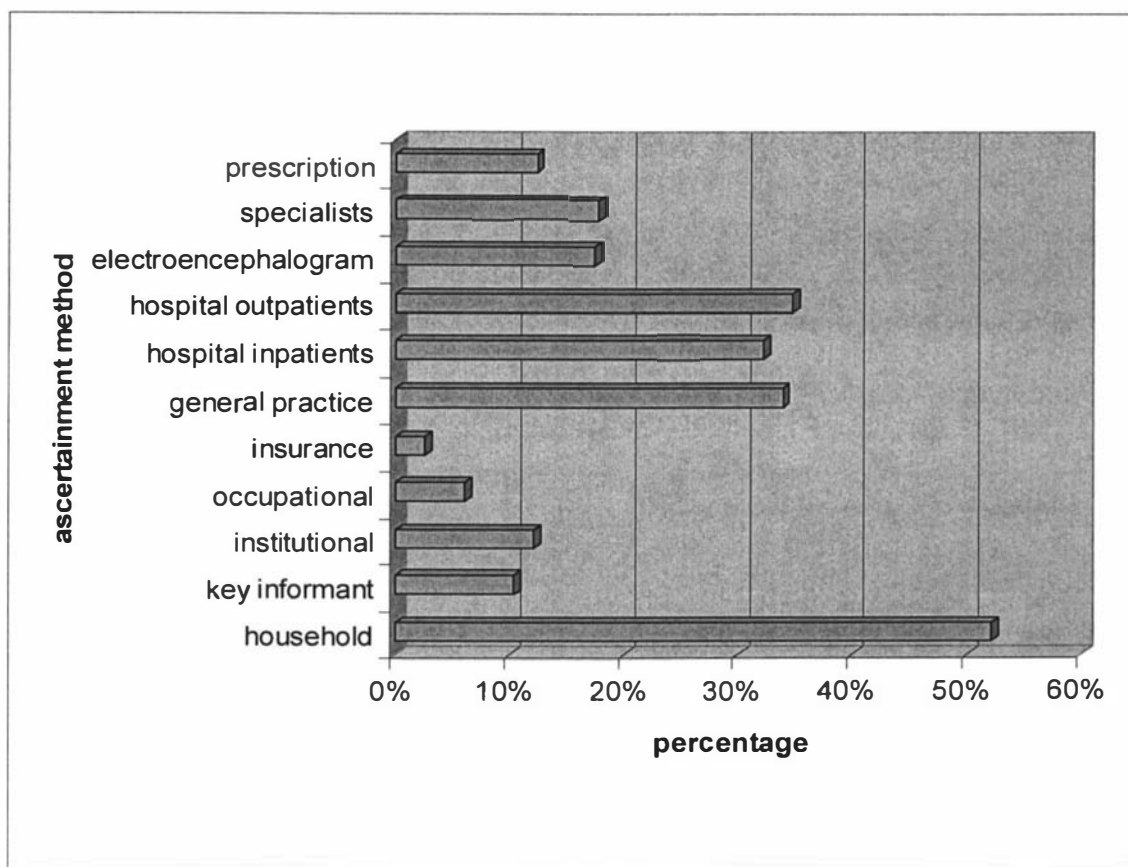
Region	Country	Ascertainment method										
		1	2	3	4	5	6	7	8	9	10	11
(Rajeh et al. 2001)	Saudi Arabia	√										
(Rajeh et al. 1990)	Saudi Arabia								√			
(Aziz H et al. 1997)	Pakistan & Turkey	√										
(Karaagac et al. 1999)	Turkey	√										
(Calisir et al. 2006)	Turkey	√										
(Ozdemir 1995)	Turkey	√										
Latin America												
(Placencia et al. 1992c)	Ecuador	√										
(Marino Jr. et al. 1987)	Brazil	√										
(Gomez et al. 1978)	Columbia	√										
(Olivares 1972)	Mexico							√	√			√
(Garcia-Noval et al. 2001)	Guatemala	√										
(Gracia et al. 1990)	Republic of Panama	√										
(Fernandes et al. 1992)	Brazil	√										
(Lavados et al. 1992)	Chile								√			
(da Mota Gomes et al. 2002)	Brazil	√										
(Melcon et al. 1997)	Argentina	√										
(Noronha et al. 2007)	Brazil	√										
(Nicoletti et al. 1999)	Bolivia	√										
(Mendizabal and Salguero 1996)	Guatemala	√										
North America												
(Pollock 1930)	United States							√	√	√	√	√
(Kurland 1959)	United States							√	√	√	√	√
(Hauser et al. 1991)	United States							√	√	√	√	√
(Haerer et al. 1986)	United States	√		√					√			

Region	Country	Ascertainment method										
		1	2	3	4	5	6	7	8	9	10	11
(Rowan and Hyman 1976)	United States	√										
(Baumann et al. 1977)	United States		√		√							
(Hauser and Kurland 1975)	United States						√	√	√	√	√	
(CDC 1994)	United States	√										
(Anderson CL 1936)	United States		√	√								
Europe												
(Wajsbort et al. 1967)	Israel					√						
(Leibowitz and Alter 1968)	Israel	√		√		√		√	√	√	√	
(Lammers et al. 1996)	Netherlands											√
(Giuliani et al. 1992)	Italy											√
(Rutgers 1986)	Netherlands						√					
(Brewis et al. 1966)	England			√			√	√	√		√	
(Wallace H et al. 1998a)	England & Wales											√
(Goodridge and Shorvon 1983)	England						√					
(Cockerell et al. 1995)	England						√					√
(MacDonald et al. 2000)	England						√					
(Crombie et al. 1960)	England, Wales & Scotland						√					
(Wright et al. 2000)	England						√					√
(Pond et al. 1960)	England						√					
(Maremmani et al. 1991)	Italy			√	√		√	√	√			√
(Granieri et al. 1983)	Italy		√				√	√	√	√	√	√
(Cornaggia et al. 1990)	Italy				√							
(Rocca et al. 2001)	Italy	√		√								
(Zeilinski 1974b)	Poland	√		√			√	√	√			
(Oun et al. 2003)	Estonia		√	√			√	√	√	√	√	√

Region	Country	Ascertainment method										
		1	2	3	4	5	6	7	8	9	10	11
(Olafsson and Hauser 1999)	Iceland						√			√		
(Keranen et al. 1989)	Finland			√		√	√	√	√	√	√	√
(de Graaf 1974)	Norway			√				√	√	√		
(Joensen 1986)	Faroe Islands						√	√	√	√		
(Krohn 1961)	Norway						√	√	√			
(Juul-Jensen 1964)	Denmark							√	√			
(Gudmundsson 1966)	Iceland		√				√	√	√		√	
(Forsgren 1992)	Sweden		√	√			√	√	√	√		
(McCluggage et al. 1986)	Northern Ireland											√
(Lloyd Jones 1980)	Wales											√
(Zander et al. 1979)	England						√					
(White and Buckley 1981)	England											√
(Taylor 1980)	England						√					
(Logan and Cushion 1958)	England						√					
(Fry 1982)	England						√					
(Tylor Fox 1939)	England			√			√	√	√		√	
(Epileptics 1928)	England		√	√								
(Tylor Fox 1937)	England			√				√				
(Reggio et al. 1996)	Italy	√										
(Luengo et al. 2001)	Spain								√			
(Guekkht et al. 1999)	Russia	√						√	√			
(Boon et al. 1995)	Belgium						√	√	√			

1= household; 2= key informant; 3= institutional; 4= occupational; 5= insurance; 6= general practice; 7= hospital inpatients; 8= hospital outpatients; 9= EEG; 10=specialists; 11= prescription
Key informants = traditional practitioners, teachers, village leaders, public health nurses and religious representative

Figure 2.1: Case ascertainment methods* in epilepsy prevalence studies from 1923-2007 (n=115)



*NB: more than one ascertainment method may be used per study so total percentages are greater than 100%

2.4 Medical sources

Methodological issues from medical sources

A common methodological issue in epilepsy case ascertainment from any medical source is under-treatment of epilepsy and therefore under-enumeration. This was highlighted by a series of studies in Warsaw, Poland comparing the prevalence in a field survey with that to a hospital-treated group (Dowzenko and Zielinski 1971, Zeilinski 1974a, Zeilinski 1974b, Zielinski 1976). At the time of survey examination, nearly two thirds of patients were not on treatment and more than one third had never received any medication. In Iceland, a survey identifying patients with epilepsy found that a quarter had never consulted a doctor (Gudmundsson 1966). However, access to epilepsy treatment has improved over time in most developed countries, with only 7% of cases in the USA (Haerer et al. 1986) and 11% in a UK sample (Goodridge and Shorvon 1983) not evaluated medically for their seizure disorders.

One explanation for non presentation to medical services is under recognition of symptoms, with many untreated patients with non-convulsive seizures not recognizing symptom manifestations that required medical treatment, even if they also had associated sporadic convulsive seizures. In addition, only 25% of them had consulted a physician and been diagnosed with epilepsy, with many others not suspecting that their transient symptoms could be of an epileptic nature.

Even when medical presentation does occur, it may be delayed, with about a third of hospital patients with new onset non-convulsive partial seizures having a history of

seizures for more than 12 months (Cockerell et al. 1997). Although also delayed, convulsive seizures present earlier compared to non-convulsive seizures with a median of three compared to 44 seizures in the preceding six months before treatment. Similarly, in the Rochester cohort, among the diagnosed cases, half occurred at an interval of more than six months, in 30% this was longer than two years, and in 15% it was longer than five years from the onset of symptoms (Hauser and Kurland 1975, Hauser et al. 1991). These studies suggested that under-representation of patients, particularly those who are off treatment, more often with non-convulsive seizures, may occur in medical samples of the condition.

Hospital

Early studies (Billinghurst et al. 1973, Cardozo and Patel 1976, Dada 1970, Dowzenko and Zielinski 1971, Gudmundsson 1966, Haddock 1967, Joensen 1986, Juul-Jensen 1964, Krohn 1961, Levy 1970, Levy and Forbes 1964, Olivares 1972, Osuntokun and Odeku 1970, Stanhope et al. 1972, Tekle-Haimanot 1984, Zeilinski 1974b), and to a lesser extent some more recent ones (Lavados et al. 1992, Rajeh et al. 1990, Ruberti and al 1985), have relied heavily on hospital-based records (outpatients, inpatients, EEG records, and specialists) to measure the frequency, distribution and prognosis of epilepsy (see Table 2.1 and Figure 2.1).

Access and presentation to hospital by patients with epilepsy may be delayed, and dependent on age, gender, and disease factors (severe disease disproportionately represented) affecting measures of demographic disease distribution. In a Zambian

study, almost two-thirds of patients were male (Cardozo and Patel 1976). This was common in the early studies in African hospitals, which are dominated by samples of males and a lack of children, probably concerned about ongoing employment in the mines, and a tolerance for not reporting minor seizures amongst children (Levy 1970, Levy and Forbes 1964). In addition, similar to studies in other developed countries, hospital cases most often present with the more prominent convulsive and less frequently with the non-convulsive forms of epilepsy (Billinghurst et al. 1973, Cardozo and Patel 1976, Dada 1970, Hauser et al. 1991, Osuntokun and Odeku 1970, Tekle-Haimanot 1984).

However, diagnosis and management by hospital-based doctors can include community forms of epilepsy (i.e. cases that are generally less severe), when access to hospital specialists is high, as seen in some countries. This has shown improvement over time. In 1936, only 62% were under any medical care in the USA (Anderson 1936). Half a century later, only 7% had not seen a specialist physician for their seizure problems, most seeing a neurologist (43.9%), neurosurgeon (13.4%) or other physician (33.7%) (Haerer et al. 1986). In the UK in 1960, between a quarter and a third of chronic cases, and about half of first seizures had never seen a consultant (Crombie et al. 1960). However, by 1980 patients had been referred for second opinion by a specialist before epilepsy was confirmed in 87% of diagnosed cases in Wales (Lloyd Jones 1980). In a study in Norway, the percentage of patients followed by specialists was found to have increased from about 10% in 1968 to 64% in 1972, illustrating how rapidly changes in referral

practices may affect disease frequency if measured exclusively from hospital sources (de Graaf 1974).

General practice

With 80% free of seizures and not having ill effects of treatment (Zander et al. 1979), cases ascertained from general practice are more likely to be better controlled and tolerant of treatment than those derived from hospitals, highlighting the disease severity bias in hospital-based samples (see Table 2.1 and Figure 2.1). However, studies suggest that patients with epilepsy may not seek medical help or the seizures may remain undiagnosed (Gudmundsson 1966, Zeilinski 1974a), with patient access and uptake of medical help being low in some developed countries (Haerer et al. 1986, Keranen et al. 1989).

Healthcare has been free at the point of access in the United Kingdom (UK) since the introduction of the National Health Service (NHS) in 1948, with general practitioners being the first point of contact for patient care and subsequent specialist referral (MacDonald et al. 2000). When patients change general practitioners, their healthcare records are sent automatically via the NHS Central Register (NHSCR) to their new doctor and all deaths and their causes are sent to this database. This ensures that for every individual in the system, there is a traceable, unique record. Over 99% of people in the UK are registered with a general practitioner, and comprehensive general practice disease databases have provided important patient population morbidity studies in epilepsy as all individuals registered can be traced efficiently (Crombie et al. 1960, Goodridge and Shorvon 1983, Logan and Cushion 1958, Olafsson and Hauser 1999).

Although more representative than specialist sources, routine statistics generated from general practice are less likely to be accurate without prior referral for specialist assessment, with general practitioners reporting diagnostic uncertainty especially in neurological disease (MacDonald et al. 2000). Specialist assessment improves diagnostic accuracy of cases. Hence, health systems with high referral practice and early access to specialist services are likely to have less diagnostic false positives and false negatives in epidemiological research, even when sampling is taken from general practice sources. Although general practitioners and their recording systems are not designed specifically for epidemiology, and are said to often fall short of the necessary standards for data collection due to poor validity and completeness, in countries with high access and uptake of specialist services false negative rates of diagnosis once attending general practitioner sources appear to be less than 1% particularly for active disease (MacDonald et al. 2000).

In earlier studies, for example 'The College of General Practitioners Survey', three quarters of patients were seen only by the general practitioner (Practitioners 1962), in contrast to a survey in Carlisle where a similar proportion had been referred and diagnosed by specialist assessment (Brewis et al. 1966). More recently, studies consistently suggest high access to tertiary health services in the UK, with 76.2% of persons seen at some time by a neurologist or paediatrician, 15.6% seen by another hospital specialist and only 8.2% not being referred to hospital (Goodridge and Shorvon 1983). This high referral to specialists appears to have further improved a decade later,

with over 96% of patients referred to a neurologist or other physician (Cockerell et al. 1995). However, half of these referred patients attend only for a short period (one to three visits), mainly for diagnostic purposes (Goodridge and Shorvon 1983).

Other developed countries share a similar experience. In an Italian study, a similar proportion of patients had their diagnosis of epilepsy confirmed (76.2%) and managed (70.7%) by a specialist, although less than half had seen a consultant neurologist (Giuliani et al. 1992). In an urban Dutch study, around two thirds of the follow-up of patients were supervised by a neurologist (solely or shared in part with the general practitioner), who was also responsible for changes in treatment (81%), and prescription writing (64%), irrespective of seizure freedom (Rutgers 1986).

Therefore, high levels of diagnostically accurate cases from primary care sources are dependent on ready access to both primary and tertiary care for epilepsy, facilitating presentation, correct diagnosis and appropriate management of seizures/epilepsy from the community.

Linked medical sources

In 1907 a young clinic associate, Henry S. Plummer introduced an indexed record filing system at the Mayo Clinic in Olmstead County, Rochester, whereby all of a patient's records could be kept in one file (Kurland and Molgaard 1981). This file included medical records, laboratory results, physician notes and correspondence, and birth and death records for local residents. It was eventually expanded to also include disease

classification, diagnoses and surgical procedures from all independent community and hospital-based sources. These linked records allowed the identification of 90% of patients with epilepsy from visits to physicians in the city and surrounding areas with a false negative rate of less than 1.5 percent, and facilitated a series of landmark studies on the incidence and prevalence of convulsive disorders (Hauser and Kurland 1975, Hauser et al. 1991, Hauser et al. 1993, Kurland 1959).

Although not using an ongoing system as in the Mayo records, The National Hospital for Neurology and Neurosurgery General Practice Linkage Scheme (NHNN-GPLS) ascertained cases from searching databases or correspondence (general practitioner letters, tests, prescriptions and handwritten notes) from hospital and general practice referral in an urban population of 100,230 persons (Cockerell et al. 1996, MacDonald et al. 2000). Checks for false negatives uncovered only three missed cases amongst 1655 notes searched, giving a false-negative rate of 0.2% for active prevalence and only 0.8% for lifetime prevalence estimates (MacDonald et al. 2000). With all patients identified from general practice record review, and no extra cases ascertained from other methods alone, this study highlights that although record linkage between primary and tertiary is desirable for epidemiological research, general practitioner sources can be a virtually complete case ascertainment source for epilepsy that presents for medical assessment in countries with high access to health services.

Antiepileptic drug prescriptions

Antiepileptic drugs (AED) have been said to have high preference and widespread use in treating diagnosed cases of epilepsy, making them a good target drug for epidemiological research (Pedro and Rosenqvist 1984). This has resulted in a number of studies (12.2% in our review of the literature, see Table 2.1 and Figure 2.1) utilising this source to identify possible cases of epilepsy to investigate features of the disorder, including estimating prevalence. Although initially more treatment specific (Pedro and Rosenqvist 1984), their indications have now expanded to include migraine, neuropathic pain, anxiety, depression, bipolar affective disorder, sedation, and impulse control.

General practice and AED prescription data patient identification are often linked in studies of epilepsy prevalence. This is not surprising considering that general practitioners are often the first point of contact, as well as the ‘gatekeepers’ for further access of health services, including prescriptions, and specialist referral (Cockerell et al. 1996, MacDonald et al. 2000, Rutgers 1986, Wallace et al. 1998a, Wright et al. 2000).

‘The General Practice Research Database’ (GPRD) (Wallace et al. 1998a), which was primarily established to prospectively track prescribing data, is a good example of this. General practices that contribute to this database enter all drugs prescribed, a diagnosis or indication of each acute prescription, the initial indication for any repeat prescription, live births, and all instances of significant morbidity. These entries are recorded directly onto the computer system, by the general practitioner and the surgery, each time a patient is seen. Although the GPRD does not including all general practices, it is large, with the

office for National Statistics holding anonymous records of 3.6 million patients for more than 500 general practices in England and Wales, representing over 6% of the total population of England and Wales (Wallace et al. 1998a). In addition, it is representative, showing almost identical age and sex distribution of the database population with that of the general UK population.

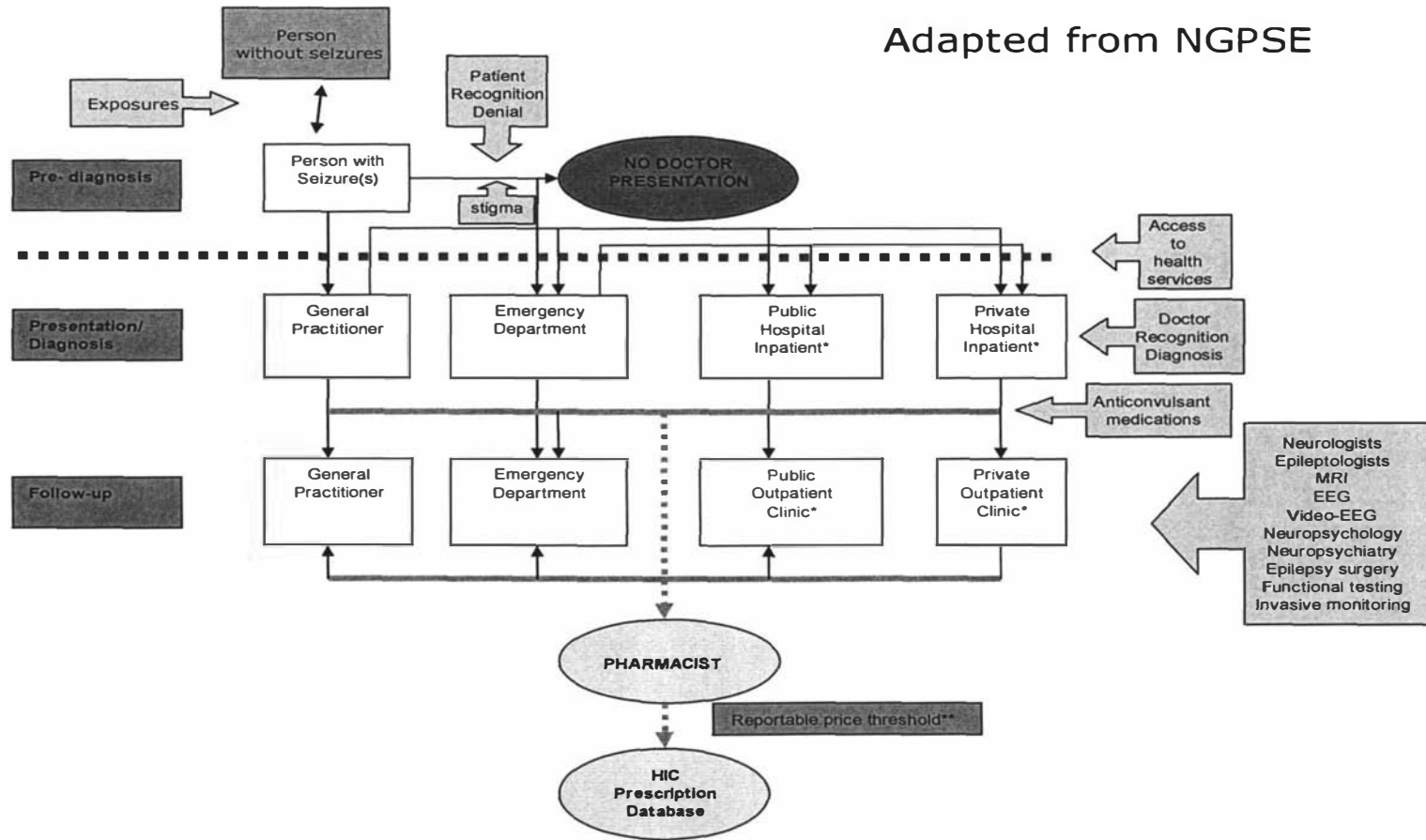
The most reliable information provided by the database relates to medication, because the database was originally set out to record drug prescribing practice and adverse events (Wallace et al. 1998a). Extensive validation in such diseases as diabetes, asthma, and schizophrenia all have shown over 90% diagnostic completeness between the GPRD and the Prescription Pricing Authority prescribing data, but there have been no comparable analyses for AED and epilepsy (Hollowell 1994, Jick et al. 1991).

However, AED prescriptions are dependent on health service access to doctor diagnosis and uptake and maintenance of medication. In a rural community study in Guatemala, almost 87.5% had sought medical care and been treated for their epilepsy at some time in their lifetime, although only about one third were currently on treatment (Mendizabal and Salguero 1996). Slightly less (78%), were known to be taking AEDs on the day of the survey with non-compliance considered to be the reason in around 40% of the remaining persons not taking AEDs despite having seizures in the last five years (Oun et al. 2003). In contrast only 9% of all cases in a Swedish and Icelandic study were not on AEDs on the day they were surveyed (Forsgren 1992, Olafsson and Hauser 1999), while a

Brazilian household survey reported universal treatment with AEDs suggesting high access to health services in the region (da Mota Gomes et al. 2002).

In Australia, all those identified as having epilepsy in a community survey sample had been prescribed anticonvulsive medication at some time, with around two-thirds on medication on survey day, and the 91% currently off medication seizure free in the last year (Beran et al. 1985a), suggesting health care access was not an important consideration in this sample (Beran et al. 1982). However, high treatment coverage is not unique to Australia, with only seven percent (Rocca et al. 2001), six percent (Bharucha et al. 1988), fourteen percent (Haerer et al. 1986) and eleven percent (Goodridge and Shorvon 1983) of people with epilepsy not treated with an AED before being surveyed. Therefore, use of prescribing information may provide an accurate prevalence estimate for treated epilepsy in countries with high access to primary care services. Figure 2.2 displays how a person with seizures may be obtain an AED in an Australian context (see Chapter 6).

Figure 2.2: Studying people with seizures (disease) versus patients with diagnosed epilepsy (illness)



NGPSE = National General Practice Study on Epilepsy.

HIC = Health Insurance Commission - The Australian federal government agency that collects and stores national AED drug information from prescription information in Australia.

Reportable price threshold = All the AED medications retail at more than \$A3.60 and there is a HIC record generated for all concession card patients receiving these drugs from a pharmacist. When medications retail at less than \$A22.40 there is no HIC record generated for general patients receiving these drugs from a pharmacist.

The lowest reported rates of AED treatment consistently arise from developing countries, meaning that surveys that involve ascertainment from medical services (including AED prescriptions) are unlikely to reflect the true prevalence of epilepsy. A widely held belief in some of these countries is that the unorthodox medical practitioners (native doctors) are best able to treat epilepsy, due to a persisting belief that epilepsy has a supernatural quality (Bondestam et al. 1990, Dada 1970, Levy 1970, Levy and Forbes 1964, Osuntokun et al. 1982). With these medicine men specialising in the prevention and treatment of this disorder by herbal remedies and ritual procedures, AED medications are used infrequently (Kaoul et al. 1988, Tekle-Haimanot et al. 1997, Tekle-Haimanot et al. 1990b), with few people with active epilepsy having the knowledge to seek out these treatment options (Bondestam et al. 1990) or being willing to take them even if available (Coleman et al. 2002).

Even with appropriate knowledge, attempts to obtain treatments are difficult because of lack of finances and/or drug supplies with only those able to buy medications from private pharmacies being on regular treatment (Coleman et al. 2002). In Pakistan, patients rarely believed (3%) epilepsy to be due to supernatural causes such as evil eye, curse, sin, evil spirit, magic, poverty, wrong food, or “God’s will”, with only a few (11.5%) visiting a traditional healer who prescribed herbal remedies. Similarly, in another study in the same country, while most individuals believed epilepsy to be a physical disorder, only about a quarter (27.5%) in an urban and 1.9% in rural areas, were treated with AED medication (Aziz et al. 1994). This treatment gap impacts on the

management of epilepsy (and use of AED for ascertainment) in developing countries (Coleman et al. 2002, Jilek-Aall 1965, Jilek-Aall 1979, Jilek and Jilek-Aall 1970).

AEDs are not exclusively prescribed for epilepsy. This makes it necessary to be able to define and exclude other conditions (false positives) prior to counting AED cases as epilepsy cases (true positives). In a study in Wellington, New Zealand, nine percent of 1,479 patients who received AEDs were suspected of receiving medication for conditions other than epilepsy. This 'false positive' group was identified when: (i) another indication was stated on their prescription; (ii) it was assumed it was taken as a sedative (adult patients receiving low dose of phenobarbitone at night), and (iii) it was assumed to be taken for neuropathic pain (if received carbamazepine only on limited supply) (Lambie et al. 1981).

Epilepsy prevalence was estimated using the PHARMO database which contains histories obtained from 27 pharmacies covering all prescription drugs dispensed in six Dutch cities of approximately 300,000 total inhabitants (Lammers et al. 1996). They identified patients by their prescription of one or more of the AED drugs for a period longer than 180 days and excluded drugs not usually prescribed as sole agents for epilepsy (diazepam, oxazepam, nitrazepam, clobazam, flunarizine, and acetazolamide). 180 days was considered sufficient for the elimination of those patients using AEDs incidentally for indications other than epilepsy. However, they acknowledge that long-term use of AED drugs could also occur in certain psychiatric disorders and neuralgia, but incorrectly assume, this only occurs in middle aged patients and older. The authors compared their

estimated prevalence with that from the study in Rochester (Hauser et al. 1991), suggesting that the observed differences were due to 20% over-reporting by AEDs in the older age groups, although even with their proposed correction factor the prevalence of epilepsy remains higher in those aged greater than 45 years compared to Rochester. (de la Court et al. 1996).

A study in Mexico City utilised a population served by a government-sponsored health care programme with data from most of four neuropsychiatric referral clinics (general outpatients & emergency department) and hospital neurology admissions to compare the prevalence of epilepsy with that estimated by AED medication consumption. The two prevalence estimates were found to be similar, but slightly higher for AEDs, with the discrepancy between these sources probably relating to the inclusion of conditions other than epilepsy treated with AEDs rather than incomplete clinic coverage (Olivares 1972).

The Italian National Health Service (NHS) collects prescription data through local health units LHM covering populations of 50,000-200,000 people. Utilising this AED prescription data, two different Italian populations found the prevalence of epilepsy to be 5.2/1000 (Giuliani et al. 1986) and 5.7/1000 (Zolo et al. 1986). The authors suggest that prevalence rates established using screening of AED drugs may be relatively more valid simply because these studies simultaneously both overestimate and underestimate the number of patients by similar amounts. Prescriptions may underestimate the number of epilepsy cases when patients purposefully obtain medications from pharmacies far from their own area to conceal their illness or in some patients not receiving medications. At

the same time, this indirect method may overestimate the number of epilepsy cases because prescriptions are sometimes prescribed for misdiagnosed epilepsy or for other diseases (Giuliani et al. 1986, Zolo et al. 1986), with one study estimating about 7% of patients receiving AEDs due to misdiagnosis (Maremmanni et al. 1991).

Almost certainly, AED recruitment is a more efficient method for generating cases, or when greater study power considerations are required to understand epilepsy's demographic distribution, co-morbid conditions or higher level syndrome prevalence. In Zambia, a door-to-door survey required 55,000 individuals to be screened to yield around 800 cases to develop a population-based registry for ongoing health programmes (Birbeck and Kalichi 2004), and an Ecuadorian survey employed more than 275 people to screen a population of 75,000 over three years to recruit about 1200 lifetime cases (Placencia et al. 1992b). If a single medical source is used, AED or general practitioner may be the most effective compared to other medical sources (hospital, specialist, EEG), with one study identifying most cases (82%) equally from either AED or family doctors compared to all other sources (Maremmanni et al. 1991).

Every person identified as having epilepsy in a door-to-door community survey in Australia had been prescribed AED medications at some time in their lifetime with treated prevalence on survey day 5.15 per 1000 compared to lifetime treated prevalence of 7.5 per thousand, a difference of about thirty percent (Beran et al. 1982), similar to the percentage difference found in the Parsi community in Bombay (4.7 vs. 3.3 per 1000) (Bharucha et al. 1988). Although the lifetime prevalence estimates are inflated to

include patients not usually defined as having epilepsy (i.e. acute symptomatic seizures such as febrile convulsions), the lifetime treated prevalence of epilepsy was only a quarter lower than the lifetime prevalence estimate in the UK between 1983 and 1993 (Cockerell et al. 1995). With 92% receiving AED treatment on prevalence day, even higher penetration of AED treatment was seen in Sweden from cases identified from medical and insurance sources (Forsgren 1992).

However, differences between prevalence and treated prevalence are greatest in communities with inadequate access to medical services, and may not be uniform even between regions in the same country, particularly in developing countries. A study in five regions in the People's Republic of China (Heilongjiang, Ningxia, Henan, Shanxi, Jiangsu) showed an almost two fold difference in lifetime prevalence and around two and a half fold difference in treated prevalence in the last week between different regions in the People's Republic of China (Wang et al. 2003).

Ascertainment by AED medications, although secondary to medical practitioner diagnosis and treatment, has the advantage that it does not rely on medical practitioner contact for enumeration, invitation, or patient participation. In a study in Wales, although ninety percent of repeat prescription cases had specialist diagnostic confirmation before a diagnosis of epilepsy was applied, about sixty percent had not consulted a doctor over the preceding year (Lloyd Jones 1980). Similarly, a study using repeat prescription data to ascertain cases over six months in nine general practices in Belfast, found that one in four cases had not attended their general practitioner or hospital outpatient department despite

repeat prescriptions for AEDs. Despite their non-attendance for doctor consultations (but not for prescription uptake) half these patients had one or more fits in the preceding twelve months suggesting that some cases of important active disease would not have been detected if recruitment had been only reliant on direct doctor contact (McCluggage et al. 1986). These studies suggest that AED ascertainment may have advantages over medical practitioner follow-up which may underestimate prevalence estimates even in regions with seemingly high access to health services.

With a quarter of the cases experiencing no seizures in the last five years, case ascertainment through AED prescriptions were found to also include mild cases often not generated in tertiary-based recruitment (Giuliani et al. 1992). Using the expected prescription numbers as an indicator, similar compliance was found between those patients with frequent (93%) compared to no seizures (89%) (White and Buckley 1981). Conversely, it has also been shown that active disease does not inevitably result in AED treatment, with 22% of all cases not taking AEDs on the day of a prevalence survey despite having had seizures in the previous five years (Oun et al. 2003).

Management practices and culture among local physicians and patients may affect prevalence estimates from AED prescriptions. For example, the typical practice in most countries is to commence AED treatment after the second unprovoked seizure. With only 1% (7/713) of people treated after a single seizure in Sweden (Forsgren 1992), patient recruitment by AED prescription is likely to yield few false positive cases due to 'early' treatment. In contrast, although conventional drugs are free of charge in Estonia and

doctor almost always prescribe AED at initial diagnosis, patients tend to withdraw from therapy more often than patients in developed countries (Oun et al. 2003).

2.5 Community sources

Insurance, 'sickness' funds' and occupational groups

Insurance and 'sickness' funds', often in occupational groups, have been used to measure disease prevalence (see Table 2.1 and Figure 2.1) (Davenport 1923, Leibowitz and Alter 1968, Wajsborn et al. 1967). In fact, the modern epidemiologic study of epilepsy probably dates from 1923, when Davenport measured the frequency of draft rejection and medical discharges from the US Army because of epilepsy, and estimated it to be 5.15 per 1000 (Davenport 1923). He compared this figure with the frequency of epilepsy found primarily in other armed service sources (army draftees, army sick reports), and also in a wide variety of other sources ('agricultural' areas, American Indian reservations, hospital outpatients, hospital inpatients and private specialists) in many countries (United States, Hawaii, Italy, Germany, France, Scotland, Britain, Germany, Denmark, Switzerland, Philippines, India, Japan, Korea, China, and New Zealand), geographic regions (urban versus country), and ethnic groups ('Negroes', 'Jews', American Indians, Māori, and Hawaiian Islanders). He found that the prevalence varied from 0.0 per 1000 in indigenous Māori New-Zealanders in an outpatient setting to 23.8 per 1000 in Korean outpatients of a missionary hospital (see Figure 2.3).

Figure 2.3: Prevalence of epilepsy by country, region, and ethnic groups from various sources (Davenport 1923)

Class, Nationality or Race, How Obtained	Rate per 1,000
United States:	
2,500,000 drafted men.....	5.15
Rural recruits	5.36
Urban recruits	4.79
Boston recruits	6.13
New York City recruits.....	5.62
Chicago recruits	4.53
Vermont recruits	12.72
Maryland recruits	7.98
New York Recruits.....	6.07
New Jersey recruits.....	4.32
Kansas recruits	3.77
Utah recruits	3.48
South Dakota recruits.....	1.20
Southern agricultural—mainly native white.....	5.65
Southern agricultural—mainly negro.....	5.13
French Canadian sections.....	6.11
Scotch settlements	5.18
German and Scandinavian settlements.....	3.99
Scandinavian settlements	3.87
Finnish settlements	2.86
Army, admission sick report, 1918, white (2,204,709).....	2.09
Class, Nationality or Race, How Obtained	Rate per 1,000
United States:	
Army, admission sick report, 1918, colored (174,846).....	7.23
Army, admission sick report, 1917, white.....	2.70
Army, admission sick report, 1917, colored.....	6.54
Scotland, Army recruits, 1917 to 1919.....	6.40
Great Britain	0.3 to 37.0
British in institutions of United States, 145 per cent. of quota.....	
Denmark, various estimates.....	1.2 to 4.0
France, recruit statistics.....	1.6
Germany:	
Admission to sick report, Prussian army, 1889 to 1890.....	2.1
Admission to sick report, Prussian army, 1895 to 1896.....	2.9
School children of Mecklenburg.....	1.15
Other areas	2.0
Italy:	
Morselli's count of 5,000 Italians.....	1.2
10,000 military recruits, rejections for epilepsy.....	11.53
Switzerland:	
Zurich, estimated	3.0
Canton Unterwalden, minimum estimates.....	2.0
Ammann's estimate for whole country.....	5.0
Jews:	
Applicants for relief, New York City.....	2.0
Russians and Poles in institutions of United States, 117% of quota	
Maoris of New Zealand.....	0.0
Hawaiian Islanders, admission to sick report, United States Army	0.54
Philippine Islanders, admission to sick report, United States Army	0.33
India:	
Admission to sick report, Europeans (1889).....	1.2
Admission to sick report, Europeans (1834).....	4.5
Admission to sick report, native Indians (1889).....	0.5
Admission to sick report, native Indians (1834).....	0.7
Missionary dispensary hospital (Macphail), 1904, patients.....	4.8
Native troops, Calcutta, admission.....	0.75
Native troops, Murraybar, admission.....	1.2
Native troops, French Rocks, admission.....	0.4
Troops at Mysore, admission (European).....	2.3
Troops at Mysore, admission (native).....	0.7
Bengal Presidency, Army admissions (European).....	1.7
Bengal Presidency, Army admissions (native).....	0.4
Japan, Navy, admission to sick report.....	0.4
Korea, Outpatients of missionary hospital.....	23.8
China:	
Shanghai hospital, patients.....	2.5
Soochow hospital	2.7
Soochow, private cases.....	5.0
Shansi, North China, hospital.....	4.3
Harvard Medical School in China.....	3.5
Amerindians:	
Hrdlicka's statistics on 70,000 Indians.....	2.1
5,000 Sioux, Rosebud Agency.....	4.6
6,690 Sioux, Pine Ridge Agency.....	2.5
6,600 Pimas	0.15
United States Draft, South Dakota Indian reservation.....	4.3
Arizona Indian section.....	1.3
New Mexico Indian section.....	8.1
Negroes:	
United States Draft, Negro sections, defect found.....	5.13
United States Army, admission to sick report, 1917.....	6.54
United States Army, admission to sick report, 1918.....	7.23
United States Army, admission to sick report, 1919.....	1.18

Although probably not as pronounced today, ‘worker’ surveys’ in previous eras often restricted their coverage to young adult men, surveying those not able to work by disability pensions (Forsgren 1992) tending to capture only the severe end of the disease spectrum. In addition, eligibility for pensions varies by disease category as it is assigned by government agencies, and is potentially subject to the current local economic and political climate. Disease disclosure in working populations may also have a bias, with participants either denying or feigning illness, depending on the advantage sought. In a study of males aged 17-18 years selected for military service in Lombardy, Italy (Cornaggia et al. 1990), a number were discovered to have epilepsy in the year after examination, suggesting that candidates were more likely to hide their epilepsy at induction in order to be allowed entry.

Household survey

With more than half of the publications utilizing this technique, the household survey is now the cornerstone of epidemiological epilepsy research (see Table 2.1 and Figure 2.1). The main advantage of household surveys versus ascertainment by other methods is their independence from medical treatment. This is an important advantage in developing countries, rural and remote communities (Gudmundsson 1966) and indigenous populations (Haerer et al. 1986), where access to health care is more likely to be inadequate. In an attempt to be independent of clinician diagnosis, Rose et al (Rose et al. 1973) appear to have been the first investigators to have critically applied household survey questionnaire methods to study the prevalence of epilepsy. Their instrument was

administered by mail to all families with a grade three child (8-9 years) in the suburban area of Washington County, Maryland.

It was the early pioneer neuro-epidemiologist Bruce Schoenberg, who developed the research design protocol employed by the majority of subsequent epilepsy epidemiology studies (Osuntokun et al. 1982). This strategy, was developed as a design method to address the research conditions felt to be universal to all developing countries with very few trained personnel for health care delivery and most of these concentrated in a few university teaching hospitals (Schoenberg 1982, Schoenberg 1983). It involved a staged design, involving a screening questionnaire administered by trained non-medical personnel, followed by a detailed neurological assessment of test positive cases either by a medical practitioner, specialist physician and/or neurologist.

Although a relative problem, the scarcity of sufficient specialised epilepsy medical personnel and diagnostic services is not only an issue in developing countries (Baumann et al. 1977). For example, in Clay County in the USA, there was a small community hospital of four general practitioners, no electroencephalogram (brain wave test for epilepsy) or other newer diagnostic facilities, and was serviced by a travelling child neurology clinic (surgeon and paediatrician) five times a year linking the county with the University of Kentucky Medical Centre, one hundred miles to the north-west.

Using their rigorously constructed and validated diagnostic questionnaire this concept of cascading specialty diagnosis was further refined in Ecuador (Placencia et al. 1992a,

Placencia et al. 1992b, Placencia et al. 1992c). Case ascertainment was conducted by a house-to-house census of the population with a standardized validated household survey by screening personnel, overseen by a team of rural doctors, checked by a team of specialist neurologists, with the final diagnosis agreed by consensus from an international neurological panel. This study exemplifies the most meticulous, rigorous, methodological approach to measuring the incidence and prevalence of epilepsy in developing country conditions. Although it almost certainly represents best practice for measuring the prevalence of epilepsy in developing countries by household survey, it highlights the considerable resources necessary with this approach, and it would be difficult to replicate logistically in most developing or developed countries. The cost of finding and verifying one case by survey in India with confirmation by a neurologist has been estimated to be US\$14, requiring 55 person-days using eight survey workers (Pal et al. 1998).

In the past, one of the difficulties in conducting prevalence surveys in developing countries was that demographic or census data were often unavailable or out of date (Osuntokun et al. 1982) making it difficult to identify all the available source population for the survey. This difficulty is highlighted in a study in Uganda where only an ill-defined denominator was available based on three different estimates yielding prevalence of 2.9, 2.1 and 3.7 per 1000 respectively (Billinghurst et al. 1973). Due to these sorts of difficulties with census data, and to enhance cooperation, a novel approach using the revolutionary party household cell structure was utilised where accurate lists of persons were available (Bondestam et al. 1990). Another problem in developing countries is

patient movement in nomadic communities, requiring survey administration on different days for complete data capture or exclusion of potential participants classified as non-permanent town residents (Tekle-Haimanot et al. 1990b).

Key informants

As questionnaires were likely to produce lower and incorrect figures, collaboration with the “medicine man” was advocated in Nigeria to produce more valid figures as a key informant seeing a large number of people with epilepsy (Dada 1970). This method is used especially in countries where traditional practitioners and religious representatives are the preferred treatment option (Debrock et al. 2000) and ‘western’ medical presentation is withheld or seizure observation is more reliably disclosed outside the family, such as from village leaders, due to social stigma (see Table 2.1 and Figure 2.1) (Debrock et al. 2000, Kaamugisha and Feksi 1988, Pal et al. 1998, van der Waals et al. 1983). Other countries have also used non-medical, non-household sources to assist in ascertainment of cases, including social workers (Maremmani et al. 1991), public authorities (Epileptics 1928), health workers, schoolchildren (Pal et al. 1998), and teachers who may witness seizures in the classroom setting (Debrock et al. 2000, Pal et al. 1998).

The main criticisms of this method is its lack of sensitivity, found to be three to eight times less than with other methods (Debrock et al. 2000, Pal et al. 1998, Thorburn et al. 1991, Kaamugisha and Feksi 1988), and uniformity in standards of diagnosis (Pollock 1930) with teachers and school children unable to detect cases due to school non-

attendance. Thus although one study suggests that generalised absence seizures, frequently missed in surveys, may be better identified from teachers (Debrock et al. 2000). However, this was not confirmed in another study using similar methods, with key informants tending to primarily detect more visible cases, but being more efficient than a survey at detecting cases relative to cost and time (Pal et al. 1998).

2.6 Multiple sources

Several studies have used a number of different sources to ascertain cases (Brewis et al. 1966, Forsgren 1992, Granieri et al. 1983, Keranen et al. 1989, Oun et al. 2003, Rocca et al. 2001), but in only a few instances have these included community sources (Brewis et al. 1966, Granieri et al. 1983) in addition to medical sources. Using the blunt question of “loss of consciousness” to screen households, half the household survey case were found not to have been previously diagnosed in medical sources (Brewis et al. 1966), while a study in Estonia found that no single source was substantially more complete than any other (Oun et al. 2003) .

2.7 The capture-recapture method

The principle of this method, used by some of the most recent prevalence studies (Bobo et al. 1994, Boon et al. 1995, Murphy et al. 1995, Pal et al. 1998), is to cross-reference information from different sources, and to estimate from the “overlap” of cases between the various sources, the number of cases not identified by any of the sources (Sekar and Deming 1949). The capture-recapture method requires all sources to be independent of each other so that the probability of a case being reported by one source is not dependent

on the probability of it being reported by another source (for example AED prescription use is probably independent of teacher reporting, whereas it is likely to be dependent on treatment by general practitioners who may supply prescriptions).

This method was used with a door-to-door survey, hospital pharmacies and key informants in Benin Africa (Debrock et al. 2000). Combining all sources produces an estimate of prevalence of 21.1 per 1000, while the prevalence is estimated to be 33.3 per 1000 (2 sources) and 35.1 per 1000 (3 sources) by capture-recapture methods (Chapman 1951, Seber 1970). With only six percent of cases from medical sources compared to the approximately 75% found by survey, this study shows major problems in using health service data to estimate prevalence in groups with poor access to health care.

2.8 Comparative studies

There is a limited number of comparative studies on efficacy (Debrock et al. 2000, Maremmani et al. 1991, Stanhope et al. 1972). Defining efficacy as the number of cases detected by a given method divided by the number of cases known from all clinical and field sources (Stanhope et al. 1972), investigators found that survey techniques were slightly more effective for detecting total known cases (0.88 and 0.87 vs. 0.82) and idiopathic cases (0.89 and 0.96 vs. 0.76), while hospital sources were more effective for detecting symptomatic cases (0.92 and 0.75 vs. 0.96). When hospital records were used alone they found under-reporting of idiopathic cases by more than a half, while ascertainment of symptomatic seizure disorders was nearly complete from these sources

(Stanhope et al. 1972). This suggests that under-reporting of idiopathic epilepsy prevalence is likely when determined only from hospital rather than community sources. However, at the time Mariana Islands neurological services were provided solely from hospital inpatient and outpatient services with no intermediate medical practitioners (general practitioner or non-hospital-based specialists) available for treatment or referral. Other studies have found that a large number of patients with epileptic seizures, initially seen in hospital, become seizure free and do not remain in contact with the hospital and hence would typically escape detection in hospital-based prevalence studies (Juul-Jensen and Foldspang 1983). Generalized seizures and syndromes, in particular absence seizures and epilepsy, are not often seen or diagnosed in hospital but are seen and diagnosed more often in a community setting (Cardozo and Patel 1976, Gudmundsson 1966, Osuntokun and Odeku 1970). However, although a more recent study in France found greater case ascertainment in community-based sources, they found that uptake could also be twice as high when “community-based” specialist private practitioners were available compared to hospital-based neurological services for generalized epilepsy (42.1% vs. 20.1%), IGE (35.8% vs. 16.2%) and all IGE sub-syndromes especially childhood absence but not localization-related epilepsy (Loiseau et al. 1991).

These findings are likely to partly reflect disease severity, with idiopathic epilepsy generally being easier to control than symptomatic epilepsy, particularly when not characterized by convulsive episodes, and therefore less likely to present to hospital. However, a study of cases aged 5-14 years found newly diagnosed clinic patients to have a similar frequency of idiopathic generalized epilepsy as a school age community

population (27.8% vs. 30.8%). This was not the case for symptomatic generalized epilepsy (21.1 vs. 3.2%) (Cavazzuti 1980), suggesting that the distribution of IGE syndromes in newly diagnosed patients may be representative of community-based disease. It also suggests that countries with better access to specialist epilepsy services are more likely to ascertain and manage community cases of idiopathic epilepsy (Cardozo and Patel 1976, Gudmundsson 1966, Osuntokun and Odeku 1970). Thus, in addition to treating severe disease, hospital services often reflect issues of health care access (Cardozo and Patel 1976, Osuntokun and Odeku 1970) with incomplete disease enumeration being especially problematic when disease referral is low (Abo Melha and Al-Rajeh 1987), with referral practices sometimes influenced by practitioner's attitudes about the appropriate therapeutic approach towards various forms of epilepsy (Granieri et al. 1983).

Using a variety of medical sources, an Italian study observed considerable overlap in case identification, with most of the 51 total cases identified (82%) equally from either AED or family doctors and almost all (50 of 51) by these sources combined. In addition, only 16% were found by a single source and AEDs make up almost two thirds of this (Maremmani et al. 1991). The authors contrast this study to one conducted earlier in the same district, finding an additional 14 cases not found previously, and attribute the differences to inferior survey methods and disease denial (Lamorgese et al. 1979, Reggio et al. 1996).

2.9 Summary

Epilepsy is rarely considered a positive condition of religious significance and the majority of cultures report a stigmatising effect of being given the label of epilepsy, leading to underestimation rather than overestimation of epilepsy prevalence, irrespective of the method of ascertainment (see Figure 2.2). Earlier epidemiological studies relied heavily on hospital-based records to measure the frequency, distribution and prognosis of epilepsy. However, as access and presentation to hospital may be delayed, and dependent on age, gender, and disease factors, ascertaining prevalent cases from this source can be affected.

With a large proportion of patients free of seizures and tolerant of treatment, in some communities cases ascertained from general practice can be a virtually complete case source for epilepsy that presents for medical assessment. However, diagnostic accuracy from primary care sources is dependent on ready access to tertiary care to limit false positives. Although secondary to medical practitioner input, AED prescription data has the advantage that it does not rely on medical practitioner contact for enumeration, invitation, or patient participation. Compared to other medical sources, when available, use of prescribing AED data may provide an accurate, effective and efficient method for estimating epilepsy prevalence in countries with high access to doctor diagnosis and uptake and maintenance of medication. As AED disease indications are not specific it is essential to define and exclude false positives prior to counting cases as true positives.

The household survey is now the cornerstone for case ascertainment in measuring the incidence and prevalence in epilepsy epidemiological research. Its main advantage compared to other methods is its independence from medical treatment, and therefore it is the only method able to potentially capture cases with unrecognised symptoms.

Household surveys also have advantages in developing countries, rural and remote communities and indigenous populations, where access to health care is more likely inadequate. Typically surveys, form part of a staged design, involving a screening questionnaire administered by trained non-medical personnel, followed by a detailed neurological assessment of test positive cases either by a medical practitioner, specialist physician and/or neurologist. Although only utilised by a few recent studies, capture-recapture methods including survey techniques almost certainly now represent best practice for measuring the prevalence of epilepsy.

Chapter Three: Methodological issues in measuring the prevalence of epilepsy II: Classification and diagnosis

3.1 Introduction

The first part of this chapter discusses the emergence and widespread adoption of the clinical and operational definitions for epilepsy, epileptic seizures and syndromes proposed by The International League Against Epilepsy (ILAE) (ILAE 1981, ILAE 1989). The second part of the chapter considers epilepsy diagnosis in prevalence studies, progressing from secondary patient records, to primary community sources without disease, requiring symptom questionnaires and expert interpretation by specialists.

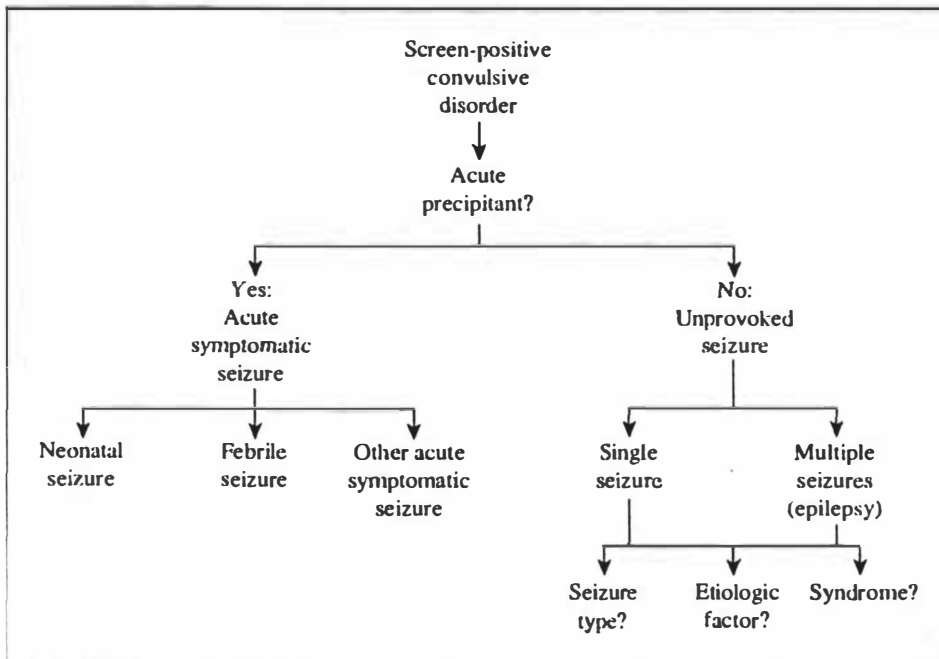
3.2 Methodological issues in classification

The word ‘epilepsy’ derives from the Greek verb ‘epilambanein’, meaning to be seized, to be overwhelmed by surprise (Anonymous 2003). In more recent times, epilepsy’s modern clinical architects have proposed the view that “convulsion is but a symptom” (Jackson 1931, Penfield and Jasper 1954), reinforcing the idea that epilepsy should be considered merely a descriptive term and not a disease.

‘Global’ classifications for epilepsy

Epilepsy is a tendency to have recurrent seizures, with a diagnosis being made after two ‘unprovoked’ seizures. The accepted clinical process for reaching such a conclusion is outlined below (see Figure 1) (Hauser et al. 1991).

Figure 3.1: Flow diagram for classification of seizures and epilepsy in epidemiologic studies from Hauser et al 1991



Seizures are classified as unprovoked in the absence of an immediate structural or metabolic insult to the central nervous system – in which case they are called acute symptomatic seizures (ILAE 1989). However, acute symptomatic seizures have sometimes been included as epilepsy cases, leading to elevation of prevalence estimates (Cockerell et al. 1995, Goodridge and Shorvon 1983, Placencia et al. 1992b, Placencia et al. 1992c, van der Waals et al. 1983, Wallace et al. 1998a). This initially came about because historically acute symptomatic seizures were not separated from unprovoked seizures, but now occurs more because of difficulties in differentiating the temporal nature of any proximate insult.

In addition, the acute period has been variously defined as: 48 hours (Hauser et al. 1991), seven days (Hauser et al. 1991), two weeks (Haerer et al. 1986), one month (Rocca et al. 2001), two months (Aziz et al. 1994), and up to 3 months of an acute process (Hauser and Kurland 1975, Hauser et al. 1991). Sometimes even within the same study the period has varied depending on the aetiology of the process: seven to 14 days after head injury; seven days after a stroke; within 48 hours of alcohol withdrawal or in association with brain tumours, metabolic disturbance, toxins; and a presentation of tumour or postoperative period “up to the time of stabilisation” (Hauser et al. 1991).

Febrile seizures, the most common form of acute symptomatic seizure, have sometimes also been categorized as epilepsy in prevalence studies. Ascertaining the febrile nature of the convulsion may be difficult and there is variation in its lower age limit from one month (ILAE 1993) to three months (Freeman 1980). In contrast, epilepsy can be the result of a ‘remote’ symptomatic insult, when an event results in cerebral damage that subsequently leads to epilepsy. This distinction between ‘acute’ versus ‘remote’ insult is also not always clear, as in the case of a evolving neurological condition e.g. a cerebral tumour (Baumann et al. 1977, Haerer et al. 1986, Keranen et al. 1989). Some studies have also included cases after a single seizure (Goodridge and Shorvon 1983, Lessell et al. 1962, Placencia et al. 1992b, Placencia et al. 1992c, Zander et al. 1979) likely leading to elevated estimates, while an Australian study defined the disorder only after at least three seizures had occurred (Beran et al. 1982).

This lack of uniformity in the definition used for the classification of epilepsy makes it difficult to compare the findings of different epidemiological studies. Although epilepsy is primarily a clinical diagnosis, some reports only include those who also had an abnormal EEG. In contrast, other investigators have only included as cases those with 'idiopathic' or 'symptomatic' epilepsy, or those with a history of a seizure and a normal EEG. In earlier studies, classification often involved a clinical 'black box', e.g. 'standard clinical definitions for diseases and syndromes' were used in a study in the UK to include cases (Brewis et al. 1966) or labelled by a neurologist without specifying a definition (Bondestam et al. 1990, de Graaf 1974, Epileptics 1928, Joensen 1986, Krohn 1961, Olivares 1972). In fact, twenty definitions have been used in the studies reviewed, with only half of the studies having used the current 'global' definition for epilepsy of two or more afebrile non-acute symptomatic seizures (see Table 3.1).

Along with the 'global' definition for epilepsy, a number of operational definitions are also reported in studies as defined by the International League Against Epilepsy (ILAE) (ILAE 1993). The most commonly reported operational definition is 'active epilepsy' defined as, 'a seizure in the preceding five years or receiving anti-epileptic drugs in the preceding five years'. This definition is particularly useful in a condition which has a tendency to sometimes remit in adulthood, and should reduce recall bias compared to lifetime prevalence estimates. However, the majority of later studies that have included an 'active epilepsy' category have also used a wide range of idiosyncratic interpretations (see

Table 3.2).

Table 3.1: Definitions for epilepsy used in prevalence studies: 1923-2007 (n=115)

Definition	Studies	
	(n)	%
Epileptic'	3	2.6%
2 or more afebrile, non acute symptomatic seizures	57	49.6%
Not specified	22	19.1%
2 or more afebrile seizures	6	5.2%
2 or more seizures	4	3.5%
2 or more afebrile seizures including acute symptomatic seizures	3	2.6%
3 or more doctor-diagnosed seizures	1	0.9%
3 or more, afebrile non-acute symptomatic	2	1.7%
Afebrile seizures	2	1.7%
1 or more afebrile, non acute symptomatic seizures	1	0.9%
1 or more seizures including febrile & provoked	5	4.3%
1 or more seizures, excluding febrile but including acute symptomatic seizures	1	0.9%
2 or more seizures and a positive EEG	1	0.9%
AEDs prescribed for epilepsy	1	0.9%
Doctor diagnosed epilepsy	1	0.9%
Epileptic fits' or on AEDs in last 2 years	1	0.9%
Grand mal' attack excluding infantile convulsions	1	0.9%
AEDs prescribed for > 180 days in last year	1	0.9%
AEDs prescribed for epilepsy/seizures including symptomatic seizures	1	0.9%
Self-reported "epilepsy, repeated seizures, convulsions or blackouts	1	0.9%

EEG = electroencephalogram, AEDs = Antiepileptic drugs

Table 3.2: Definitions of ‘active’ epilepsy used in prevalence studies: 1923-2007 (n=115)

Definition	Studies (n)
If not on an AED, at least one seizure in last 2 yrs; or if on an AED, two seizures in last 5 years with at least one seizure in last 3 yrs	1
On an AED, or 2 or more seizures with a seizure in the last 12 months	1
One seizure in the last 5 years if on an AED or one seizure in the last 12 months if not on a AED	3
One seizure occurring in the last 5 years, and/or on an AED at time of survey	6
One seizure in the preceding 24 months, on an AED or both	1
One seizure in the last 2 years	3
Two or more seizures in the last 12 months	1
One seizure in the last 5 years	9
On an AED or seizure in the last 6 months	1
Two seizures or one episode of status in the last 12 months	1
One seizure in the last 3 years, or on an AED	1
On an AED and one seizure in the last 5 years	1
On an AED or a seizure in the last 6 months	1
On an AED or a seizure in the last 5 years	17
One or more seizures or on an AED in last 2 years	4
Seizure in the last 12 months or on an AED at time of survey	2
Two or more seizures in the last 2 years	1
On an AED, one seizure in last 3 years; not on an AED one seizure in the preceding 12 months	1
Epilepsy, repeated seizures, convulsions, or blackouts in the preceding 12 months	1
Two or more seizures in the last 2 years or on an AED	1
seizure or on an AED in the last 12 months	1
Seizure in the last five years or treated with an AED for epilepsy in last 12 months	1

AED = anti-epileptic drug

The classification of ‘more specific forms of epilepsy’

As outlined in Figure 3.1, after confirmation of two or more unprovoked seizures and a ‘global’ diagnosis of epilepsy, a person is then further sub-classified with a ‘more specific forms of epilepsy’ (see Appendix 1)(ILAE 1989). However, classification systems for ‘more specific forms of epilepsy’ have changed over the years and this has led to difficulties when comparing studies.

Changes in classification of ‘more specific forms of epilepsy’

Penfield and Jasper (Penfield and Jasper 1954) first attempted to classify epilepsy by relating the type of seizure to the cause using a system based on clinical and EEG findings, pathology and therapeutic considerations (McNaughton 1952, Penfield 1948). In contrast, Lennox used a purely seizure-based approach classifying epilepsy into five major categories: petit mal triad, convulsive triad, autonomic, unclassified, or combined seizures (Lennox and Lennox 1960). Utilised in a Nigerian study (Osuntokun and Odeku 1970) and although still semiologic, Williams divided generalised epilepsy to include: grand mal attacks without aura, petit mal and variants, myoclonic seizures and akinetic attacks with all other forms regarded as focal (Williams 1958).

In the late 1950s, a United Kingdom general-practice-based study involved surveying consultations for epilepsy and their subtypes and classified ‘petit mal’, ‘grand mal’, status epilepticus, and other epilepsy types (Logan and Cushion 1958), ‘grand mal’, encompassed all convulsive events, and ‘petit mal’ included ‘absence’ and ‘psychomotor’ events. Psychomotor epilepsy was originally confined to seizures of temporal lobe

origin, but has now evolved to mean complex partial seizures involving any lobe (Brewis et al. 1966). In the older terminology, convulsive seizures were synonymously diagnosed as 'grand mal' encompassing seizure both or partial and generalised onset. Similarly, non-convulsive seizures diagnosed as 'petit mal' likely included the current absence seizure and complex partial seizure phenomenology.

A study in Norway divided patients into: temporal, extra-temporal and centre-encephalic epilepsy types (Krohn 1961), while an early Danish study used four main groups: petit mal, focal symptomatic, non-focal symptomatic, epilepsy of unknown cause and the additional 'lipothymia group' consisting of patients in whom seizures were of a postural nature (Juul-Jensen 1964), synonymous to 'akinetik' attacks. Two Kenyan studies further highlight the idiosyncratic nature of classification, with one using the 1973 WHO criteria (Merlis 1970) to include events termed as 'Salaam attacks' (Ruberti et al 1985), while the second uses: diffuse, awakening, and sleeping for 'grand mal' syndromes (Telang and Hettiaratchi 1981).

These changes highlight the potential improved precision in classification by the use of standardized terminology, and its likely effect on comparisons between studies and time trend data (da Mota Gomes et al. 2002, Hauser and Kurland 1975). In the Rochester study, incidence rates for partial seizures more than doubled from the first to the second interval (from 14.2 to 30.4), whereas absence seizures decreased (from 5.7 to 3.4) (Hauser and Kurland 1975). This may also be the reason for the prevalence of each seizure type

(except for epilepsy characterised primarily by myoclonic seizures) increasing by a factor of two or more between 1940 and 1980 (Hauser et al. 1991).

Standardising seizure and syndrome classification

With the involvement of the International League Against Epilepsy (ILAE) in the early 1960s a more standardised approach to seizure and syndrome classification emerged (Gastaut 1969a, Gastaut 1969b, Gastaut 1970, Gastaut et al. 1964). Prior to this the classification of epilepsy in prevalence studies involved clinical data alone (Kurland 1959), which was later modified to also include EEG findings (Wajsbort et al. 1967). However, the main distinction this new approach provided was an essentially dichotomous ‘second level’ category of generalised-onset seizures, which were presumed to involve the entire brain from the outset, or partial-onset seizures, in which seizures begin in a localized brain region (Lavy et al. 1972). The ILAE classification of seizures and epilepsy syndromes was generally used to classify epilepsy in prevalence studies after their further revision in 1981 to also involve the ‘third level’ ‘idiopathic’, ‘cryptogenic’ and ‘symptomatic’ categories, along with some more detailed ‘fourth level’ higher sub-syndromes e.g. Juvenile Myoclonic Epilepsy (ILAE 1981, ILAE 1989) combining information on seizure types, age at onset, aetiology, clinical course, and electroencephalography (see Appendix 17 and Appendix 18).

However, the uses of these ‘third-level’ syndrome categories “idiopathic”, “cryptogenic” and “symptomatic” have also changed over time. “Idiopathic” used in an earlier context meant epilepsy without a definite cause (Kurland 1959), but is currently used for

epilepsies presumed to have a genetic aetiology. “Cryptogenic”, previously used as a presumption of a non-genetic aetiology, but with insufficient evidence to assign a specific aetiology, now is used for epilepsies without an identifiable structural lesion but with a presumption of one, while the “symptomatic” epilepsies remain the only testable term, as they are due to a radiologically visible brain injury, e.g. brain infection, stroke, head injury, brain tumour etc. (Hauser et al. 1991).

Even using a high level of expertise to diagnose cases from general practice records, up to two-thirds of diagnoses fall into non-specific ILAE categories such as partial cryptogenic (Kellinghaus et al. 2004, Manford et al. 1997). Although some of the diagnostic imprecision which was found in this study relates to its use of medical records to diagnose syndromes (Bodensteiner et al. 1988), other studies have also found few cases in the general population for some of the specific syndromes and categories described by the ILAE (Oka et al. 2006, Olafsson and Hauser 1999, Osservatorio Regionale per l'Epilessia (OREp) 1996). This has led some authors to suggest that the current ILAE system lacks diagnostic precision and does not identify internally aetiologically homogeneous or mutually exclusive groups (Manford et al. 1997).

A major reason for the imprecision in the ILAE system in diagnosing partial syndromes is due to the recent significant advances in neuro-imaging techniques. Skull x-rays and CT brain scans were an appropriate part of epilepsy assessment in earlier studies, but are no longer routinely used today in tertiary hospital epilepsy centres (Cardozo and Patel 1976, Sridharan et al. 1986, Young et al. 1982). Increasingly sensitive magnetic

resonance imaging of the brain (MRIB) is able to identify previously undetectable partial epilepsy etiologies (Jack et al. 1995, Jackson et al. 1990) and along with newer functional neuro-imaging techniques (Stevens et al. 1996) now play a central role in syndrome diagnosis of the partial epilepsies (Awada et al. 1991), yet these investigational modalities have not been integrated into the current revised ILAE classification systems (Engel 2001).

A hospital-based study in Austria classified patients according to the ILAE 1981 and 1989 classification systems, and found that with MRI the most frequent localization-related epilepsies were those caused by a structural abnormality 1258/1609 (78.2%). The cryptogenic group (n=335), those only ‘thought’ to have a structural lesion, were often re-classified as clearly having a structural aetiology when MRI was performed (Bauer 1994). Lack of expert MRI assessment makes measures of the “cryptogenic category” in previous studies rather arbitrary as neuro-imaging frequently can reclassify this group into “symptomatic” epilepsy (Ohtsuka et al. 1993). Therefore, it becomes difficult to define partial epilepsies on the basis of cortical localization and cryptogenic, symptomatic or idiopathic categories (Berg et al. 1999) without more extensive video-EEG monitoring and neuro-imaging investigations, which is often impractical in community-based epidemiological studies. Taken together, these studies suggest that the facility to classify epilepsy by less resource intense methods without a loss in validity would have great benefits in clinical practice and population-based research (Everitt and Sander 1999).

It is now well established that the idiopathic group of epilepsy syndromes have a major genetic contribution (Ottman et al. 1998a). This evidence is derived from studies demonstrating increased familial aggregation (Annegers and Hauser 1982, Annegers et al. 1982), higher concordance rates in monozygotic versus dizygotic twins (Berkovic et al. 1994, Lennox and Lennox 1960), genetic linkage and gene identification studies in human epilepsies (Gardiner and Lehesjoki 2000), and studies of human Mendelian disorders with seizures as part of the phenotype (Anderson et al. 1999). Familial aggregation studies suggest a significant genetic contribution with the standardized morbidity ratio for epilepsy in relatives of index cases with epilepsy with onset prior to age 16 years being 2.5 in siblings (95% CI 1.3-4.4) and 6.7 in offspring (95% CI 1.8-17.1) (Annegers and Hauser 1982, Annegers et al. 1982).

I GE is clinically characterized by absence, myoclonic, tonic-clonic, astatic, atonic and occasionally tonic seizures (ILAE 1981) with the EEG pattern of bilateral, synchronous and symmetrical spike and wave or polyspike and wave discharges. On the basis of the predominant seizure type, seizure pattern and age of onset, the international classification now recognises seven main sub-syndromes: benign myoclonic epilepsy of infancy, epilepsy with myoclonic absences, epilepsy with myoclonic astatic seizures, childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and idiopathic generalised epilepsy not otherwise specified (Engel 2001).

Although phenotypic concordance of these sub syndromes among first degree relatives of juvenile myoclonic epilepsy, and the absence epilepsies (childhood absence and juvenile

absence) is about one third (Beck-Mannagetta et al 1991, Garcia et al. 1993, Marini et al. 2004), these studies all show overlap of sub-syndromes within families suggesting that these epilepsies are genetically closely related, with childhood absence and juvenile absence being somewhat more distinct entities than juvenile myoclonic epilepsy. In addition there is emerging evidence of distinct genetic effects on absence and myoclonic seizures rather than their sub-syndrome phenotypes (Winawer et al. 2003), which is not surprising, as the presence of specific seizure types and their expression drives both the diagnosis of IGE and its sub-syndromes and underlines the importance of better genotype-phenotype understanding if we are to ultimately dissect the genetics of IGE.

Idiopathic Generalised Epilepsy (IGE) is said to be a common group of epilepsies accounting for about 20-40% of all epilepsies (Gastaut et al. 1975, Janz et al. 1992;) and there are considerable increasing worldwide attempts to discover the suspected large genetic contributions to their aetiology (Mulley et al 2004.). However, their prevalence estimates have been derived solely from hospital-based observations with no community-based studies been performed, making it difficult to judge their relative importance from a public health perspective to the epilepsies as a whole.

3.3 Methodological issues in diagnosis

Difficulties in diagnosis

Only a few studies draw attention to the group of conditions often masquerading as seizures. Although not well documented, alternative diagnoses for events that mimic seizures such as syncope, psychogenic events, migraine and vertigo can be present in up

to one-fifth of samples (Keranen 1987, Leibowitz and Alter 1968). In a US study, spells following pain or emotional upset and consisting of the subject becoming limp were considered fainting episodes and were not counted as seizures, while spells in children under five years which occurred followed pain, crying and which consisted of apnoea and limpness were considered as breath-holding attacks and were also not counted as seizures (Baumann et al. 1977).

The ILAE classification system used since 1981 denotes impairment of consciousness by a person's "degree of awareness and/or responsiveness to external stimuli" to define simple partial and complex partial seizures (ILAE 1981). This can be difficult, especially for the patient and sometime even the witness. Absence seizures (like complex partial seizures) may only manifest as brief periods of inattention which may be difficult to detect without close observation and interaction with the patient. These seizures have been found to be often missed with written screening questionnaires (Rajeh et al. 2001, Rajeh et al. 1993) or when concealed by the patient (Rocca et al. 2001). In a study in Israel, almost one-third of patients were unable to be classified, with misdiagnosis being more likely between 'petit mal' and 'temporal lobe' epilepsy (Leibowitz and Alter 1968).

Hence, patients with absence or temporal lobe onset epilepsy have a longer interval between onset and diagnosis from those with other types (Hauser et al. 1991), particularly if characteristic abnormalities on the patient's EEG record are considered diagnostically necessary (Loiseau et al. 1991). In a study in Bolivia, absence or complex partial seizures were not separated in 10% of patients (Nicoletti et al. 1999) with inter-ictal EEG

recordings. There was a tendency to reclassify generalised seizures as partial, mostly when seizures were convulsive rather than non-convulsive (i.e. absence only from 10 to 9, myoclonic only from 10 to 9, but tonic clonic from 63 to 43, and secondarily generalised from 33 to 56, tonic also altered with EEG from 5 to 2 but was rare).

In an adult outpatient setting in Lagos University teaching hospital in Nigeria, about 10% of epilepsy patients (80/796) were unclassifiable (Danesi 1985), while a Pakistani study found that in 5.6% of cases, the seizures could not be classified into any categories (Aziz et al. 1994). Using clinical EEG and CTB data, a study in Saudi Arabia found that in about a half of patients it was impossible to determine if seizures were partial or generalized in onset because patients were unable to give clear details of their symptoms or the EEG failed to show definitive diagnostic changes. As in most studies, the authors conceded that the diagnostic questionnaire they used probably had lower sensitivity for detecting non-convulsive seizures, particularly absence seizures (Rajeh et al. 2001, Rajeh et al. 1993). A Finnish study managed to solely classify 82.5% of 1220 patients (Keranen et al. 1988) a figure similar to that obtained in several other studies (Gastaut et al. 1975, Oka et al. 1995, Osservatorio Regionale per l'Epilessia (OREp) 1996, Oun et al. 2003), but less than the figure of greater than ninety percent seen in some other studies (Granieri et al. 1983, Joensen 1986, Juul-Jensen and Foldspang 1983, Oka et al. 2006, Senanayake 1993, Viani et al. 1988). It is not readily explained by the level of investigational complexity used (see Table 3.3).

Table 3.3: Proportion of unclassifiable seizures in epilepsy prevalence studies from 1923-2007 (n=115)

Study	Country	Cases n	ILAE 1981	Unclassified %
Africa				
(Rwiza et al. 1992)	Tanzania	201	yes	10.1
(Tekle-Haimanot et al. 1990b)	Ethiopia	316	yes	5.0
(Goudsmit et al. 1983)	Liberia	123	yes	ns
(Levy 1970)	Rhodesia	130	no	4.5
(Coleman et al. 2002)	Gambia	80	yes	ns
(Debrock et al. 2000)	Benin	66	yes	6.1
(Osuntokun et al. 1987)	Nigeria	101	no	18.8
(Danesi 1985)	Nigeria	945	no	3.0
(Danesi and Oni 1983)	Nigeria	396	yes	ns
(Ruberti and al 1985)	Kenya	912	ns	3.3
(Tekle-Haimanot 1984)	Ethiopia	468	ns	6.9
(Osuntokun and Odeku 1970)	Nigeria	522	no	ns
(Hurst et al. 1961)	South Africa	51	no	ns
(Snow et al 1994)	Kenya	30	yes	20.0
Asia, India & The Middle East				
(Bharucha et al. 1988)	India	66	yes	ns
(Kaoul et al. 1988)	India	157	yes	9.6
(Pal et al. 1998)	India	132	yes	20.0
(Attia-Romdhane et al. 1993)	Tunisia	141	yes	ns
(Sridharan et al. 1986)	Libya	568	yes	ns
(Onal et al. 2002)	Turkey	17	yes	11.8
(Aziz et al. 1994)	Pakistan	241	yes	5.6
(Rajeh et al. 2001)	Saudi Arabia	136	yes	51.0
(Rajeh et al. 1990)	Saudia Arabia	741	yes	ns
(Loh et al. 1997)	Singapore	121	yes	9.0
(Lessell et al. 1962)	Mariana Islands	111	no	ns
(Marino Jr. et al. 1987)	Brazil	91	no	ns
(Garcia-Noval et al. 2001)	Guatemala	46	yes	2.0
(Gomez et al. 1978)	Columbia	168	no	ns
	Republic of	19	yes	5.0

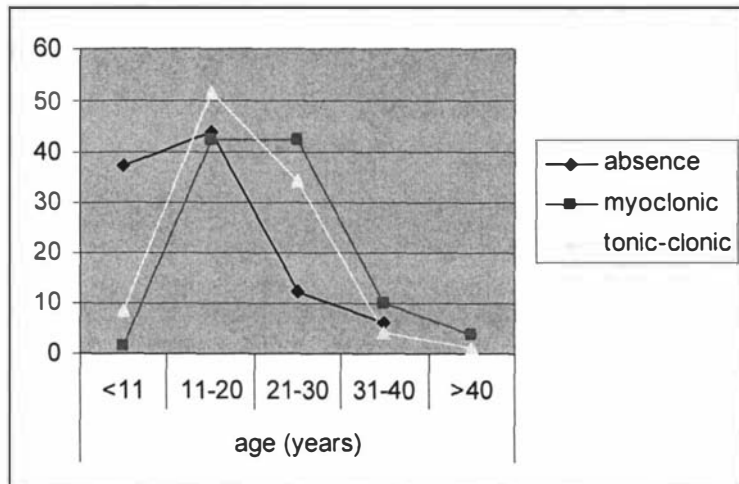
Study	Country	Cases n	ILAE 1981	Unclassified %
(Gracia et al. 1990)	Panama			
(Fernandes et al. 1992)	Brazil	113	ns	21.6
(Lavados et al. 1992)	Chile	297	yes	ns
(da Mota Gomes et al. 2002)	Brazil	20	yes	25.0
(Nicoletti et al. 1999)	Bolivia	124	yes	ns
(Mendizabal and Salguero 1996)	Guatemala	16	yes	ns
(Placencia et al. 1992c)	Ecuador	881	yes	2.0
North America				
(Kurland 1959)	USA	295	no	1.5
(Hauser et al. 1991)	USA	66	yes	ns
(Hauser et al. 1991)	USA	124	yes	ns
(Hauser et al. 1991)	USA	198	yes	ns
(Hauser et al. 1991)	USA	285	yes	ns
(Hauser et al. 1991)	USA	383	yes	ns
(Haerer et al. 1986)	USA	246	yes	13.8
(Hauser and Kurland 1975)	USA	242	no	2.5
Europe				
(Giuliani et al. 1992)	Italy	256	no	7.4
(Rutgers 1986)	Netherlands	88	yes	2.0
(Brewis et al. 1966)	England	360	no	ns
(Goodridge and Shorvon 1983)	England	122	yes	17.0
(Cockerell et al. 1995)	England	126	yes	14.0
(Wright et al. 2000)	England	1561	yes	ns
(Maremmani et al. 1991)	Italy	51	yes	ns
(Granieri et al. 1983)	Italy	278	yes	7.2
(Cornaggia et al. 1990)	Italy	258	yes	5.7
(Rocca et al. 2001)	Italy	81	yes	3.0
(Oun et al. 2003)	Estonia	317	yes	19.9
(Olafsson and Hauser 1999)	Iceland	428	yes	2.0
(Keranen et al. 1989)	Finland	1220	yes	17.6
(Krohn 1961)	Norway	919	no	ns
(Gudmundsson 1966)	Iceland	987	no	2.2
(Forsgren 1992)	Sweden	713	yes	7.6
	Northern			
(McCluggage et al. 1986)	Ireland	242	no	5.0
(Zander et al. 1979)	England	52	no	23.1
(White and Buckley 1981)	England	64	no	ns

ns = not specified. ILAE 1981 (ILAE 1981)

Uncertain epileptic syndromes were found in 11.6% (995/8750) of patients in a study in Lombardy, France (Osservatorio Regionale per l'Epilessia (OREp) 1996) in which diagnostic uncertainty was influenced more often by atypical seizure features (e.g. excessive amount of myoclonias resulting in a reluctance by the authors to diagnose absence epilepsy in patients with concomitant absence seizures) rather than atypical age of seizure onset (i.e. 23.1% due to atypical features vs. 3.3% atypical age of onset) or later timing of data collection (i.e. syndrome diagnosis similar for data collected within one year vs. one to five years).

Therefore, although age of onset is one of the most useful discriminating factor in diagnosing the likely IGE seizure type, it is a continuous rather than dichotomous relationship. This is illustrated by the study of Senanayake (Senanayake 1993) where, seizure onset was before 40 years of age for all IGE seizure types with: absence seizures greatest up to 20 years of age; myoclonic greatest between 11-30 years of age; and tonic clonic seizures greatest between 11-30 years (see Figure 3.2).

Figure 3.2: Frequency of generalised seizure types by age of onset (absence = 16, myoclonic = 182, tonic clonic = 93) (Senanayake 1993)



This same hospital-based study in Sri Lanka classified 1250 patients using seizure symptomatology alone. The diagnosis was confirmed by EEG in a number of cases, particularly absence seizures (absence 81.3%, myoclonic 45.6%, and GTCS 30.9%) but changed the diagnosis in only a few (less than 3%), therefore confirming that a good standardized questionnaire is the key instrument in classifying epileptic seizures and is of particular relevance for epidemiologic studies in developing countries. The investigators found that the most important factor in making a diagnosis, in particular for specific seizure types, is an eye-witness account of the patient's seizures (Senanayake 1993).

An Australian study retrospectively classified 1902 consecutive patients from a single neurological consultant practice over 30 years and identified 1637 patients with epilepsy. Patients were seen three times on average although 42.3% were seen only once and most (89.3%) had an EEG performed. The proportion of undetermined epilepsy (22.4%)

decreased with increasing number of occasion on which patients were seen, with generalized epilepsies tending to be increasingly diagnosed when seen more than once. The author diagnosed syndromes to the second level (i.e. idiopathic generalized), but suggested that this could have been performed to the third level for generalized syndromes, as this is primarily dependent on age of onset information. However, it was difficult to classify partial epilepsies to the same third level (i.e. cortical region) with confidence as brain imaging was not routinely available (Eadie 1996).

Although one study found the diagnosis of epilepsy syndromes to be easier in paediatric compared to adult patients (21% vs. 5%) (Kellinghaus et al. 2004), most studies find adult cases to be more readily classifiable than childhood cases (Gastaut et al. 1975, Joshi et al. 1977), when attempting to discern whether seizures are partial in onset, the presence of absence or myoclonic seizures (Mendizabal and Salguero 1996, Pal et al. 1998) and particularly severe epilepsies in childhood (Farrell 1993). In a study involving children less than 6 years of age, many patients lacked specific clinical or EEG features making sub-classification into epileptic syndromes difficult (Ohtsuka et al. 1993). These diagnostic problems in childhood epilepsy may relate to greater syndrome complexity, e.g. the complex secondary generalized epilepsies emerge during this period (17.5% vs. 1.9%), a more delayed period of complete syndrome evolution, or the diagnostic difficulties when relying solely on witnessed seizure information through a parent (Gastaut et al. 1975)

Thus, diagnosis of seizures and syndrome can be difficult depending on the quality of the information obtained. Diagnostic precision improves over time, with an eye-witness account of seizures, increased diagnostic expertise, and the level of investigation undertaken (only in partial seizure types), but there remains some residual uncertainty. Although some case series (Bauer 1994, Danesi 1985, Eslava-Cobos 1989, Loiseau et al. 1991, Viani et al. 1988) have reported a low rate of unclassified seizures, a high proportion of unclassified seizures may be seen especially in retrospective analyses of clinical data (Olafsson and Hauser 1999). The lower diagnostic rates between studies may partly relate to the quality of historical data obtained from patients and relatives, due to incomplete medical records in those without history, and difficulties obtaining good seizure history from patients and relatives.

Expertise of interview and interpretation

Although primarily intended to test the ability and use of the recently devised ILAE classification system, a hospital-based study involving the EEG laboratories in Marseille also reports the prevalence of seizures and syndromes (Gastaut et al. 1975). It was based on one of the largest groups of patients to date and compares the diagnoses obtained by two teams of doctors in 6000 (team A) and 562 (team B) cases. Team A comprised neurologists and paediatricians who based their diagnoses on personal history and interpretation of EEGs, while team B comprised various physicians, most not specialized in either neurology or paediatrics based solely on histories. Team A was able to classify 76.5% of patients, whereas team B managed only 54.4%. However, similar results were obtained at the generalized (37.7 vs. 40.2) and partial (62.3 vs. 59.8) level of diagnostic

differentiation by both groups, suggesting that specific syndrome classification rather than broad epilepsy-onset type may be more dependent on a higher level of expertise.

Only diagnose predominant seizure

Another problem in seizure prevalence studies is the tendency to diagnose only the predominant seizure type rather than all seizure types independently (Keranen et al. 1989, Olafsson and Hauser 1999). This has meant that when a patient had a combination of seizures e.g. absence and tonic-clonic seizures, patients were often classified only with tonic-clonic seizures (Brewis et al. 1966, Forsgren 1992). This approach may not be as useful in an evolving classification system, particularly for future genotype-phenotype associations, since most patients experience multiple seizure symptoms, and it is unclear which symptoms may be most predictive of genotype (Choi et al. 2006, Winawer et al. 2003).

3.4 Questionnaires

The very earliest studies attempting to measure the population prevalence of epilepsy lacked uniformity and standards of diagnosis (Pollock 1930). In the Rochester epilepsy epidemiological studies, all available medical records of residents with a diagnosis of epilepsy or seizures were reviewed, and diagnoses were based on the impression of the study neurologist from these secondary sources (Hauser et al. 1991). In their series of studies, the diagnosis of epilepsy type was based solely upon the clinical description of the seizure patterns, augmented in some cases by interviews with patients, without regard to the EEG patterns (Hauser and Kurland 1975).

Screening Questionnaires

Rose and collaborators appear to have been the first investigators to have critically applied household survey questionnaire technology to study the prevalence of epilepsy in children, by administering a mail questionnaire to all families in County Maryland and validating ten percent of their sample with examination by health-care personnel (Rose et al. 1973). As in most early studies they used a screening questionnaire, as distinct from a diagnostic questionnaire (discussed later), designed to select the subgroup of the population containing the majority of people with epilepsy (i.e. high sensitivity). As they have a low degree of specificity, epilepsy screening instruments ultimately require diagnostic confirmation, usually by expert neurological opinion (Debrock et al. 2000, Meneghini et al. 1991, Osuntokun et al. 1982, Placencia et al. 1992b, Tekle-Haimanot et al. 1990a) (see Table 3.5).

Screening questionnaires are most commonly conducted with personal face-to-face interviews (Attia-Romdhane et al. 1993, Aziz et al. 1991, Aziz et al. 1994, Baumann et al. 1977, Bharucha et al. 1988, Birbeck and Kalichi 2004, Coleman et al. 2002, Gomez et al. 1978, Lessell et al. 1962, Mani et al. 1998, Mathai et al. 1968, Nicoletti et al. 1999, Rajeh et al. 2001, Rajeh et al. 1993, Rocca et al. 2001, Rwiza et al. 1992, Tran et al. 2006), but have also been conducted by mail (Rose et al. 1973) and they can involve a sample of households or a census (CDC 1994, Gomez et al. 1978, Haerer et al. 1986, Mathai et al. 1968, NCHS 1990). However, completion rates have been shown to be highest in telephone mode (66%), intermediate in personal interview mode (37%) and

poorest in mail mode (24%) with similar results obtained from the telephone and personal interview modes, suggesting that the telephone moded is more cost-effective (Rowan and Hyman 1976).

Screening surveys are usually administered door-to-door to households (CDC 1994, Nicoletti et al. 1999, Reggio et al. 1996, Rocca et al. 2001, Tran et al. 2006), institutions or key informants (Baumann et al. 1977), typically by direct self-report (CDC 1994), or alternatively by indirect case reports from a parent, guardian or spouse (Baumann et al. 1977, Pal et al. 1998, Rocca et al. 2001). When interviewing a witness to ascertain the past presence of seizure symptoms or diagnosis for an individual family member of a household, most surveys have interviewed the mothers (Garcia-Noval et al. 2001, Tekle-Haimanot et al. 1990b) , who may be the most reliable keeper of disease information for the family especially for disease family history and early life events (Baumann et al. 1977, Pal et al. 1998).

Screening questionnaires have typically been performed as part of a validated diagnostic process (see Table 3.4).

Table 3.4: Main validated epidemiological protocols for epilepsy prevalence studies

- The WHO Neuroepidemiology Protocol
- The International Community-based Research Group (ICEBERG) Protocol
- The Sicilian Neuroepidemiology Study (SNES)
- The Institute of Neurological Epidemiology and Tropical Neurology Protocol

The WHO Neuroepidemiology Protocol

In cooperation with the US National Institute of Health, the World Health Organisation (WHO) developed a protocol to measure the prevalence of major neurological diseases, including epilepsy, in countries with limited neurologists, hospitals and investigations (WHO 1981). This protocol has been used in a number of developing countries as well as the United States (Attia-Romdhane et al. 1993, Birbeck and Kalichi 2004, Coleman et al. 2002, Kaoul et al. 1988, 1988 #37, Li et al. 1985, Rajeh et al. 2001, Rajeh et al. 1993) and involves a door-to-door screening survey by lay interviewers, followed by diagnostic confirmation from a neurologist.

The screening questionnaire (see Appendix 1) and examination was designed to select individuals with completed stroke, epilepsy, peripheral neuropathy, movement disorders and migraine headache, as well as those with persistent dysfunction of strength, coordination, sensation, vision, and hearing, rather than epilepsy specifically (Osuntokun et al. 1982). The trained health workers carry out a simple neurologic evaluation for subjects above the age of six years, with those identified by the screening interview and examination as possibly having epilepsy then being examined by a neurologist; a review of available medical records and tests is also sometimes performed (Li et al. 1985).

Within these broad diagnostic categories, the screening instrument has 95% sensitivity and 80% specificity (see Table 3.5). Its cross-cultural validity appears relatively robust with an Arabic translation of a modified version of the WHO protocol showing sensitivity of 98% and specificity of 89% for neurological disease or deficit and questionnaire re-administration by a neurologist/supervisor for quality control demonstrating negligible

errors or omissions (Rajeh et al. 2001, Rajeh et al. 1993). A further study in Tanzania used this WHO screening questionnaire for seizures, with the additional question: “Have you ever had any episodes of falling or dropping down without any obvious cause or which you could not recall?”, to increase seizure sensitivity (Rwiza et al. 1992).

Modelled with modifications on the WHO questionnaire and translated into Amharic, the official Ethiopian language, a screening questionnaire aimed at separating those with neurological disorders was developed and tested in Ethiopia (see Appendix 9), and followed by a questionnaire containing more detailed neurological inquiry (see Appendix 10) (Tekle-Haimanot et al. 1990a). Only two questions in the screening questionnaire related to epilepsy: “unconscious fit, especially with frothing, biting of tongue or incontinence of urine” and “sudden jerking movements”. For those with epilepsy, an additional questionnaire was administered to obtain more detailed information on the characteristics of seizures in the affected person. The sensitivity and specificity of the screening instrument was found to be 91% and 85% respectively for the common neurological conditions (epilepsy, mental retardation and poliomyelitis) and 93% and 90% for epilepsy (Tekle-Haimanot et al. 1990a, Tekle-Haimanot et al. 1990b) (see Table 3.5).

The International Community-based Research Group (ICEBERG) Protocol

The International community-based research group (ICEBERG) subsequently developed the ICEBERG protocol (Placencia et al. 1992b, Placencia et al. 1992c) which probably represents the most meticulous, standardized and validated household survey performed. In addition to the screening questionnaire they were the only study to develop and publish

strict operational definitions that they used in all phases of the study, making it likely that seizure diagnoses were more reliable and reproducible (see Appendix 2 and 3), with all personnel involved being trained to achieve a high degree of uniformity. Epileptic seizures were classified in accordance with the seizure type classification of the ILAE, without the use of EEG data (ILAE 1981). In addition, the question wording was eventually changed as a result of a linguistic workshop, held by the principal investigator in the study area, to ascertain whether the terminology used in the screening questionnaire and the other instruments would be easily understood by the local population. Initially, a screening questionnaire was developed and piloted (see Appendix 5) comprising nine questions derived from an original list of 20 questions (see Appendix 4) considered a priori to be the most likely to uncover possible cases of epilepsy. The 20 questions were validated on 227 healthy and epileptic patients and showed 100% sensitivity and 50.8% specificity. Following a cluster analysis of response rates, nine questions were chosen which improved specificity but still maintained excellent sensitivity giving the screening instrument specificity of 92.9%, sensitivity of 79.3%, positive predictive value of 18.3%, negative predictive value of 99.6% and a Youden's index of 0.72 (see Table 3.5).

Table 3.5: Validity of screening questionnaires used in epilepsy prevalence study

	Country	Sensitivity %	Specificity %	PPV %	NPV %	Youden's Index
Neurological Diseases						
(Li et al. 1985)	China	95	80			
(Rajeh et al. 1993)	Saudi Arabia	98	89			
(Tekle-Haimanot et al. 1990a)	Ethiopia	91	85			
Epilepsy						
(Rowan and Hyman 1976)	USA	77				
(Zeilinski 1974b)	Poland	86	84			
(Osuntokun et al. 1982)	Nigeria	95	80	57		
(Osuntokun et al. 1987)	Nigeria	95	80.0			
(Tekle-Haimanot et al. 1990a)	Ethiopia	93	90			
(Placencia et al. 1992c) – 20 item	Ecuador	100	51			
(Placencia et al. 1992c)- 9 item (clinic)	Ecuador	98	92	94	97	0.90
(Placencia et al. 1992c)- 9 item (field)	Ecuador	79	93	18	100	0.72
(Birbeck and Kalichi 2004)	Zambia		86	92		
(Wang W Z et al. 2003)	China	100	79			
(Bharucha et al. 1988)	India	100				
(Mani et al. 1998)	India	72				
(da Mota Gomes et al. 2002)	Brazil	93	73			
(Pal et al. 1998)	India	58	39			
(Meneghini et al. 1992)	Italy	96	86			
(Preux and Druet-Cabanac 2005)	France	85-95	50-65			

PPV = positive predictive value, NPV = negative predictive value

The screening questionnaire was found to have a false positive rate of 15.5%, so inter-observer reliability of the neurological diagnosis was assessed and in 11.5% of the 349 cases selected the diagnosis of epileptic seizures was questioned (Placencia et al. 1992b, Placencia et al. 1992c). The assessment of the unreliability of their instrument enabled subsequent prevalence estimates to account for this diagnostic uncertainty, giving three different values with a minimum, maximum and range for prevalence rather than a single estimate. In addition, the investigators used an even more detailed cascade system of diagnostic confirmation than the WHO protocol with: screening by non-medical personnel; examination by rural doctors; examination by senior neurologists; and finally review and consensus diagnosis by an international panel. This system allowed the input of specialists to be more focused and enable their time to be used more efficiently.

A study in Zambia adapted the Ecuador screening instrument translated forward and backwards and reconciling discrepancies before testing it in general medical and epilepsy clinics (Birbeck and Kalichi 2004). Comprehension of the questionnaire was satisfactory, but high false positive rates were found, primarily among children with seizures related to malaria, i.e. acute symptomatic seizures. Given the few physicians in this region during the time of the survey (3.5 full-time positions for the entire population of 55,000), the authors wanted an instrument with a high positive predictive value.

Therefore, three questions were added to eliminate acute symptomatic febrile and malaria associated seizures and prefaced each question with “In the past year, have you or anyone in this household” to estimate the active prevalence in the last 12 months (see Appendix 6).

This adapted questionnaire exhibited 86% specificity, with the positive predictive value improving to 92% (see Table 3.5), with all those screening negative judged not to have epilepsy by a neurologist (i.e. false negatives were zero). False positive screens occurred primarily among children who have experienced more than one acute symptomatic seizure during recurrent malaria infections. However, the more probable explanation, as suggested by the researchers, is that the false negative rate is an underestimate, since the instrument is best able to detect convulsive seizures, and individuals with non-convulsive seizures who do not also experience other convulsive seizures may go under-recognised. This lack of sensitivity for absence and myoclonic seizures with this instrument is an important deficiency as these seizures may be the sole manifestation of epilepsy (e.g. Childhood Absence Epilepsy) or critical syndrome discriminator (e.g. Juvenile Myoclonic Epilepsy, Juvenile Absence Epilepsy) (Bharucha et al. 1988); in contrast, the other non-convulsive seizures (atypical absence and tonic) seldom occur without other seizure types (Mani et al. 1998) meaning that their individual insensitivity would have less impact on the false negative rate for diagnosing their associated higher level epilepsy syndrome (e.g. Symptomatic Generalised Epilepsies).

Modified versions of the ICEBERG screening instrument have also been used in a number of other studies (da Mota Gomes et al. 2002, Mani et al. 1998, Pal et al. 1998, Wang et al. 2003)(see Appendix 7 and Table 3.5).

The Sicilian Neuroepidemiology Study (SNES)

The Sicilian Neuroepidemiology Study (SNES) also used a similar methodological approach as in the ICEBERG tiered design with a validated screening instrument, including a symptom questionnaire and a set of seven physical tasks in adults to measure the prevalence of neurological disease (see Appendix 11) (Rocca et al. 2001). The questionnaire was designed for structured, face-to-face interviews about neurological symptoms and has also been translated into Spanish and used with modification, combining EEG recordings in Bolivia (Nicoletti et al. 1998, Nicoletti et al. 1999). However, the adult survey was administered by physicians rather than non-medical personnel and involved four questions concerning epilepsy, with one question relating to previous diagnoses and three to symptoms; subjects less than 12 years were screened through a parent. The symptom questions addressed episodes of impaired consciousness, episodes of uncontrolled movements of arms or legs, and short periods of staring into space (with eyes blinking and rolled back). The question on “staring into space” was intended only for the subjects aged 12 years or younger with screened positive cases invited for further evaluation in phase 2.

The survey instrument, validated for epilepsy in a hospital setting, demonstrated a sensitivity of 96% and a specificity 86% using hospital visitors free of any of the study neurological diseases as negatives (Meneghini et al. 1991, Meneghini et al. 1992) (see Table 3.5). The small numbers (about 20 disease positives and 20 disease negatives) used to validate the instruments meant that they were unable to test the questionnaire’s ability to detect specific subtypes of epilepsy, such as complex partial or absence

seizures. However, an item analysis of the screening instrument showed: impaired consciousness sensitivity of 81.8% and specificity of 90.5%; uncontrolled movements of limbs sensitivity 100% and specificity of 54.5%; and absence spells a sensitivity of 50% with specificity not reported. The authors acknowledge that validation of the instrument was based on a small number of observations in a hospital setting, and may not reflect the actual performance of the instrument in a community setting; epilepsy requiring hospitalisation can have severe symptoms or long disease duration, and may not represent the complete spectrum of severity in the general population.

The Institute of Neurological Epidemiology and Tropical Neurology Protocol

More recently a French questionnaire for investigation of epilepsy in tropical countries has been developed and tested (Appendix 12) (Debrock et al. 2000). It was developed through collaborative work involving the Institute of Neurological Epidemiology and Tropical Neurology of Limoges in France, the Pan-African Association of Neurological Sciences and the ILAE Commission on Tropical Diseases, 1993-1997. Patients who gave at least one positive response to the screening part of the questionnaire were further investigated by a physician to confirm or reject the diagnosis of epilepsy. The sensitivity of the screening questionnaire ranged between 85-95% and the specificity between 50-65% (Preux and Druet-Cabanac 2005). This questionnaire has been used in a number of French-speaking tropical countries, and with a few exceptions (Le et al. 2007, Tran et al. 2006). The findings have been published mostly in French language publications (Diagana et al. 2006).

Other screening questionnaires

A study in the Mariana Islands utilised a neurological disease screening questionnaire and neurological exam as part of a prevalence study on neurological conditions (Mathai et al. 1968). Similar to best clinical practice today, the seizure description questionnaire involves both the subject and witness recalling the ictus or seizure, any aura or warning and the post ictal period. Descriptions of symptoms of convulsive disorders, ‘petit mal’ psychomotor phenomena and focal seizures involved questions relating to “momentary loss of consciousness, staring look, dreamy state, paroxysmal abnormal behaviour, localized twitching, or sensory phenomena” and included important direct questioning, still used today, regarding “direction of turning of head and eyes, and the site of onset of convulsions” to diagnose the partial-onset nature of symptoms.

A study in Covich County, in the United States used a screening neurological questionnaire with eligible cases then being examined by the principal investigator (Appendix 13) (Anderson et al. 1982, Haerer et al. 1986) with non-neurologist diagnosis only accepted with a confirmatory EEG by an expert. They categorised definite independent of EEG tracings, along with probable or possible for diagnoses. “Probable” and “possible” were defined by two ictal events where the most likely explanation was epilepsy. Screening questions were “pre-tested to assure high level of sensitivity in detecting persons with epilepsy”, although the authors did not state specifically what the results showed. Another US study mainly used a screening questionnaire for finding potential cases, but supplemented this with the responses from other major neurologic

screened disorders which could also manifest with seizures e.g. stroke, dementia, and Parkinson's disease (Rowan and Hyman 1976).

A study in Clay County, Kentucky used the affirmative response to the question "epileptic fits, spells, convulsions, blackouts, seizures, fever fits, worm fits, or other types of passing out spells" (Baumann et al. 1977). Those answering 'yes' were examined by a neurologist and clinically assessed as to whether a seizure had occurred. A number of the uncertain responses were also examined by the neurologist to ascertain the nature of the suspected event. A family member, usually the mother, was asked to describe the spell in detail with specific reference to the subject activities prior to the episode, the presence of warning or aura, the subject's activities during the spell, and the presence of sleepiness, confusion or other changes after termination of the spell. Special weight was given to spells which were unrelated to environmental stimuli, which interrupted ongoing activity, and which were associated with rolling back of the eyes and tonic-clonic movements and which were followed by sleepiness or confusion.

An Australian survey used a self-reported mail questionnaire to assess the prevalence of epilepsy by identifying patients using the three previous doctor-diagnosed seizures (see Appendix 15), and also estimated that a quarter of patients may conceal this diagnosis during surveys (Beran et al. 1985a, Beran et al. 1982). In a study in Pakistan, a six-item screening questionnaire was used and any positive results were confirmed by a neurologist (see Appendix 16). Diagnosis was primarily clinical and determined mainly on the basis of witness descriptions of seizure manifestations, with a person classified as

having epileptic seizures sufficient to cause clinically detectable events apparent either to the subject or an observer (Aziz et al. 1994).

Finally, unpublished questionnaires have been used in: Poland (Zeilinski 1974b); two regions in Guatemala, using an unspecified 20 item questionnaire, followed by neurological assessment, EEG and neuroimaging (Garcia-Noval et al. 2001); and in the USA using “self-reported epilepsy, repeated seizures, convulsions, or blackouts” data during the preceding 12 months averaged over the period to give annual rates from the National Health Interview Survey (NHIS) (CDC 1994, NCHS 1990).

Diagnostic questionnaires

Although diagnostic questionnaires have been proposed for use in large scale epidemiological studies (Ottman et al. 1990, Reutens et al. 1992) they have still primarily been used in family-based genetic studies.

Children

No diagnostic questionnaire studies have been performed in children. The reliability of diagnoses based on 1981 ILAE criteria (ILAE 1981), was tested by analysis of agreement among doctors who classified children’s seizures based on descriptions in the medical records (Bodensteiner et al. 1988). Diagnoses were performed by an epilepsy specialist and three training neurologists, and agreement was assessed using weighted kappa’s to reward close but less than complete agreement, e.g. simple partial seizures and complex

partial seizure categories only differ by the presence or absence of subject awareness compared with no agreement (i.e. partial and generalised seizure types).

Although they tried to use verbatim responses recorded in the medical notes to classify seizures, these were found to be highly variable. Depending on the level of observer training, 22-51% of descriptions were considered unclassifiable. Inter-rater agreement, assessed by the kappa statistic, was low ($k = 0.26$, 95% CI 0.24-0.38) when all the descriptions were included and increased after descriptions that lacked specific detail or were otherwise unclassifiable were excluded ($k = 0.47$, 95% CI 0.34-0.51). When specific seizure types were considered, and only detailed descriptions were included, kappa ranged from fair to excellent for most types ($k = 0.45$ -0.90) for the best observer pair. Agreement was less for atypical absences ($k = 0.11$ -0.28), partial seizures with secondary generalization ($k = 0.26$ -0.40) and generalized motor seizures ($k = 0.29$ -0.32).

This study highlights the poor diagnostic information obtained from medical data and interpretation of EEGs (Demlo et al. 1978, Houfek and Ellingson 1959), and the importance of using specific criteria when making diagnoses (Boyd et al. 1979). The use of diagnostic criteria and mutual discussion have been demonstrated to provide better agreement (kappa 0.96) than a neurologist using clinical judgement working alone (kappa 0.58) (Rinaldi et al. 2000, van Donselaar et al. 1989). However, investigator attempts at classifying too many diagnostic categories should probably be discouraged as it is likely to lead to greater opportunity for disagreement and unreliable estimates (Dorsey et al. 1986).

In another paediatric study of 613 children with a median age of about five years, diagnostic inter-rater reliability between three paediatric neurologists was assessed using an unspecified seizure history interview, as well as the paediatric neurologist's medical records and EEG data (Berg et al. 1999). The authors measured diagnostic agreement for patients at different levels of syndrome complexity, once again allowing for partial disagreements by using weighted kappas at the second and fully specified syndrome level. The first level corresponded to the epilepsy onset-type (e.g. localized vs. generalised), while the second level corresponded to the broad syndrome group (e.g. idiopathic vs. symptomatic vs. cryptogenic epilepsy), and the highest level corresponding to the specific epilepsy syndrome (e.g. childhood absence epilepsy vs. juvenile absence epilepsy).

Although there was diminishing agreement with increasing level of syndrome complexity (90.0% complete agreement at first level, 83.7% complete agreement on first and second level combined, and 80.7% agreement on full syndrome) they still demonstrated excellent agreement ($k > 0.81$) even for un-weighted kappa's at all levels. Idiopathic generalized epilepsy had higher overall agreement compared to symptomatic/cryptogenic generalized epilepsy (92% vs. 75% all agreed) with closer agreement found for the commoner idiopathic generalised epilepsy syndromes (childhood absence, juvenile myoclonic, epilepsy with myoclonic absences) compared to the rarer ones (juvenile absence, generalised tonic-clonic seizures on awakening, epilepsy with myoclonic astatic seizures and Lennox-Gastaut Syndrome). Above age two years, the most common discrepancy

was determining whether partial epilepsy was idiopathic, cryptogenic or symptomatic (Berg et al. 1999).

Adults

There have been only two diagnostic seizure classification questionnaires used in adults.

The Semi-Structured Seizure Classification Interview

Ottman et al developed the semi-structured seizure classification interview (SSCI) because diagnoses from medical records had shown poor accuracy and reliability (Bodensteiner et al. 1988) (see Appendix 18). Although this questionnaire was initially developed for large epidemiological field surveys, following its initial testing it has primarily been used in family-based genetic studies (Ottman Ruth et al. 1990, Ottman R et al. 1993). It contains both structured and semi-structured questions answered in discrete categories (e.g. yes, no, or don't know) along with open-ended questions answered in the patients' own words. Open-ended questions precede structured questions, e.g. "in your own words, can you describe how you feel before a big seizure starts?" with verbatim responses recorded.

The second part provides semi-structured questions asking "Do you have any warning (or aura) that a big seizure is about to happen?" If the answer to the second question is "yes", a description of the types of auras usually experienced is requested again. Finally, detailed direct questions are asked on the nature and pattern of seizure symptoms requiring a "yes" or "no" response. Following administration, the questionnaire is

interpreted by a research assistant using a set of unpublished guidelines to classify seizures with reference to specific questions in the interview and consulted the study neurologist in ambiguous cases.

The questionnaire has been validated against the seizure diagnoses obtained from a neurologist's medical records involving 50 adult patients with epilepsy (Ottman et al. 1990). The sample did not contain any patients with alternative diagnoses (i.e. no false positive cases or non-epileptic seizures) and did not attempt to validate seizure types with a prevalence of less than 10% in their sample (i.e. all non-convulsive idiopathic generalised seizures such as myoclonic and absence seizure types).

Interview diagnoses agreed with those of physicians for broad partial-onset and generalised-onset seizure-type classifications in 88% of patients, and with detailed combinations of seizures in 64% of patients. Non-chance agreement between the two sources, assessed by the κ statistic, was excellent for any partial-onset seizure ($\kappa = 0.83$), secondarily generalised ($\kappa = 0.81$), and primary generalised tonic-clonic seizures ($\kappa = 0.76$), fair to good for any generalised-onset ($\kappa = 0.70$), simple partial ($\kappa = 0.56$), complex partial ($\kappa = 0.54$), and generalised non-convulsive seizures ($\kappa = 0.56$). Although sensitivity was greater for partial onset seizures (0.60 to 1.0) than generalised onset seizures (0.43 to 0.67), specificity was perfect for generalised onset seizures and ranged from 0.60 to 0.87 for partial onset seizures. These findings suggest that the SSCI can produce accurate diagnoses for most major seizure categories but is more likely to misclassify a generalized-onset seizure as partial-onset than to make

an error in the opposite direction. This may relate to the more direct questioning approach, resulting in a higher sensitivity and lower specificity for partial-onset seizures, allowing patients and doctors to consider relatively non-specific symptoms as an aura, coupled with a lower sensitivity for detecting the presence of non convulsive generalized seizures (Sensitivity 43%, Specificity 100%), the presence of which is often critical in making the diagnosis of a generalized-onset epilepsy, the IGE syndrome and its sub-syndromes (childhood absence, juvenile absence and juvenile myoclonic).

These findings are the opposite of those in most prevalence studies which have reported seizure as well as global epilepsy prevalence (see following chapter). These have tended to lump partial onset secondarily generalised seizures as generalised-onset tonic clonic seizures, and complex partial seizures as absence seizures, probably leading to over-estimation of generalized onset seizures (Kurland 1959, Zander et al. 1979). This may relate to studies predominantly diagnosing seizures from the recorded descriptions in medical records, which seldom allow greater distinction than a broad category of convulsive seizure, with a danger of greater likelihood of classifying a generalised tonic clonic seizure (Hauser and Kurland 1975, Hauser et al. 1991, Osuntokun and Odeku 1970).

In a second study, agreement between various lay reviewer pairs, and between each non-medical reviewer and the neurologist, was assessed to make seizure interpretation following patient interview and medical record review, less dependent on expert neurological assessment. The authors used operational diagnostic criteria to enable lay

reviewers to assess this information and reach seizure diagnoses finding this approach to have moderate to almost perfect agreement (kappa 0.46 to 1.0) for the broad seizure categories generalized-onset and partial-onset. Within partial-onset seizures, agreement for all three pairs was substantial for secondarily generalised seizures (kappa 0.66 to 0.69), and substantial to almost perfect for complex partial seizures (kappa 0.68 to 0.87).

Within generalised-onset seizures, agreement was moderate to substantial for generalised tonic clonic (kappa 0.63 to 0.73), absence (kappa 0.55 to 0.79), and atonic (kappa 0.59 to 0.66) and almost perfect (kappa > 0.87) for myoclonic seizures (Ottman et al. 1993).

A French study translated and further validated a French version of this questionnaire (Picot et al. 1999) against the diagnoses obtained from an epilepsy specialist's assessment including clinical, EEG and neuroimaging data. Once again, children less than 15 years of age were excluded, but importantly patients with non-epileptic conditions mimicking epilepsy were included in the sample (17/67). The sensitivity of the French questionnaire in diagnosing an epileptic seizure was 100%, with a specificity of 94%, an important consideration with regards to using the questionnaire in community-based samples where seizure mimickers are likely to be present (Keranen 1987). The authors obtained virtually identical findings and encountered similar problems to the earlier English-language study (Ottman et al. 1990), with interview-based diagnoses showing very good agreement to those of physicians in 90% of patients for broad seizure categories (i.e. generalized or focal in origin, $k = 0.74$). When diagnoses agreed on a partial origin, the agreement of seizure types was almost perfect for simple or complex partial seizures ($k = 0.84$) with agreement less but also good for generalized-onset seizures ($k = 0.60$).

Disagreement for generalized seizures involved patients who presented several non-convulsive seizure types in combination with generalised convulsive seizures (e.g. GTCS and absence or GTC and myoclonic) with the main problem being differentiating absences and partial seizures with isolated impairment of consciousness. The SSCI lacks questions relating to myoclonic seizures, and these seizures may go un-noticed, sometimes for many years, without specific direct questioning (Gram et al. 1988). Although, this is likely to have affected identification of the idiopathic epilepsy syndromes, the agreement for these was still moderate ($k = 0.73$, 95% CI 0.39-1.0) using only anamnestic data without EEG. Although involving low numbers for generalized epilepsies, the level of agreement for the idiopathic/cryptogenic ($n=9$) and symptomatic ($n=1$) categories was 100% while for partial epilepsies, the level of agreement was only 71% for these higher categories ($k=0.44$) (Picot et al. 1999).

More recently Choi et al (Choi et al. 2006) attempted to improve the classification of partial seizures from the seizure classification proposed by Luders (Luders et al. 1998), for use in genetic research on the epilepsies, by expanding the inventory of partial seizure categories and improving the consistency of their interpretation without the use of EEG data. Their classification attempts to document all symptom experiences of the patient occurring immediately preceding and during a partial seizure, rather than only the predominant experience, as it remains unclear which symptoms may be most predictive of genotype (Ottman et al. 1995, Winawer et al. 2000).

The Unstructured Seizure Classification Interview

Reutens et al developed a diagnostic interview predominantly comprising open-ended questions, in a structure similar to clinical history taking (see Appendix 20) (Reutens et al. 1992). Although it was developed for use in population studies, its format and design makes it less suitable with respect to administration and interpretation for large-scale epidemiological research, as it is constructed to obtain predominantly verbatim recording from the patient and witness on seizure descriptions. Direct questions are also used to determine mostly the number and any order of progression of different seizure types, but its strength lies in having more questions on specific generalised non-convulsive seizures. However, this only differed with respect to the SSCI with respect to, a question for rare tonic seizures, a more colloquial description for absence seizures, five more specific questions relating to the body parts affected for the rare atonic seizures, as well as predominantly formatting changes related to myoclonic seizures (see Appendix 20).

The authors tested its validity by administering it directly by telephone, or by face-to-face interviews, and supplementing the information with interictal EEG findings. It showed good overall k value for all seizures ($k=0.74$), almost perfect agreement in classification of patients into those with seizures of either generalized ($k=0.87$) or focal origin ($k=0.87$), with substantial to almost perfect agreement reached in diagnosis of patients with most individual seizure types (simple or complex partial, $k=0.78$, simple partial $k=0.50$, complex partial $k=0.63$, and secondarily generalised $k=0.85$), even for non-convulsive generalized seizure types (GTCS $k=0.86$, absence $k=0.78$, myoclonic $k=0.70$, atonic $k=1.0$).

For most seizure types, the sensitivity, specificity and PPV of the questionnaire was greater than 0.8. Despite only formatting changes between questions asked on myoclonic seizures, compared to the SSCI, the questionnaire showed substantial agreement in diagnosis of this seizure type, which suggests that their detection is even superior to the physician 'gold standard' which may have missed their occurrence in four patients. Agreement in the diagnosis of absence seizures was also substantial, once again despite only minor colloquial differences between these questionnaires. The authors emphasize that convulsive seizures are difficult to differentiate into generalised-onset or partial-onset unless co-existent partial or generalized non-convulsive seizures are taken into account, suggesting that high validity is needed for individual minor complex partial or non-convulsive generalised seizure types for high diagnostic accuracy (van Donselaar et al. 1990).

A history of myoclonic seizures is often difficult in adults and children, without a systematic diagnostic seizure interview, even when patients are seen by a specialist (Cockerell et al. 1995, Reutens et al. 1992), while the presence of an aura is an important point of distinction between generalized-onset seizures and focal onset seizures, it may not definitely distinguish between these two types of seizures (van Donselaar et al. 1990) or provide specific localising power. This is not surprising, as few clinical features have a well circumscribed anatomic correlate to a single cortical region, with many distant cortical areas having close interconnections which therefore may result in falsely localising value (Pribram 1987), while other areas where seizures may arise may be

difficult to perceive for the patient, or not have many outward manifestations for a witness.

Given these relatively minor changes between questionnaires, an alternative explanation for the Reutens questionnaire improved overall ability to correctly classify generalized-onset type seizures and partial onset type seizures may relate to a high rate of informant administration in addition to the person with epilepsy (Senanayake 1993). This is demonstrated by the highest level of overall agreement between physician and questionnaire-based diagnoses being achieved when an informant was available for interview (informant only $k = 0.76$, both patient and informant $k = 0.75$), rather than when a subject was the only source of diagnostic information available for interview ($k = 0.41$). As seizures can affect memory, it is not surprising that clinical diagnosis ideally should involve interviews with a person who has 'witnessed' the patient's seizure(s).

Other possible explanations for these differences are the improved collection of verbatim symptom responses or the expertise of questionnaire interpretation by the neurologist assessing these responses (Bodensteiner et al. 1988, Boyd et al. 1979, Bodensteiner et al. 1988). Then the most important means of ensuring diagnostic validity is having the questionnaire analysed and interpreted by a neurologist with expertise in epilepsy (Berg et al. 1999, Ottman et al. 1998b, Placencia et al. 1992b, Reutens et al. 1992). In addition, few studies explicitly state the rationales on which each syndrome classification is based (Placencia et al. 1992b, Sander and Shorvon 1987) and standardized specific diagnostic guidelines/criteria for seizures and epilepsy syndromes would improve accuracy in

diagnosis (van Donselaar et al. 1989) and reproducibility between studies (Eadie 1996, Oka et al. 1995).

3.5 Summary

Epilepsy is not a single disease, but rather a descriptive term for a tendency to have recurrent seizures. Prior to the development of an accepted classification for epilepsy, seizures and epilepsy syndromes, there was a lack of uniformity in its definition. The very earliest studies to measure the population prevalence of epilepsy were often based solely upon the clinical description of the seizure patterns in the medical notes, augmented very rarely by interviews with patients. Most of these early studies involve a screening questionnaire followed by diagnostic confirmation, usually by expert neurological opinion. However, poor diagnostic information obtained from medical data and interpretation of EEGs has led to the development of diagnostic seizure questionnaires that can reliably produce accurate diagnoses for the presence of epilepsy, most major seizure categories and ‘more specific forms of epilepsy’, including idiopathic generalised epilepsy. This potentially provides an alternative less resource intense method, without loss in validity, for classifying ‘more specific forms of epilepsy’ in population-based epilepsy studies, particularly if coupled with written diagnostic criteria.

Chapter Four: The prevalence of epilepsy, seizures and idiopathic generalized epilepsy – A summary of the literature

4.1 Introduction

As discussed in the previous two chapters, it was not until after the widespread adoption of more uniform standards in case ascertainment, diagnosis and classification that we were better able to address major methodological problems hindering the accurate estimation of the prevalence of epilepsy. In the first half of this chapter, I will now briefly outline our current knowledge of the overall prevalence of epilepsy and its distribution by age, gender, region, ethnicity and socioeconomic status, before summarizing in the second half of this chapter, the prevalence of seizures and ‘more specific forms of epilepsy’, with particular emphasis on the idiopathic generalized epilepsy syndrome (IGE).

4.2 The prevalence of epilepsy

The International League Against Epilepsy (ILAE) divides the world into six regions comprising: Africa, Asia-Oceania, Eastern Mediterranean, European, Latin America and North America. Figures 4.1a-e show estimates of the lifetime prevalence of epilepsy from all identified English-language published studies conducted which have not focused on a particular age-group. With a few exceptions, in developed countries, the lifetime prevalence of epilepsy is between 5 and 9 per 1000, while in developing countries lifetime prevalence can be higher than 10 per 1000. Therefore, with three quarters of the world’s population currently living in developing countries, epilepsy in the developing world contributes the major proportion of total world morbidity for this disorder.

Figure 4.1a: The lifetime prevalence of epilepsy from studies in Africa (n=19)

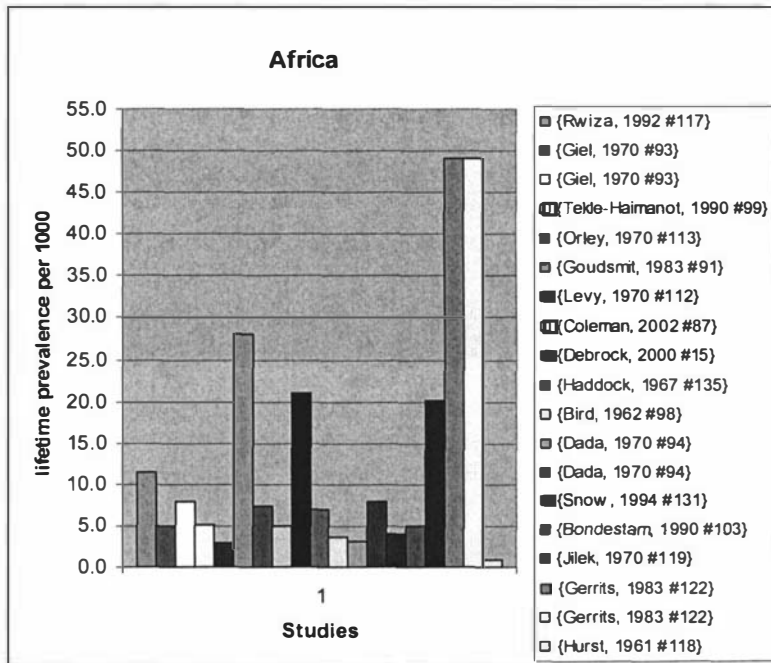


Figure 4.1b: The lifetime prevalence of epilepsy from studies in Latin America (n=12)

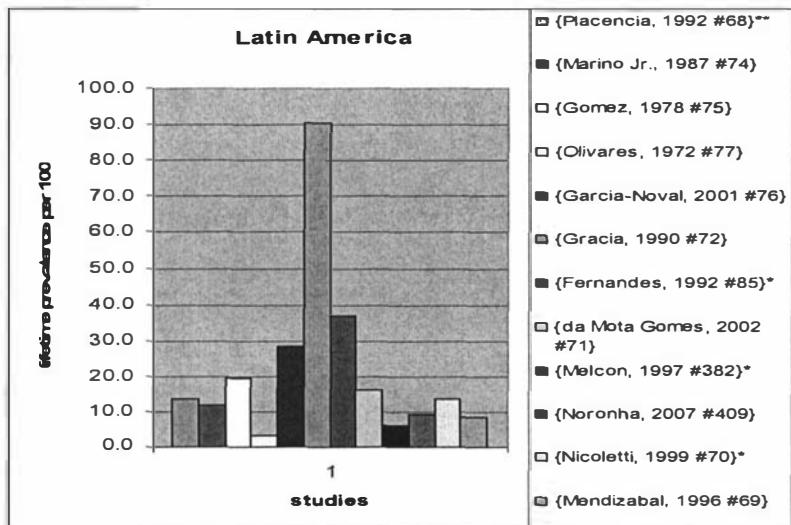


Figure 4.1c: The lifetime prevalence of epilepsy from studies in Eastern Mediterranean (n=4)

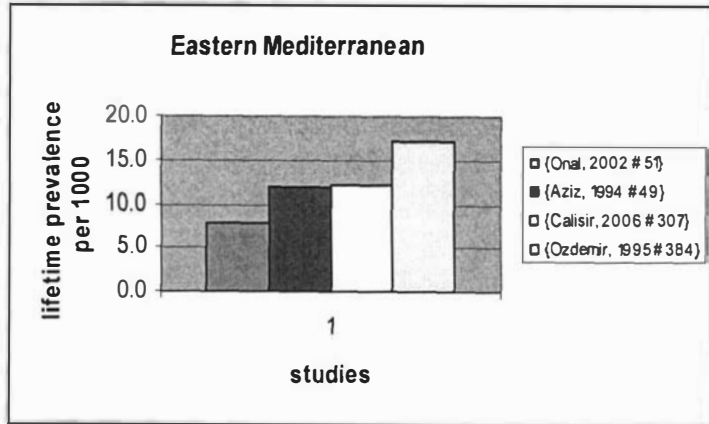


Figure 4.1d: The lifetime prevalence of epilepsy from studies in Europe (n=23)

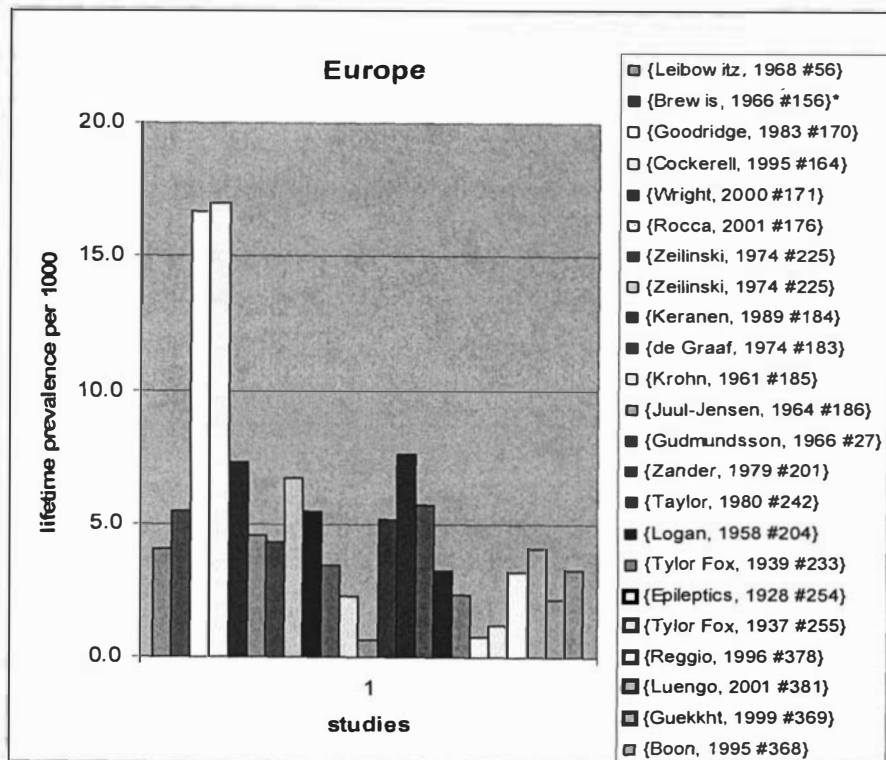


Figure 4.1e: The lifetime prevalence of epilepsy from studies in North America (n=13)

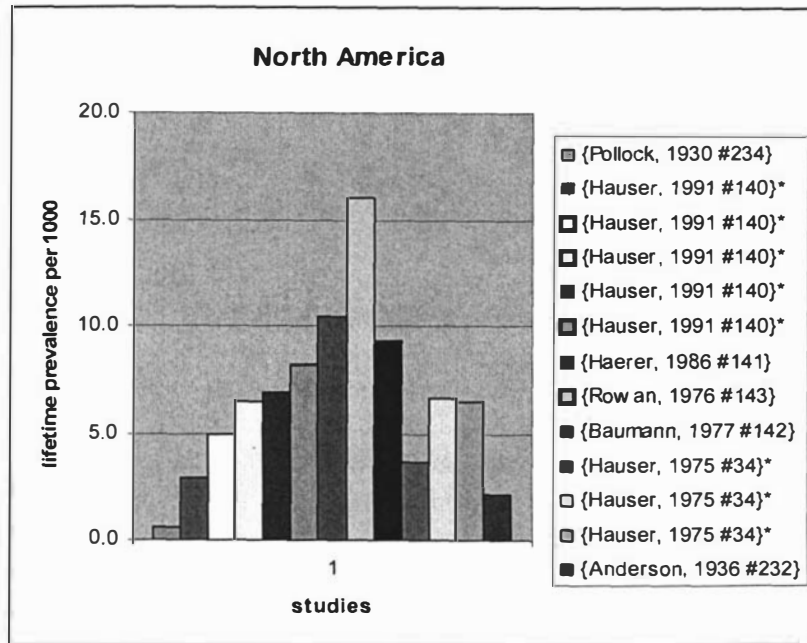
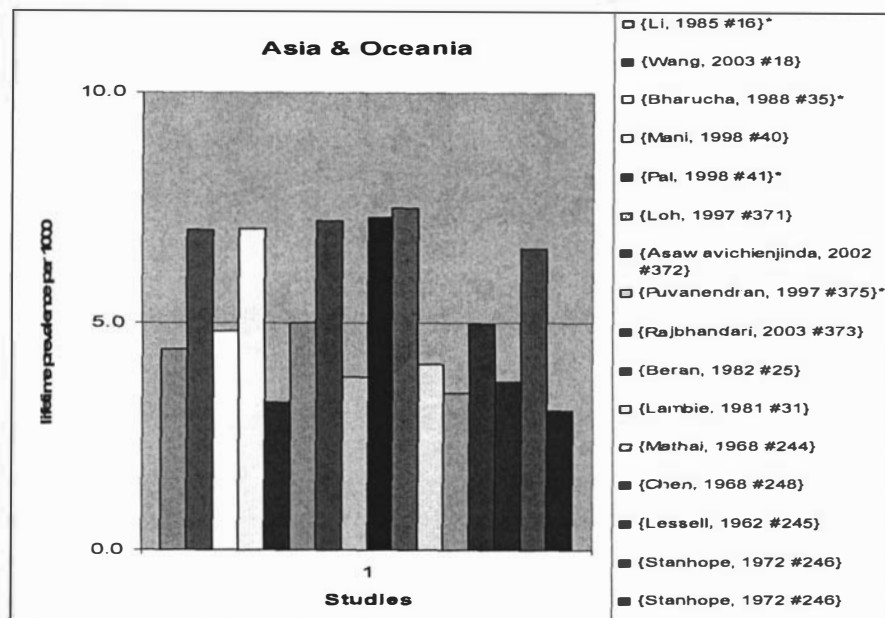


Figure 4.1f: The lifetime prevalence of epilepsy from studies in Asia & Oceania (n=16)



The Asia-Oceania region, which includes Australia and New Zealand, extends from India, in the west, to the Pacific Islands in the east, and has a shorter history of epilepsy prevalence research commencing in 1962 and accounting for 20 (17.4%) published studies. Despite its great geographic and cultural diversity, the overall prevalence in this region is between 3 and 8 per 1000, a similar range to that seen in the developed world (see Figure 4.1e).

4.3 The demographic distribution of epilepsy

Age

Probably due to wide variability in definitions and study methods no general conclusions on age-specific patterns can be drawn. A bimodal age-specific pattern with high prevalence in childhood and the elderly has been observed (Birbeck and Kalichi 2004, Dowzenko and Zielinski 1971, Hauser et al. 1991, Osuntokun et al. 1982, Wajsborn et al. 1967, Zielinski 1974b). This pattern is consistent with what might be expected of a chronic illness with low mortality that affects all age groups but has its highest incidence in the very young and in the elderly. Although not often emphasized, an institutional study noted that people in early middle life have high relative epilepsy prevalence (Epileptics 1928). This finding was replicated in the US household survey of 1.1 million persons which found that the age specific prevalence ratio was highest amongst the group aged 15-64 (CDC 1994). More specifically, age specific prevalence rates have been found to be highest in those aged 20 to 29 years (Aziz et al. 1994, Bharucha et al. 1988, Cockerell et al. 1995), 20 to 39 (Bharucha et al. 1988), and 31-40 years (Cockerell et al. 1995).

The highest age specific prevalence rates occur in children in a number of developing countries (Attia-Romdhane et al. 1993, Bondestam et al. 1990, Rajeh et al. 1990), with almost one-third of first seizures occurring before the age of 20 years (Garcia-Noval et al. 2001, Osuntokun et al. 1987). More detailed age-specific analyses have suggested that this pattern is seen particularly in those under five years of age (Brewis et al. 1966, Haerer et al. 1986, Kurland 1959); ten years of age (Gudmundsson 1966, Leibowitz and Alter 1968), between 10-19 years of age (Epileptics 1928, Granieri et al. 1983, Osuntokun and Odeku 1970), and between the ages of 15 and 24 (Crombie et al. 1960). Therefore, with a larger proportion of the population under 20 years of age (India 1981, Rajeh et al. 2001, Rajeh et al. 1993, Rwiza et al. 1992), epilepsy continues to be an important childhood neurological disease in developing countries.

In earlier studies, this high prevalence in childhood was also seen in developed countries (Brewis et al. 1966, Crombie et al. 1960, Epileptics 1928, Gudmundsson 1966, Haerer et al. 1986, Krohn 1961, Kurland 1959, Leibowitz and Alter 1968), leading to the not unreasonable general belief that epilepsy is primarily a disease of younger age. However, more recently, there is a suggestion that this pattern has reversed with prevalence lowest in children less than 14 years in some developed countries (Aziz et al. 1994, Cockerell et al. 1995, Hauser et al. 1991, Lammers et al. 1996, Wallace et al. 1998a).

In contrast, in a study in the United States, the prevalence ratios increased steadily and then declined in the 60-years-and-over category (Haerer et al. 1986). Similarly, in the

United States household survey, the prevalence was found to be lowest for those aged more than 65 years (CDC 1994). In Estonia, prevalence rates were also lower in those greater than 70 years of age (Oun et al. 2003). However, when lifetime prevalence is estimated, some of this decreased epilepsy prevalence in the elderly may be explained by recall bias, with some adults, especially elderly persons, having difficulty recalling spells that occurred years before (perhaps during childhood).

In contrast, 'active' epilepsy prevalence, as it is typically calculated for the preceding five years, estimates may be less likely to be affected to the same extent by these recall issues. This is demonstrated in the Rochester studies which found that between 1940 and 1980 the age-adjusted prevalence of active epilepsy increased from 2.7 to 6.8 per thousand in Rochester, in the United States (Hauser et al. 1991). In 1940 prevalence was highest amongst residents aged less than ten years, but by 1950 the prevalence rates were lowest amongst these residents. The most dramatic change in active prevalence was noted in persons aged greater than 75 years, increasing from 1.9 per 1000 in 1940, to 14.8 per 1000 in 1980. With each decennial prevalence estimate, there was a general tendency for prevalence to be relatively lower in the first five years of life and to be relatively higher in the elderly.

The higher prevalence recently observed in the elderly is perhaps a reflection of the accumulation of chronic cases of childhood and adult-onset with improved survivorship, combined with a more rapid accumulation of new cases of epilepsy because of the high incidence of the oldest age groups and longer duration of treatment (Hauser et al. 1991).

Alternatively, high incidence in older age groups may reflect better access to health services in this group due to differences in people's attitudes toward seeking expert medical advice, along with improved recognition and diagnosis of seizures and epilepsy (Granieri et al. 1983, Hauser et al. 1991). However, case ascertainment cannot be the only cause of this difference as, even in surveys based on extensive case ascertainment methods, the age-adjusted prevalence figures have remained consistent (Forsgren 1992, Forsgren and Nystrom 1990).

Gender

While a few studies have found a higher prevalence in females than males (Gomez et al. 1978, Goodridge and Shorvon 1983, Osuntokun et al. 1982, Rwiza et al. 1992), and some have found no gender differences (Attia-Romdhane et al. 1993, Bondestam et al. 1990, CDC 1994, Epileptics 1928, Gudmundsson 1966, Lammers et al. 1996), the majority have found greater prevalence in males compared to females (Bharucha et al. 1988, Dowzenko and Zielinski 1971, Granieri et al. 1983, Haerer et al. 1986, Hauser et al. 1991, Krohn 1961, Kurland 1959, Osuntokun and Odeku 1970, Oun et al. 2003, Rajeh et al. 2001, Rajeh et al. 1993, Tekle-Haimanot 1984, Zeilinski 1974b, Zielinski 1972) at all age groups (Haerer et al. 1986, Oun et al. 2003).

The high prevalence in men has been suggested to be caused by head trauma, or a poorer prognosis (Keränen et al. 1989). However the incidence of post traumatic epilepsy is too small to explain these sex differences (Rajeh et al. 2001, Rajeh et al. 1993, Sander and Shorvon 1987). The greater proportion of female subjects compared to males is an

observation almost exclusively observed in developed countries (Rwiza et al. 1992). One possible explanation, is that this may be due to higher mortality among male patients, involved in dangerous occupations such as fishing and climbing after the second decade of life (at which time the difference begins to appear) or that the negative social stigma attached to epilepsy with males makes them more likely to deny its presence (Osuntokun et al. 1982). However, the impact of social stigma also affects women with epilepsy, for example in their marital prospects, so is unlikely to be a major factor for these gender differences (Rajeh et al. 2001, Rajeh et al. 1993) which still remain largely unexplained.

Region

It is difficult to compare regional prevalence rates as few studies with validated, standardized methods and sufficient power have been performed. A similar prevalence was observed in different regions in the United States in the household survey study (CDC 1994) and in Copparo, Italy (Granieri et al. 1983). Higher urban prevalence has been noted in two studies (Gudmundsson 1966, Olafsson and Hauser 1999). In the latter study in Iceland, the highest prevalence was seen in the capital city of Reykjavik, with the authors suggesting that this may be due to greater access to doctor diagnosis (Granieri et al. 1983, Gudmundsson 1966) or due to relocation of people with chronic illness from rural to urban settings (Olafsson and Hauser 1999).

More commonly, a number of studies have found higher prevalence in rural compared to urban settings, but once again most have involved relatively small numbers (Aziz et al. 1994, Bondestam et al. 1990, Giel 1970, Rwiza et al. 1992, White and Buckley 1981). It

has been speculated that these lower urban prevalence rates may be due to effective primary health care with emphasis on prevention of child infectious diseases, improved antenatal care, and systems of health education in urban settings (Osuntokun et al. 1987, Rwiza et al. 1992).

One study with identical methods and reasonable statistical power compared regional differences between Pakistan and Turkey (Aziz et al. 1997). They observed active epilepsy to be twice as prevalent in rural vs. urban regions within these countries (14.8 per 1000 vs. 7.4 per 1000 in Pakistan versus 8.8 per 1000 and 4.5 per 1000 in Turkey). Using the same rigorous design and having sufficient power, an Ecuadorian study found large differences in prevalence in two sub-regions of their survey area (lifetime prevalence of 11.2/1000 vs. 24.8/1000). Although the prevalence of epilepsy was higher in rural than in urban surroundings in both regions (15.4/1000 vs. 9.1/1000), the difference was not sufficient to account for the regional variation and no clear aetiological reasons for these differences were identified (Placencia et al. 1992b, Placencia et al. 1992c). One distinct possibility is that these regional differences relate to a high level of intermarriage among people with a strong family history of epilepsy, as seen in other isolated communities (Goudsmit et al. 1983, Osuntokun 1978, van der Waals et al. 1983), alternatively it may reflect socio-economic differences between low (rural) and high (urban) populations (Aziz et al. 1997).

Another study in Nigeria observed a difference in the prevalence ratio of epilepsy between Aiyete, a rural village, and Igbo-Ora, a town inhabited by the same ethnic group

of Nigerians and only 20 km away (Osuntokun et al. 1987), with the authors suggesting that the residents of Ayiete might have felt less embarrassed to disclose their illness, as they are a small isolated community.

Epilepsy prevalence and treated epilepsy prevalence do not necessarily have a strong correlation. A study comparing the prevalence and treatment gap in five regions in the People's Republic of China (Heilongjiang, Ningxia, Henan, Shanxi, Jiangsu) allowed the prevalence of treated epilepsy to be indirectly estimated (Wang et al. 2003). This study showed an almost two fold difference in prevalence which was unrelated to the two and a half fold difference in current treated prevalence between different regions in the People's Republic of China. It suggests that comparing treated prevalence between populations may not always reflect true prevalence differences if the comparative populations have inadequate and variable access to health care (Haerer et al. 1986).

Ethnicity

Only five studies have examined ethnic differences in prevalence. The first study, performed early in the nineteenth century, expressed the opinion that “increasing insanity and epilepsy among negroes” was due to the “removal of the beneficial physical effect of slavery; and equally explained on the grounds of increasing hybridization with whites” (Spratling 1904). The theme of racial purity is later continued in the collection and interpretation of statistics concerning epilepsy of ‘negroes’ and ‘mulattoes’ (white and black admixed) in the United States. “In areas where a large proportion of full-blooded ‘negroes’ was high; so, on the contrary, the ‘negroes’ from other parts of the country,

who are really for the most part mulattoes, show a great predominance of epilepsy over the whites". As an argument against inbreeding, this view attempted to support the socio-political theory at the time that human hybrids in general are disharmonious, and show a preponderance of nervous defects over "purer" races (Davenport 1923).

More contemporary studies have estimated the epilepsy prevalence in specific ethnic groups in community surveys (Bharucha et al. 1988), but there have been few good comparative studies. A study of a military cohort in Singapore, with small numbers, showed non-significant differences between Chinese ($94/16613 = 5.7$ per 1000), Indians ($5/1046 = 4.8$ per 1000) and Malay ($7/2407 = 2.9$ per 1000) (Loh et al. 1997). Another study undertaken in an urban primary care setting in Bradford, England, compared the prevalence of patients of South Asian origin with other ethnic groups. Ethnicity was identified using a validated software program used to identify South Asian names and religious and linguistic origin, with manual checks of patient names (Wright et al. 2000). The study involved a population of 360,000 with the South Asian population comprised almost a quarter of which 80% were of Pakistani origin and found that the age-standardized rate for patients of South Asian origin was 3.7 per 1000 compared to 7.8 per 1000 for the rest of the population (OR 0.46; 95% CI 0.38, 0.57).

In a US study, the age-adjusted estimates were lower for "whites" than "blacks" for the lifetime prevalence of epilepsy (1.0% overall, 0.9% whites and 1.2% blacks), with a similar pattern being seen for active epilepsy (0.7% overall; 0.5% whites and 0.8% blacks). These differences were attributed to inadequate access to healthcare for black

compared to whites, with a higher percentage of blacks never having been medically evaluated (black male 10%, black female 10%, white male 3%, white female 5%) or having seen a neurosurgeon (black male 8%, black female 6%, white male 20%, white female 23%) (Haerer et al. 1986). These ethnic differences were confirmed in the later US household survey, with a higher age-adjusted prevalence of epilepsy among blacks compared to whites (6.7 vs. 4.5) especially for persons aged 35-54 years where the prevalence rate was two to three times higher in blacks (CDC 1994).

Social class

Only a few studies have attempted to investigate social class differences in epilepsy prevalence (Beran et al. 1985b, Cornaggia et al. 1990, Noronha et al. 2007, Pond et al. 1960). In a study in England, in which social class was classified according to the Registrar General's classification of occupations, there was a significant excess of epilepsy in young single men of low social class (Pond et al. 1960). In contrast, when considering the family's real estate, room size for each family member and family salary as a measure of social class, no significant associations between epilepsy and social class were found in an Italian study (Cornaggia et al. 1990). Using occupation as a measure of social class is problematic as patients often choose and restrict their work options when exposed to the risk of seizures, which may partly explain the higher prevalence of epilepsy in persons engaged in light office activities in an Italian study (Granieri et al. 1983). An Australian study, utilizing address of home dwelling to identify social class, found a similar prevalence of epilepsy with increasing social class (Beran et al. 1985b) but this was based on only 35 doctor-diagnosed cases. More recently, a study in Brazil

using validated instruments and adequate statistical power observed active epilepsy (5.4 per 1000 overall) was higher in people of lower compared to higher socio-economic status (7.5 per 1000 compared with 1.6 per 1000) (Noronha et al. 2007).

4.4 The prevalence of seizures, epilepsy-onset type and epilepsy syndromes

Few studies have reported the more detailed prevalences of seizures, epilepsy onset-types or epilepsy syndromes. Convulsive tonic clonic seizures, without specification into partial onset or generalized onset, are often the most common type of seizure across all studies (Bharucha et al. 1988, Forsgren 1992, Lavados et al. 1992, Leibowitz and Alter 1968, McCluggage et al. 1986, Oun et al. 2003) with non-convulsive seizure types less common (Bharucha et al. 1988, Osuntokun and Odeku 1970).

The frequency of partial-onset seizures versus generalized-onset seizures

There is conflicting information on the relative frequency of partial versus generalised seizures and epilepsy (see Table 4.1). Earlier studies tended to classify all generalized convulsive seizures as generalized-onset epilepsy, thus tending to elevate these estimates and consequently deflate estimates of partial-onset epilepsy. This is illustrated in a US study where three-quarters had generalised convulsive seizures and no other seizure type, making it highly likely that seizures with a focal onset with secondary generalization were misclassified as generalized (Haerer et al. 1986). This is also the likely reason for the relatively high estimates noted in other studies that found that the most frequent type of seizures and syndrome was generalised (Granieri et al. 1983, Li et al. 1985, Wang et al. 1983). Although two studies suggest that misinterpretation of focal abnormalities on

EEG may partially explain observations of lower partial-onset epilepsy (Olafsson Elias and Hauser 1999, Tekle-Haimanot 1984), diagnostic uncertainty is the more likely reason for difficulty in discriminating between generalised or partial onset of convulsive seizures (Aziz et al. 1994).

Table 4.1: Frequency of seizure onset-types in epilepsy prevalence studies from 1923-2007 (n=61)

	Country	Cases n	ILAE 1981	Seizure onset types			
				Generalised %	Partial %	Unclassified %	Multiple %
Africa							
(Rwiza et al. 1992)	Tanzania	201	yes	58.0	31.9	10.1	ns
(Tekle-Haimanot et al. 1990b)	Ethiopia	316	yes	75.0	20.0	5.0	ns
(Goudsmit et al. 1983)	Liberia	123	yes	37.4	62.6	ns	ns
(Levy 1970)	Rhodesia	130	no	91.0	ns	4.5	ns
(Coleman et al. 2002)	Gambia	80	yes	48.0	44.0	ns	ns
(Debrock et al. 2000)	Benin	66	yes	68.1	19.7	6.1	ns
(Osuntokun et al. 1987)	Nigeria	101	no	25.7	55.4	18.8	ns
(Danesi 1985)	Nigeria	945	no	23.4	76.6	3.0	ns
(Danesi and Oni 1983)	Nigeria	396	yes	25.4	74.6	ns	ns
(Ruberti and al 1985)	Kenya	912	ns	58.3	31.0	3.3	ns
(Tekle-Haimanot 1984)	Ethiopia	468	ns	60.1	30.9	6.9	ns
(Osuntokun and Odeku 1970)	Nigeria	522	no	52.3	45.2	ns	ns
(Hurst et al. 1961)	South Africa	51	no	80.4	15.7	ns	ns
(Snow and al 1994)	Kenya	30	yes	53.0	27.0	20.0	ns
Asia, India & The Middle East							
(Bharucha et al. 1988)	India	66	yes	45.5	54.5	ns	ns
(Kaoul et al. 1988)	India	157	yes	72.6	11.5	9.6	ns
(Pal et al. 1998)	India	132	yes	30.0	42.0	20.0	3.8
(Attia-Romdhane et al. 1993)	Tunisia	141	yes	93.0	3.0	ns	ns
(Sridharan et al. 1986)	Libya	568	yes	55.6	43.8	ns	ns
(Onal et al. 2002)	Turkey	17	yes	47.0	41.2	11.8	ns

	Country	Cases n	ILAE 1981	Seizure onset types			
				Generalised %	Partial %	Unclassified %	Multiple %
(Aziz et al. 1994)	Pakistan	241	yes	55.6	34.9	5.6	ns
(Rajeh et al. 1990)	Saudi Arabia	741	yes	65.0	29.0	ns	ns
(Loh et al. 1997)	Singapore	121	yes	69.0	22.0	9.0	ns
Australia, New Zealand & The Pacific Islands							
(Lessell et al. 1962)	Mariana Islands	111	no	91.0	5.4	ns	ns
South America, Central America & The Caribbean							
(Marino Jr. et al. 1987)	Brazil	91	no	57.1	38.5	ns	ns
(Garcia-Noval et al. 2001)	Guatemala	46	yes	57.0	42.0	2.0	ns
(Gomez et al. 1978)	Columbia	168	no	72.8	26.7	ns	ns
(Gracia et al. 1990)	Peru	19	yes	64.0	31.0	5.0	ns
(Fernandes et al. 1992)	Brazil	113	ns	32.4	45.9	21.6	ns
(da Mota Gomes et al. 2002)	Brazil	20	yes	40.0	35.0	25.0	ns
(Nicoletti et al. 1999)	Bolivia	124	yes	46.8	53.2	ns	ns
(Mendizabal and Salguero 1996)	Guatemala	16	yes	50.0	43.7	ns	ns
(Placencia et al. 1992c)	Ecuador	881	yes	49.0	49.0	2.0	ns
North America							
(Kurland 1959)	USA	295	no	39.7	46.9	1.5	ns
(Hauser et al. 1991)	USA	66	yes	40.7	55.6	ns	ns
(Hauser et al. 1991)	USA	124	yes	38.6	58.7	ns	ns
(Hauser et al. 1991)	USA	198	yes	31.5	66.7	ns	ns
(Hauser et al. 1991)	USA	285	yes	36.8	61.4	ns	ns
(Hauser et al. 1991)	USA	383	yes	33.8	58.8	ns	ns
(Haerer et al. 1986)	USA	246	yes	75.0		13.8	4.5
(Hauser and Kurland 1975)	USA	242	no	33.1	64.5	2.5	ns

	Country	Cases n	ILAE 1981	Seizure onset types			
				Generalised %	Partial %	Unclassified %	Multiple %
Europe							
(Giuliani et al. 1992)	Italy	256	no	61.7	ns	7.4	ns
(Rutgers 1986)	Netherlands	88	yes	20.0	78.0	2.0	ns
(Brewis et al. 1966)	England	360	no	88.9	4.4	ns	ns
(Goodridge and Shorvon 1983)	England	122	yes	41.0	ns	17.0	ns
(Cockerell et al. 1995)	England	126	yes	37.0	ns	14.0	ns
(Wright et al. 2000)	England	1561	yes	59.1	32.7	ns	ns
(Maremmanni et al. 1991)	Italy	51	yes	35.0	65.0	ns	ns
(Granieri et al. 1983)	Italy	278	yes	60.1	32.7	7.2	ns
(Cornaggia et al. 1990)	Italy	258	yes	44.3	48.1	5.7	ns
(Rocca et al. 2001)	Italy	81	yes	74.0	23.0	3.0	ns
(Oun et al. 2003)	Estonia	317	yes	5.8	74.2	19.9	ns
(Olafsson and Hauser 1999)	Iceland	428	yes	63.0	35.0	2.0	ns
(Keranen et al. 1989)	Finland	1220	yes	26.5	55.9	17.6	ns
(Krohn 1961)	Norway	919	no	47.0	53.0	ns	ns
(Gudmundsson 1966)	Iceland	987	no	61.3	29.2	2.2	1.6
(Forsgren 1992)	Sweden	713	yes	31.8	60.3	7.6	ns
(McCluggage et al. 1986)	Northern Ireland	242	no	40.0	55.0	5.0	ns
(Zander et al. 1979)	England	52	no	61.5	15.4	23.1	ns
(White and Buckley 1981)	England	64	no	84.4	15.6	ns	ns

ILAE 1981(ILAE 1981)

ns = not specified

Probably due to variability in definitions and study methods, of the classifiable epilepsies, partial epilepsy appears to have a wide range, from 4.4% to 78% of cases (Brewis et al. 1966, Rutgers 1986), with a time trend analysis showing partial epilepsy accounting for about three-quarters of all cases on all prevalence days (Hauser et al. 1991). Although partial epilepsy has been found to be the most common in children in a few studies (Alving 1979, Kramer et al. 1998, Oka et al. 1995, Oka et al. 2006, Shah et al. 1992), most studies suggest that it is more common above 15 years of age, being present in about three-quarters of cases (Danesi 1985, Gastaut et al. 1975, Osservatorio Regionale per l'Epilessia (OREp) 1996, Senanayake 1993).

Although in developing countries partial seizures are usually recorded with higher frequency, the range is much wider, from one-third (Granieri et al. 1983) to three-quarters (Alving 1978, de Graaf 1974, Gastaut et al. 1975, Zeilinski 1974b). This relates partly to the domination of hospital or specialised neurological clinic populations in these studies where a greater proportion of persons aged greater than 40 years and hence more prevalent partial epilepsy is seen (Tekle-Haimanot et al. 1990b).

Idiopathic partial epilepsy is rare, and along with the generalized epilepsies caused by a structural lesion which are also usually uncommon, is almost exclusively confined to children (Alving 1979, Cavazzuti 1980, Danesi 1985, Osservatorio Regionale per l'Epilessia (OREp)). One exception for this comes from a sample of 258 army draftees, where idiopathic partial epilepsy with a prevalence of 29.1% was the most prevalent type of epilepsy (Cornaggia et al. 1990). Although, there is a progressive rise with age in the

percentage of epilepsy cases caused by a structural lesion, this form of epilepsy is also common in the first decade of life (Osuntokun and Odeku 1970) with partial cryptogenic or symptomatic epilepsies accounting for more than half of the adult patients and about one third of paediatric patients (Osservatorio Regionale per l'Epilessia (OREp) 1996). However, a single anatomic ILAE site is not often able to be defined in these cases, almost certainly due to the lack of neuroimaging performed in these studies (Eadie 1996, Oka E et al. 1995, Osservatorio Regionale per l'Epilessia (OREp)).

The frequency of generalised seizures and the idiopathic generalized epilepsy syndrome (IGE)

Most studies typically indicate that the prevalence of generalized-onset seizures declines with advancing age. This is likely to relate to a higher incidence of generalized seizures with a good prognosis in childhood and early adolescence (Kurland 1959, Stanhope et al. 1972). Therefore, although in developing countries the majority of patients with either generalised or partial epilepsy have their first seizure before the age of 20 years, two-thirds of patients with generalised epilepsy have their first seizure before the age of ten years and a significantly higher percentage of patients with partial epilepsy had their first seizure between the ages 11 and 20 and after the age of 21 years (Danesi 1985).

Although generalized epilepsy has been seen with a similar frequency in those above and below 20 years of age (Joshi et al. 1977), most studies suggest that it is higher below 15 years of age (Danesi 1985, Gastaut et al. 1975, Joshi et al. 1977). With more participants less than 19 years of age, this has been put forward as the explanation as to why a

relatively high proportion of primary generalized seizures was observed in an African study compared to other studies (Tekle-Haimanot et al. 1990b). Frequencies in childhood of 2% to 40% have been noted (Eslava-Cobos 1989, Joshi et al. 1977, Ohtsuka et al. 1993, Oka et al. 1995, Oka et al. 2006, Shah et al. 1992, Viani et al. 1988) but are typically about 30% (Alving 1979, Danesi 1985, Eadie 1996, Kramer et al. 1998, Oka E et al. 1995). Above 15 years of age, slightly less than a quarter of cases typically have a generalized epilepsy (Alving 1979, Juul-Jensen and Foldspang 1983, Senanayake 1993). Although a study found 6.6% with idiopathic generalized epilepsy in this age group (Oun et al. 2003) and another 10.8% (Manford et al. 1997), in adults, with these notable exceptions, the proportion of patients with idiopathic generalized epilepsy is remarkably consistent across studies, ranging from 17.5% to 23.9% (Alving 1979, Danesi 1985, Eadie 1996, Osservatorio Regionale per l'Epilessia (OREp)).

Absence seizures occur in 1% to 17.8% of total cases, depending on whether the population is adult, includes all ages, or solely childhood, and whether it is hospital or community-based (Alving 1978, Alving 1979, Aziz H et al. 1994, Billingham et al. 1973, Danesi 1985, Gastaut et al. 1975, Granieri et al. 1983, Joensen 1986, Joshi et al. 1977, Juul-Jensen 1964, Loiseau et al. 1991, Tekle-Haimanot 1984, Viani et al. 1988). These seizures peak in younger patients (Danesi 1985, Gastaut et al. 1975, Joshi et al. 1977), particularly the 5-10 year age group (Rajeh et al. 1990). With children under 15 years representing about a half of all cases, this may be one reason why a greater percentage of absence epilepsy cases was observed in a study in Benin (6.1%) compared with other studies (Debrock et al. 2000).

Although juvenile myoclonic epilepsy has been observed to be the most prevalent idiopathic generalised epilepsy syndrome in one study (Olafsson and Hauser 1999), the measured frequency of specific childhood idiopathic epilepsy syndromes is wide with juvenile myoclonic epilepsy ranging from 0.05% to 8.6%, childhood absence epilepsy from 1.5% to 10.4%, juvenile absence epilepsy from 0.2% to 1.6%, epilepsy with grand mal on awakening from 0.5% to 0.8%, Idiopathic Generalised Epilepsy not specified 4.1% to 24.5%, myoclonic atstatic epilepsy 0.1% to 12.6%, epilepsy with myoclonic absences 11.1%, and severe myoclonic epilepsy in infancy 1.6% (Alving 1979, Eadie 1996, Juul-Jensen and Foldspang 1983, Oka al. 1995, Oka et al. 2006, Viani et al. 1988).

Table 4.2: The frequency of generalized seizure types in epilepsy prevalence studies from 1923-2007

ILAE Region	Country	Cases n	ILAE 1981	Generalised seizure types								
				Tonic clonic	Generalised non-convulsive	Absence	Myoclonic	<i>Akinetic</i>	Tonic	Atonic	Mixed	Infantile spasms
Africa (Rwiza et al. 1992) (Tekle-Haimanot et al. 1990b) (Goudsmit et al. 1983) (Levy Laurence F 1970) (Coleman et al. 2002) (Debrock et al. 2000) (Osuntokun et al. 1987) (Danesi 1985) (Danesi and Oni 1983) (Ruberti and al 1985) (Tekle-Haimanot 1984) (Osuntokun and Odeku 1970)	Tanzania	201	yes	54.1		1.0	1.0		1.4	0.5		
	Ethiopia	316	yes	75.0		0.3						
	Liberia	123	yes									
	Rhodesia	130	no			4.5						
	Gambia	80	yes	48.0	8.0							
	Republic of Benin	66	yes	68.1		6.1						
	Nigeria	101	no	20.8		3.0						
	Nigeria	945	no	17.9		11.2						
	Nigeria	396	yes	18.2		3.7	3.2			0.5		
	Kenya	912	ns	58.3		3.7	2.5					0.8
	Ethiopia	468	ns	60.1		2.1						
	Nigeria	522	no	52.3		1.9	0.4	0.2				

ILAE Region	Country	Cases n	ILAE 1981	Generalised seizure types								
				Tonic clonic	Generalised non-convulsive	Absence	Myoclonic	<i>Akinetic</i>	Tonic	Atonic	Mixed	Infantile spasms
(Hurst et al. 1961) (Snow and al 1994) Asia, India & The Middle East (Bharucha et al. 1988) (Kaoul et al. 1988) (Pal et al. 1998) (Attia-Romdhane et al. 1993) (Sridharan et al. 1986) (Onal et al. 2002) (Aziz H et al. 1994) (Rajeh et al. 2001) (Rajeh et al. 1990) (Loh et al. 1997) Australia, New Zealand & The Pacific Islands (Lessell et al.	South Africa	51	no	80.4		3.9						
	Kenya	30	yes	53.0								
	India	66	yes	42.4		1.5	1.5					
	India	157	yes	72.6		0.6	0.6		0.6			2.5
	India	132	yes	30.0		0.8	0.8					
	Tunisia	141	yes	93.0	3.0							
	Libya	568	yes			0.5	0.9					
	Turkey	17	yes									
	Pakistan	241	yes			1.0	5.8		5.8	5.8		
	Saudi Arabia	136	yes			2.9						
	Saudi Arabia	741	yes		65.0	4.0				2.0		
	Singapore	121	yes									

ILAE Region	Country	Cases n	ILAE 1981	Generalised seizure types								
				Tonic clonic	Generalised non- convulsive	Absence	Myoclonic	<i>Akinetic</i>	Tonic	Atonic	Mixed	Infantile spasms
1962) South America, Central America & The Caribbean (Marino Jr. et al. 1987) (Garcia-Noval et al. 2001) (Gomez et al. 1978) (Gracia et al. 1990) (Lavados et al. 1992) (da Mota Gomes et al. 2002) (Nicoletti et al. 1999) (Mendizabal and Salguero 1996) (Placencia et al. 1992c) North America (Kurland 1959)	Mariana Islands	111	no	91.0		6.3						
	Brazil	91	no	57.1		4.4						
	Guatemala	46	yes	57.0								
	Columbia	168	no	64.1		8.7						
	Republic of Panama	19	yes	53.0		11.0						
	Chile	297	yes	77.4		2.1	1.3		3.0	9.1	7.0	
	Brazil	20	yes	40.0								
	Bolivia	124	yes	34.7		7.3	2.4		1.6	0.8		
	Guatemala	16	yes	50.0						6.2		
	Ecuador	881	yes	43.0	3.0							3.0
United States	295	no	39.7			11.9						

ILAE Region	Country	Cases n	ILAE 1981	Generalised seizure types								
				Tonic clonic	Generalised non-convulsive	Absence	Myoclonic	<i>Akinetic</i>	Tonic	Atonic	Mixed	Infantile spasms
(Hauser et al. 1991)	United States	66	yes	29.6		3.7	7.4					
(Hauser W. Allen et al. 1991)	United States	124	yes	30.4		4.3	2.2					
(Hauser W. Allen et al. 1991)	United States	198	yes	20.4		5.6	5.6					
(Hauser W. Allen et al. 1991)	United States	285	yes	21.1		8.8	7.0					
(Hauser W. Allen et al. 1991)	United States	383	yes	25.0		8.8	4.4					
(Haerer et al. 1986)	United States	246	yes	75.0		0.4						
(Hauser and Kurland 1975)	United States	242	no	20.2		7.0					5.8	
Europe												
(Giuliani et al. 1992)	Italy	256	no	61.7		12.9						
(Rutgers 1986)	Netherlands	88	yes	18.0		2.0						
(Brewis et al. 1966)	England	360	no	88.9		6.7						
(Goodridge and Shorvon 1983)	England	122	yes	41.0		3.0					4.0	
(Cockerell et al. 1995)	England	126	yes	37.0		7.0					7.0	
(Wright et al. 2000)	England	1561	yes	47.5		3.4	3.2		0.8	1.0		

ILAE Region	Country	Cases n	ILAE 1981	Generalised seizure types								
				Tonic clonic	Generalised non-convulsive	Absence	Myoclonic	<i>Akinetic</i>	Tonic	Atonic	Mixed	Infantile spasms
(Granieri et al. 1983)	Italy	278	yes	45.0		12.9					2.2	
(Cornaggia et al. 1990)	Italy	258	yes	44.3	19.2							
(Rocca et al. 2001)	Italy	81	yes	54.3		7.4	2.5		7.4		2.5	
(Oun et al. 2003)	Estonia	317	yes	2.8		1.5	1.5					
(Olafsson Elias and Hauser 1999)	Iceland	428	yes	57.2		2.8	3.3					
(Krohn 1961)	Norway	919	no	41.0		6.0						
(Gudmundsson 1966)	Iceland	987	no	61.3		7.0						
(Forsgren 1992)	Sweden	713	yes	18.5		1.0	4.3		8.7			
(Zander et al. 1979)	England	52	no	55.8		5.8						
(White and Buckley 1981)	England	64	no	84.4		15.6						

Table 4.3: The frequency of seizure and ‘syndromes’ in studies prior to The International League Against Epilepsy Syndrome 1989 Classification System

Classification	Alving 1979		Joshi 1977		Gastaut 1975 (private)		Gastaut 1975 (clinic)	
	N	%	N	%	N	%	N	%
Total	1508		1000		6000		562	
Unclassifiable	52	3.4	191	19	1409	23.5	256	45.6
Classifiable	1456	96.6	809	81	4591	76.5	306	54.4
Generalised epilepsy	348	23.1	163	20	1731	37.7	123	40.2
Primary generalised epilepsy (mainly)	320	21.2	121	15	1306	28.4	114	37.3
grand mal seizures	210	13.9	54	7	517	11.3	75	24.5
petit mal seizures	48	3.2	28	3	453	9.9	31	10.1
myoclonus	62	4.1	12	2	187	4.1	8	2.6
other (clonic, unilateral clonic etc)	0		27	3	149	3.2	0	0.0
Secondary generalised epilepsy	28	1.8	42	5	425	9.3	9	2.9
LGS	26	1.7	33	4	235	5.1	9	2.9
West syndrome	0		2	0.2	61	1.3	0	0.0
other	2	0.1	7	0.8	129	2.8	0	0.0
Partial epilepsy, with	1108	73.5	646	80	2860	62.3	183	59.8
elementary symptomatology	278	18.4	466	58	459	10.0	66	21.6
complex symptomatology (+/- equivalent to TLE)	576	38.2	58	7	1821	39.7	83	27.1
secondarily generalised seizures	254	16.9	122	15	580	12.6	34	11.1

Table 4.4: The frequency of the Idiopathic Generalised Epilepsies based on the International League Against Epilepsy Syndromes Classification 2003

Study	sampling unit	cases N	ages	IGE 2003	<i>BNFC</i>	<i>BNC</i>	<i>BMEI</i>	<i>MAE*</i>	<i>EMA*</i>	<i>CAE</i>	<i>JAE</i>	<i>JME</i>	<i>GTCS</i>
				%	%	%	%	%	%	%	%	%	%
(Bauer 1994)	hospital	2956	mainly adult	23.8	0.0	0.1	0.0	0.0	0.1	3.8	3.7	3.8	12.4
(Eadie 1996)	private neurologist	1637	all ages	23.9									
(Osservatorio Regionale per l'Epilessia (OREp) 1996)*	hospital	8570	all ages	17.9	0.0	0.0	0.3	0.9	0.2	4.3	1.9	3.0	7.3
(Osservatorio Regionale per l'Epilessia (OREp) 1996)**	hospital	8570	all ages	3.4	0.0	0.0	0.1	0.3	0.1	0.6	0.3	0.4	1.6
(Manford et al. 1997)	general practice	814	all ages	6.8	0	0	0	0	0	1.6		1.1	4.1
(Oka et al. 1995)***	hospital & general practice	1872	children < 10	26.2	0.0	0.0	0.0	0.0	0.0	1.5	0.0	0.2	24.5

*definite = 7332, ** "uncertain" = 995, ***taken as percentage of classifiable cases; *ILAE* = International League Against Epilepsy
BNFC = Benign Neonatal Familial Convulsions; *BNC* = Benign Neonatal Convulsions; *BMEI* = Benign Myoclonic Epilepsy of Infancy; *MAE** = epilepsy with myoclonic astatic seizures; *EMA** = epilepsy with myoclonic absences; *CAE* = Childhood Absence Epilepsy; *JAE* = Juvenile Absence Epilepsy; *JME* = Juvenile Myoclonic Epilepsy; *GTCS* = Generalised Tonic Clonic Seizures not otherwise specified (including grand mal on awakening)

4.5 Summary

Although we now have good estimates of epilepsy prevalence for most countries, with the more recent studies addressing the methodological problems of case ascertainment and non-standardisation in diagnosis and classification, we still lack knowledge on the demographic distribution of epilepsy by ethnicity, region, socioeconomic status along with the changing age-group patterns that appear to be emerging between developed and developing countries. In addition, the distribution of seizures, epilepsy onset-types or epilepsy syndromes have only been presented in a few studies, with only a single study reporting the prevalence of epilepsy syndromes performed outside a hospital setting. Better understanding of the demographic distribution of epilepsy and prevalence of higher level epilepsy syndromes in community-based settings would help improve our understanding of this disorder at the population level.

Chapter Five: The diagnosis of seizures, epilepsy and Idiopathic Generalised Epilepsy by computer-assisted-telephone-interviewing using standardised diagnostic guidelines - A validation study

5.1 Introduction

In the following four chapters I now focus on measuring the prevalence of the Idiopathic Generalised Epilepsy Syndrome (IGE) and associated seizure types in a population context. I commence by firstly developing and validating diagnostic instruments to accurately classify this group of epilepsies and capable of being administered on a large scale. Secondly, I recruit a community-based cohort of patients through the Australian national prescription database and discuss the relative strengths and limitations of case ascertainment by this approach. Thirdly, I estimate the prevalence and distribution of treated epilepsy in Tasmania by imputation methods. Finally, using my validated questionnaire, I estimate the prevalence and distribution of IGE in Tasmania.

To better understand the aetiology and prognosis of epilepsy, epidemiology needs to develop standardized population methods to facilitate recruitment and diagnosis of the large cohorts required to study ‘more specific forms of epilepsy’. Classification of epilepsy for large-scale epidemiological studies still generally involves a ‘screening’ questionnaire followed with diagnostic confirmation by sometimes multi-tiered clinical neurological assessment (Calisir et al. 2006, Placencia et al. 1992b, Schoenberg 1982). This diagnostic cascade usually results in cases classified either with the presence or absence of epilepsy, rather than differentiation into ‘more specific forms of epilepsy’

such as Idiopathic Generalised Epilepsy (IGE)(Olafsson Elias et al. 2005). Epilepsy classification by diagnostic rather than screening questionnaires, integrated with standardized interpretation of clinical information, could potentially reduce the dependence on an expert neurologist opinion and improve the reliability of syndrome classification in large-scale epidemiological studies (Boyd et al. 1979, Choi et al. 2006).

‘Diagnostic’ questionnaires have shown good agreement against physician-based diagnoses when evaluating the presence of seizures and broad epilepsy syndrome types (Ottman Ruth et al. 1990, Reutens et al. 1992). Although administration can be effectively performed by non-medical personnel, these instruments involve open-ended questioning and detailed symptom evaluation which typically also requires interpretation by an epilepsy specialist. To date, most published studies have primarily been family-based genetic studies, and provide limited detail as to how syndrome diagnoses were derived from questionnaire responses. These survey settings are likely to influence the utility and reproducibility of these instruments if they were to be used in more heterogeneous community-based surveys.

Therefore, in this Chapter, I set out to develop standardized epilepsy diagnostic guidelines for use with a modified version of two previously validated questionnaires (Ottman et al. 1990, Reutens et al. 1992) and assessed its validity against an epilepsy specialist’s diagnoses in patients attending specialist epilepsy clinics. To improve the efficiency of implementation, interviews were conducted by computer-assisted-telephone-interviewing (CATI). This ‘call-centre’ technology automates much of the

interviewing process, allowing answers received by telephone to be entered directly into computer memory by keyboard. It has been used with success in other disease groups (Anie et al. 1996) and could provide major benefits in the complex interviewing of the large sample volumes required in epilepsy syndrome-based population studies.

5.2 Methods

Recruitment

Four epilepsy specialists invited consecutive patients referred for epilepsy diagnostic evaluation from their public and private practices (TO, MC, SB, WD see acknowledgments), to contribute to the study. Following recruitment, patients were given a unique identification number to ensure that telephone interviewing, questionnaire interpretation and the epilepsy specialist's diagnosis were performed blinded of patients' diagnoses. The epilepsy specialists classified each patient's epilepsy with respect to seizure type(s), seizure-onset type (partial-onset, generalized-onset, uncertain whether partial or generalized and non-epileptic), and the idiopathic generalized epilepsy (IGE) syndrome according to the ILAE classification for epilepsy seizures and syndromes (Engel 2001, ILAE 1981, ILAE 1989).

The 'gold standard' diagnoses of seizure types, epilepsy onset types and generalized epilepsy syndrome type(s) were ascertained by each treating epilepsy specialist independently over the course of their usual clinical interactions. This typically included prospectively collecting a history from the patient and/or witnesses when available, routine and often sleep-deprived EEG(s), and brain MRI performed with an epilepsy

protocol (T1 and T2 inversion recovery with coronal flair images on an oblique axis through the temporal lobes). Other diagnostic tests may have been performed when considered necessary for characterization or when epilepsy surgery was considered. These could include: inpatient video-EEG monitoring, fluoro-deoxyderibose glucose positron emission testing (FDG-PET), and single photon emission computerized tomography (SPECT).

Diagnostic epilepsy interviews

I used a modified version of two previously validated questionnaires to diagnose patients' seizures, seizure onset-types and idiopathic generalized epilepsy (Ottman et al. 1990, Picot et al. 1999, Reutens et al. 1992). When possible, both the patient and a witness were questioned by the interviewer. A witness interview without a patient interview was: patients less than 13 years of age, or when an intellectual or language disability did not allow direct telephone interviewing. Questionnaires were administered by telephone interviewing by a team of non-medical interviewers using computer-assisted-telephone-interviewing (CATI). CATI allows questions to be stored in computer memory, recalled in programmable sequences, and displayed for each interviewer on a video display terminal. Interviewers enter answers received by telephone directly into computer memory, by means of individual keyboards. CATI automates call-back procedures, skip patterns from earlier answers, and in-process data cleaning thereby streamlining the interviewing process.

Interviewers underwent training before commencing the telephone interviewing. This involved attending a one day workshop where interviewers were taught general techniques in conducting an epilepsy diagnostic interview. They were not taught how to diagnose seizures or epilepsy, but rather to systematically extract and record seizure symptoms as part of a structured interview. They were instructed specifically: 1) not to “lead” the patient/witness but to use ‘open-ended’ questioning before more ‘direct’ questioning; 2) to record patient’s verbatim responses rather than interpreting their words; 3) To think of the seizure as occurring in three stages (although these stages are not distinct) for verbatim responses: (i) a ‘warning’ stage where patient’s memory is retained; (ii) the ‘seizure’ stage where the patient’s memory may be impaired (witness important); and (iii) the ‘recovery’ stage where the patient’s memory may also be impaired; 4) that the patient’s account is critical for warning symptoms, while the witness account is critical for seizures where consciousness may be impaired and for seizure manifestations, e.g. automatisms, behavioural arrest, limb posturing, staring, eye version, eyelid blinking etc; 5) to focus on key features of each event type, i.e. age at onset, duration of episode, relationship to sleep-wake cycle, lateralized/localized body distribution at onset and post-ictally, and the presence of certain responses suggesting non-epileptic or partial-onset seizures (see Appendix 22).

Practice interviews were then conducted with patients with epilepsy whose seizures, epilepsy onset type, and epilepsy syndrome was known (but not disclosed). Non-participating interviewers observed the interviews. The process was then discussed and interviewing techniques again reinforced. Following this each interviewer completed

between 3-5 interviews each and the process was discussed in a group with any interviewing or diagnostic issues further clarified.

Questionnaires

The diagnostic interview is a modified version of two diagnostic questionnaires, each previously shown to have substantial to almost perfect agreement with physician-based diagnoses in classifying seizure types and broad epilepsy-onset types (Ottman et al. 1990, Picot et al. 1999, Reutens et al. 1992). I primarily used the structured questionnaire of Ottman et al (version 28/09/1998, personal communication Ottman, R 2002, See Appendix 19) modified to include the direct questions relating to the evaluation of generalized non-convulsive seizures (absence, myoclonic, astatic, atonic, tonic) from the Reutens et al questionnaire (see Appendix 20). This essentially involved the addition of: (i) a more colloquial description for absence seizures (“go blank”, “switch or go off the airwaves”, or “out of it” from the Reutens et al questionnaire compared with the term “change in mental state or awareness of surroundings” or “daydream or stare into space” from the Ottman et al questionnaire); (ii) three further questions for myoclonic seizures (including eyelid “twitching” or “blinking” rather than “fluttering”), none of which involved any additional symptom descriptions; (iii) a series of direct questions specifying “sagging” or “limpness” of particular body parts for atonic/astatic seizures; and the addition of another tonic seizure question, “limbs held stiff” (see Appendix 21).

Statistical analysis

I assessed the level of agreement by the Kappa statistic (Cohen 1960, Landis and Koch 1977) between the diagnoses obtained by my modified questionnaire, interpreted with my standardized qualitative guidelines (see Appendix 22) and the diagnoses of an epilepsy specialist. The Kappa statistic (κ) represents the level of agreement above that due to chance alone: almost perfect, $\kappa > 0.81$; substantial, $\kappa = 0.61-0.8$; moderate, $\kappa = 0.41-0.61$; fair, $\kappa = 0.21-0.40$; and poor, $\kappa < 0.20$ (Landis and Koch 1977). When obtained agreement equals chance agreement, $\kappa = 0$. Greater than chance agreement leads to positive values of κ , less than chance agreement leads to negative values. The upper limit of κ is +1, occurring when there is perfect agreement. The lower limit of κ is -1, occurring when there is perfect disagreement. Sensitivity (SENS), specificity (SPEC), positive predictive value (PPV), negative predictive value (NPV) and Youden's index (YI) were also calculated. YI is the sum of sensitivity and specificity minus 1 and has been proposed as a summary measure of validity for prevalence surveys (Pearce 1998, Youden 1950). The level of agreement and validity was calculated independently for the whole sample ($n=99$) at each level of category for seizures, epilepsy, seizure onset-type and IGE. "Uncertain" diagnoses from specialist or questionnaire were categorized as 'no' in each, except with the overall seizure-onset type category for agreement, which remains a kappa value for a 4-category classification.

5.3 Results

Demographic and interview features

Table 5.1 shows the demographic features and disease characteristics of the study participants. There were 14 patients (14.1%) below the age of 20 years and 16 (16.1%) above the age of 60 years of age. Collectively the 99 patients had experienced more than 382 seizures/events in their lifetime. 59 patients had partial-onset, 22 had generalized-onset, 12 patients had non-epileptic and 6 patients had unclassified-onset seizures. Two of the patients classified as non-epileptic seizures also had epileptic seizures (one cryptogenic temporal, one symptomatic frontal). Although they contribute to both groups, for seizure types, their ultimate epilepsy-onset and syndrome classification for this study was non-epileptic. **There** were 16 patients with IGE, with a maximum of five patients in any IGE sub-syndrome. 157 interviews were performed: 58 (58.8%) had both subject and witness interviews, 21 (21.2%) a witness-only interview and 20 (20.2%) a subject-only interview.

Agreement

Table 5.2 shows the levels of agreement for seizures, epilepsy, seizure-onset types and IGE using the questionnaire compared with the ‘gold standard’ of the epilepsy specialist’s diagnoses.

Table 5.1: Demographic features and disease characteristics of study participants (n=99)

	Seizures n	Patients n
Age Range (years)*		
0-9		4
10-19		10
10-29		15
30-39		18
40-49		20
50-59		16
60-69		12
70-79		4
Gender of subject		
Male		55
Female		44
Time between diagnosis and interview		
< 1 year		0
1-4 years		15
5-9 years		14
10+ years		68
Unknown		2
Number of events in lifetime		
2		6
3		2
4 or more		91
Seizure types		
Localized-onset		59
simple partial	16	
complex partial	59	
secondarily generalised	51	
Generalized-onset		22
tonic-clonic	20	
non-convulsive	29	
myoclonic	9	
absence	8	
atypical absence	7	
atonic	1	
tonic	2	
astatic	4	
Non-epileptic [†]		12
Unclassified [‡]		6

	Seizures n	Patients n
Syndrome Types		
Idiopathic generalized epilepsy		16
childhood absence epilepsy	1	
juvenile absence epilepsy	5	
juvenile myoclonic epilepsy	5	
idiopathic generalized epilepsy unspecified	4	
epilepsy with myoclonic astatic seizures	1	
Symptomatic generalized epilepsy		6
Lennox-Gastaut Syndrome	5	
Other	1	
Idiopathic partial epilepsy		2
benign epilepsy with centro-temporal spikes	1	
benign occipital childhood epilepsy	1	
Symptomatic partial epilepsy		31
hippocampal sclerosis	9	
tumour	6	
stroke	4	
meningitis/encephalitis	1	
traumatic	7	
cortical dysplasia	2	
Acardia Syndrome	1	
dementia	1	
Cryptogenic partial epilepsy		29
temporal	12	
frontal	1	
occipital	1	
lobe(s) uncertain	15	
Non-epileptic [†]		12
Uncertain whether partial or generalized [‡]		6

*Mean age of subjects is 40.3 years, standard deviation 17.6 (as at 01.01.04).

†includes two participants with both non-epileptic and partial-onset seizures classified only as non-epileptic onset type.

‡includes three participants classified ultimately as uncertain partial or generalized with mixed seizure types

Table 5.2: Diagnostic agreement for the presence of epilepsy, seizures, seizure-onset types[§], and the idiopathic generalized epilepsy syndrome from telephone interviews versus epilepsy specialists' assessment

	κ value [†]	95% CI [‡]
Partial Seizures		
Simple partial/complex partial	0.87	[0.78-0.97]
Partial, secondarily generalised	0.74	[0.60-0.87]
Generalised Seizures		
Generalised tonic-clonic	0.79	[0.64-0.94]
Generalised non-convulsive*	0.82	[0.66-0.97]
Myoclonic seizure	0.68	[0.40-0.95]
Astatic	0.39	[-0.06-1.00]
Absence	0.73	[0.47-0.99]
Atypical absence	0.43	[-0.06-0.92]
Presence of epilepsy	0.94	[0.83-1.00]
Seizure onset-type[§]	0.84	[0.74-0.94]
Partial	0.83	[0.72-0.94]
Generalised	0.88	[0.76-1.00]
Non-epileptic	1.00	NA
Idiopathic generalised epilepsy syndrome**	0.82	[0.65-0.99]

* Includes the low frequency tonic (n=2) and atonic (n=1) seizures

§ This remains a kappa value for a 4-category classification, where the 4 categories are either localized, generalized, "non-epileptic" and epileptic unclassified.

† The Kappa statistic (κ) represents the level of agreement above that due to chance alone where: almost perfect, $\kappa > 0.81$; substantial, $\kappa = 0.61-0.8$; moderate, $\kappa = 0.41-0.61$; fair, $\kappa = 0.21-0.40$; and poor, $\kappa < 0.20$ (Landis and Koch 1977)

‡ 95% CI = 95% Confidence intervals for kappa were calculated using <http://graphpad.com/quickcalcs/kappa1.cfm> with a normal approximation.

The questionnaire demonstrated almost perfect agreement in diagnosing simple or complex partial seizures ($\kappa=0.87$, 95% CI 0.78-0.97), any generalized non-convulsive seizure ($\kappa=0.82$, 95% CI 0.66-0.97), the presence of epilepsy ($\kappa = 0.94$, 95% CI 0.83-1.00), seizure-onset types ($\kappa = 0.84$, 95% CI 0.74-0.94), and IGE ($\kappa = 0.82$, 95% CI 0.64-0.97). Although still substantial, agreement was not as close for secondarily generalized seizures ($\kappa = 0.74$, 95% CI 0.59-0.85), and generalized tonic-clonic seizures ($\kappa = 0.79$, 95% CI 0.64-0.94).

Validity

Table 5.3 shows the sensitivity, specificity, positive predictive value, negative predictive value and Youden's Index for the presence of epilepsy, seizures, seizure-onset types and epilepsy syndromes using the questionnaire compared with an epilepsy specialist's diagnoses. With values of about 0.9 or higher, diagnostic interviewing had high validity in classifying simple or complex partial seizures, the presence of epilepsy, and seizure-onset types. The diagnosis of generalized seizures and IGE also had generally high specificity, positive predictive value (except myoclonic and absence seizures both with PPV of 0.75), and NPV but lower sensitivity than the partial seizures. Perfect or near perfect YI is seen for the diagnosis of "non-epileptic seizures" and the "presence of epilepsy" categories. With the exception of astatic (0.25) and atypical absence seizures (0.29), reasonable YI is seen for all diagnostic categories and ranges from 0.65 to 1.00.

Table 5.3: Sensitivity, specificity, positive predictive value, negative predictive value and Youden's Index (YI) for the presence of epilepsy, seizures, seizure-onset type[§], and idiopathic generalized epilepsy from telephone interviews versus epilepsy specialists' assessment

	SENS	95% CI‡	SPEC	95% CI‡	PPV	95% CI‡	NPV	95% CI‡	YI	95% CI‡
Partial Seizures										
Simple or complex	0.93	[0.85–0.98]	0.95	[0.85–.99]	0.97	[0.90–0.99]	0.90	[0.79–0.97]	0.88	[0.79-0.88]
Secondarily generalized	0.92	[0.82–0.97]	0.82	[0.69–.91]	0.84	[0.73–0.92]	0.91	[0.80–0.97]	0.76	[0.65-0.89]
Generalised Seizures										
Tonic-clonic	0.78	[0.59–0.91]	0.97	[0.92–1.00]	0.90	[0.72–0.98]	0.93	[0.87–0.98]	0.75	[0.58-0.93]
Generalised non-convulsive*	0.74	[0.52–0.89]	1.00	[0.96–1.00]	1.00	[0.82–1.00]	0.94	[0.88–0.98]	0.74	[0.54-0.93]
Myoclonic seizure	0.67	[0.37-0.89]	0.98	[0.93-1.00]	0.75	[0.42-0.95]	0.97	[0.92-0.99]	0.65	[0.33-0.95]
Astatic	0.25	[0.03-0.67]	1.00	[0.97-1.00]	1.00	[0.22-1.00]	0.97	[0.92-0.99]	0.25	[-0.17-.67]
Absence	0.75	[0.42-0.95]	0.98	[0.93-1.00]	0.75	[0.42-0.95]	0.98	[0.93-1.00]	0.73	[0.43-1.03]
Atypical absence	0.29	[0.06-0.62]	1.00	[0.97-1.00]	1.00	[0.37-1.00]	0.95	[0.89-0.98]	0.29	[-0.05-.62]
Presence of epilepsy	0.99	[0.95–1.00]	1.00	[0.74–1.00]	1.00	[0.95–1.00]	0.90	[0.63–0.99]	0.99	[0.97-1.01]
Seizure onset-type[§]										
Partial	0.93	[0.85–0.98]	0.90	[0.78–0.97]	0.93	[0.85–0.98]	0.90	[0.78–0.97]	0.83	[0.72-0.95]
Generalised	0.90	[0.73–0.98]	0.97	[0.92–1.00]	0.90	[0.73–0.98]	0.97	[0.92–1.00]	0.87	[0.75-1.01]
Non-epileptic	1.00	[0.74–1.00]	1.00	[0.97–1.00]	1.00	[0.74–1.00]	1.00	[0.97–1.00]	1.00	[1.00-1.00]
Idiopathic Generalised Epilepsy **	0.73	[0.50–0.90]	1.00	[0.97–1.00]	1.00	[0.78–1.00]	0.95	[0.90–0.99]	0.73	[0.51-0.96]

SENS = sensitivity, SPEC = specificity, PPV = positive predictive value, NPV = negative predictive value, YI = Youden's Index

* Includes the low frequency tonic (n=2) and atonic (n=1) seizures which, given their low numbers are not shown individually

† The Kappa statistic (κ) represents the level of agreement above that due to chance alone where: almost perfect, $\kappa > 0.81$; substantial, $\kappa = 0.61-0.8$; moderate, $\kappa = 0.41-0.61$; fair, $\kappa = 0.21-0.40$; and poor, $\kappa < 0.20$ (Landis and Koch 1977)

‡ 95% CI = 95% Confidence intervals for SENS, SPEC, PPV and NPV are exact, "shortest confidence intervals" as calculated on the website http://www.causascientia.org/math_stat/ProportionCI.html. This is the most appropriate method when the number of trials is low or where the estimated proportion is close to 1.

§ Seizure onset types are either: generalized-onset, partial-onset or "non-epileptic". Sensitivity, specificity, PPV and NPV can not be calculated for a variable with more than 2 possible values.

** Idiopathic Generalised Epilepsy Syndrome = Any Childhood Absence Epilepsy, Juvenile Absence Epilepsy, Juvenile Myoclonic Epilepsy, Idiopathic Generalised Epilepsy Unspecified or Myoclonic Astatic Epilepsy.

5.4 Discussion

My modified questionnaire administered by CATI and interpreted by standardized diagnostic guidelines, was in close agreement with an epilepsy specialist's clinical assessment in diagnosing the main seizure types, presence of epilepsy, seizure-onset types, and IGE. Questionnaire modifications aimed at previous diagnostic deficiencies in classifying non-convulsive generalised seizures substantially improved agreement and validity. However, diagnosis still remained less than ideal for discriminating the onset-type of generalized convulsive seizures. These deficiencies relate more to under-recognition of individual generalized non-convulsive seizures than to misinterpretation of partial seizures. Despite these limitations, this modified diagnostic questionnaire should provide an effective more practical alternative to screening questionnaires coupled with neurological assessment, in the population-level study of 'more specific forms of epilepsy', particularly the Idiopathic Generalised Epilepsies.

Although I did not set out to ensure my sample represented all possible syndromes it was reasonably representative of the broad range and prevalence of syndrome groups seen in a typical adult epilepsy outpatient setting (Alving 1979, Danesi 1985, Eadie 1996, Osservatorio Regionale per l'Epilessia (OREp)). In particular, excluding the non-epileptic category, 18% of my sample had IGE. Lack of representativeness of the validation sample could have potential impact on the kappa statistic, positive predictive value and the negative predictive value which are all affected by the prevalence of the diagnostic category under consideration (Kraemer 1979). In particular, if the validation sample involved cases that were more severe, on average, than would have been obtained

from a random population-based sample, then the findings of the validation study may not be completely generalisable. However, my findings, at least with respect to the IGE category, may at least be reliable in these settings. I did not contemplate further 'splitting' of the IGE seizure types (e.g. absence) or IGE syndromes into their subtypes (e.g. childhood absence epilepsy), as this was likely to add unnecessary complexity to the validation process (Dorsey et al. 1986) and involve too few numbers to draw meaningful conclusions.

The use of epilepsy questionnaires arose with the shift from hospital-based to community-based epidemiological studies (Rose et al. 1973) along with the knowledge that medical records often involve poor accuracy and reliability of diagnostic information (Bodensteiner et al. 1988, Demlo et al. 1978, Hauser and Kurland 1975, Hauser et al. 1991). The diagnostic interpretation of information from indirect sources is highly dependent on the experience of the observer, with unclassifiable descriptions of seizures ranging from 22-51% when either a training neurologist or neurologist is making the diagnosis (Bodensteiner et al. 1988). One of the most important means of ensuring diagnostic validity has been the analysis and interpretation of information by a specialist with expertise in epilepsy (Berg et al. 1999, Ottman et al. 1998b, Placencia et al. 1992b, Reutens et al. 1992) with mutual discussion among experts providing even better agreement than a neurologist using clinical judgment working alone (Rinaldi et al. 2000, van Donselaar et al. 1989). This improved diagnostic agreement can be substantial, with mutual consultation ($k = 0.86$) much higher than individual clinical judgment ($kappa = 0.58$). However, the use of specific criteria has the greatest diagnostic yield ($kappa =$

0.96) (van Donselaar et al. 1989). Hence, developing standardised diagnostic guidelines for seizures and epilepsy syndromes is critical, not only to enable diagnosis to become less dependent on expert opinion (Placencia et al. 1992b, Placencia et al. 1992c), but ultimately to improve the reproducibility of clinical and epidemiological epilepsy research (Oka et al 1995; Eadie 1996).

I used written guidelines, extended with my own clinical experience from previous operational definitions (Placencia et al. 1992b, Sander and Shorvon 1987) for syncope, psychogenic non-epileptic seizures, partial seizures, and the generalized seizure types and syndromes to assist in interpretation of the verbatim and direct questionnaire responses in my patients. I acknowledge that these are by no means definitive, but hope the formalization of this clinical process will lead to more transparent and testable future refinements. To further improve reproducibility for field studies, I elected to reach my questionnaire diagnoses without the use of EEG recordings. Although, interictal EEG information can enhance symptom histories and help differentiate seizure types (Picot et al. 1999, Reutens et al. 1992), it can also be unhelpful (Houfek and Ellingson 1959, McCluggage et al. 1986), more often confirming rather than changing diagnosis (Senanayake 1993). Therefore, EEG recordings may not be cost-effective when conducting epidemiological studies in resource-constrained communities. More critical to diagnosis is an eye-witness account of the patient's seizures (Reutens et al. 1992, Senanayake 1993), with the highest level of overall agreement between physician and questionnaire-based diagnoses achieved when an informant is available for interview (informant only $k = 0.76$, patient and informant $k = 0.75$) rather than when a subject is the

only source of diagnostic information ($k = 0.41$) or the additional use of EEG ($k = 0.78$) (Reutens et al. 1992). Hence, my emphasis on high witness participation (80%) is likely to have been a key factor contributing to my findings.

Diagnostic questionnaires have had limited testing on samples containing patients with non-epileptiform events (syncopal, psychogenic, migrainous etc) (Picot et al. 1999) which also commonly present as seizure ‘mimickers’ in community-based samples. Differentiating epileptic seizures from other paroxysmal symptoms can be problematic, with 24% of patients misdiagnosed as epilepsy from case records having non-epileptic seizures (Keranen 1987). I agree that it might have been better to include more total NES categories, but the case mix in the study reflects the fact that it was based on invitations extended to a random sample of each neurologist’s list of patients referred to their outpatient clinics where seizures were considered a differential diagnosis. Consistent with this previous study (Picot et al. 1999), my modified diagnostic questionnaire had almost perfect agreement and validity to diagnose the “presence of epilepsy”.

My diagnostic interview is a modified version of two questionnaires each previously shown to have very good to almost perfect agreement, with physician-based diagnoses, in classifying seizure types and broad epilepsy-onset types (Ottman et al. 1990, Picot et al. 1999, Reutens et al. 1992). The questionnaire of Reutens et al predominantly comprises open-ended questions, with a structure similar to clinical history taking, while more detailed direct questioning in the semi-structured interview questionnaire makes it more amenable to administration in large-scale epidemiological studies, particularly with the use of CATI. In an attempt to better identify the specific non-convulsive generalized seizures (and their related syndromes) diagnosed generally with higher agreement and

validity from Reutens et al, my modified questionnaire included the direct questions relating to their classification. With the exception of the questions relating to the rarer seizures, my modifications could be considered fairly minor, and an alternative explanation for the observed differences between these two original diagnostic questionnaires could relate to the more skill-dependent collection of symptoms (especially the verbatim recordings) or the interpretation of these responses. Nevertheless, with these additions, the overall agreement for most seizures, the presence of epilepsy, seizure onset-types, and IGE was almost perfect, and closer to that seen with the questionnaire of Reutens et al (Ottman et al. 1990, Picot et al. 1999, Reutens et al. 1992), particularly for the critical IGE seizure types, absence (0.73 vs. 0.78) and myoclonus (0.68 vs. 0.70). The better agreement for generalized non-convulsive seizures is likely to have also led to its improved ability to discriminate convulsive seizures as either generalized-onset (0.79) or partial-onset (0.74). With both high sensitivity (0.93) and specificity (0.95) in diagnosing simple partial or complex partial seizures my modified questionnaire does not appear to misinterpret partial seizures to a great degree (van Donselaar et al. 1990). This suggests that further diagnostic gains for convulsive seizures are more likely to result from improved recognition of the individual generalized non-convulsive seizure types (i.e. absence, myoclonus, astatic, tonic, atonic etc) rather than better recognition of warning symptoms.

After confirming the presence or absence of epilepsy, my subsequent focus was to diagnose with confidence the generalized epilepsies to the second level, i.e. idiopathic generalized, rather than to classify focal-onset epilepsy to the second or third level (i.e.

cryptogenic vs. symptomatic or specific lobar involvement). Although the ILAE still attributes these partial syndromes to sites of the cerebral cortex by historical data and EEG findings (Engel 2001, ILAE 1981, ILAE 1989, Stevens et al. 1996), few clinical features having a well defined anatomic correlate (Pribram 1987). In contrast, MRI is better able to identify symptomatic etiologies (Jack et al. 1995, Jackson et al. 1990) and along with newer functional neuro-imaging techniques (Stevens et al. 1996), plays a central role in syndrome diagnosis of the partial epilepsies (Awada et al. 1991).

In contrast, neuro-imaging is not generally clinically useful for the idiopathic epilepsies with diagnosis often reached following interview from the patient and eye-witness, sometimes supplemented with family seizure history. Therefore, while the cryptogenic and symptomatic epilepsies require detailed investigations not readily available outside major metropolitan centres, I have demonstrated that the idiopathic epilepsies can be classified primarily with historical data when interpreted with written guidelines, facilitating their study in large scale population studies by questionnaire. Further improvements in discriminating the individual non-convulsive generalized seizure types and a more quantitative approach to questionnaire interpretation will further enhance the utility of these field instruments for epilepsy syndrome-based population research.

Chapter Six: The Tasmanian Epilepsy Register – A community-based cohort: Background and methodology for patient recruitment from the Australian national prescription database

6.1 Introduction

In this chapter, I use the Australian national prescription database to recruit a cohort of patients with epilepsy that is representative of community-based disease (D'Souza et al 2007c). The population sample generated will form the basis of my estimate of the prevalence and distribution of epilepsy, IGE, and their associated generalised seizures in the following two chapters.

Door-to-door household surveys have become the foundation for case ascertainment in epidemiological studies designed to measure the incidence or prevalence of epilepsy (Placencia et al. 1992b). They were originally established for use in studies in developing countries, as part of a two-stage methodological design typically involving a screening questionnaire followed by diagnostic confirmation from a clinical neurological assessment (Meneghini et al. 1991, Osuntokun et al. 1982). This approach is considered necessary to comprehensively capture undiagnosed and untreated disease, usually only seen outside a hospital setting, particularly in populations with inadequate access to specialist neurology services (Schoenberg 1982).

However, rigorous survey design requires considerable resources and is a relatively inefficient mechanism for generating sufficient cases when studying specific syndromes,

etiological factors, or co-morbid conditions associated with epilepsy. The development of ascertainment methods primarily focused on effective and efficient case recruitment would be invaluable, particularly if the samples generated were representative of community-based disease (Sander and Shorvon 1987).

The Australian federal parliament passed legislation in December 2000 enabling data to be linked from the national prescribed medicines database and an individual's national health information identifier. I was one of the first to utilize this relatively unique patient database for disease recruitment. In this chapter, I describe the recruitment methodology used to establish a large community-based epilepsy cohort in the Australian island state of Tasmania and discuss its relative strengths and limitations.

6.2 Methods

Geography and Population

Tasmania is an island state situated off the south-eastern tip of mainland Australia, comprising an area of 68,000 square km, with a population of 472,672 in 2002 (Australian Bureau of Statistics 2003) (see Figure 6.1a). The state is divided into the three main geographic and administrative regions comprising Southern (231,662), Northern (134,701) and Mersey-Lyell/North-Western (106,309) (see Figure 6.1b). The first European settlers arrived in 1804, and by 1847 there were around 13,000 females in the total population of 70,000. Tasmania has attracted fewer immigrants than other Australian states, and it is estimated from genealogical records that in 6-7 generations approximately 65% of Tasmania's current population are direct descendants of these

13,000 female founders, many of whom were related. This makes Tasmania's population more genetically homogeneous than the populations of mainland states. This is supported by the Australian census, where 88.7% of Tasmanians indicated that both parents were of North Western European ancestry, compared, for example, to 69.4% of Australians from the state of Victoria (Australian Bureau of Statistics 2003). Tasmania was chosen for this study as it has considerable benefits for conducting epidemiological research. Firstly, the state has significant goodwill towards medical research, leading to very high participation rates. Secondly, Tasmania's relatively stable migration patterns over the last 150 years mean that participants in longitudinal cohort studies (and studies dependent on family-based designs) are easily traced, as they remain resident within the state (Jones et al. 2003).

Figure 6.1a: Map of Australia

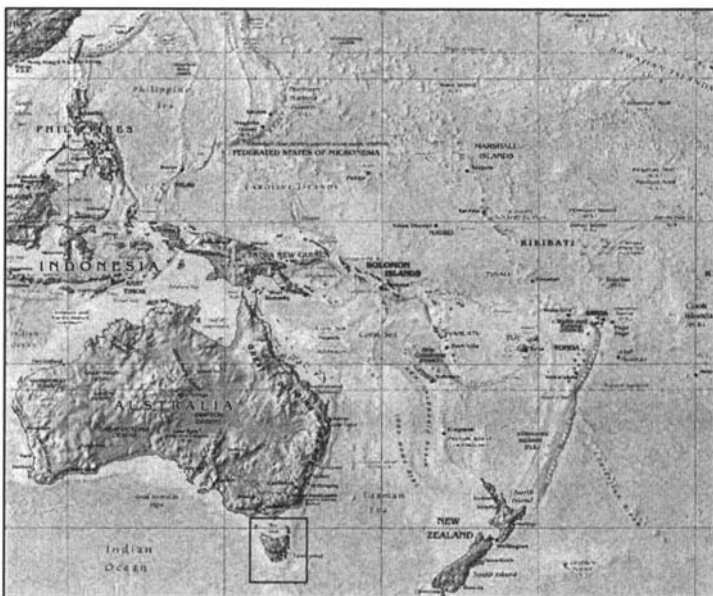


Figure 6.1b: Map of Tasmania



Medical provider services

In Australia, consultative and investigational health services are significantly funded by the federal government allowing universal means-independent access to health services. General practitioners and specialists can either charge only the federally-funded rebate amount (and claim it directly from the HIC) or alternatively choose to charge above this amount, with the patient then paying the whole service fee to the doctor before claiming the rebate portion from a HIC Medicare rebate outlet. Consultations with public hospital specialists do not incur any fee directly to the patient. Patients can also be diagnosed and managed by a private specialist, but must be referred by a general practitioner, for this service to attract a federally funded specialist rebate (Care 2000). In Tasmania, regional specialist physicians comprised: six paediatricians, four general physicians and two neurologists residing in the south; three paediatricians, two general physicians and one neurologist residing in the north; and two paediatricians and three general physicians

residing in the north-west. In addition, three interstate epileptologists visit the south (two bi-monthly, one monthly) and one the north (every 3-4 months).

Pharmaceutical benefits scheme and the Australian National Prescription Database

National prescription data records are generated when the government contributes to the cost of a pharmaceutical product dispensed under the Australian Pharmaceutical Benefits Scheme (PBS) and Repatriation Pharmaceutical Benefits Scheme (RPBS). The PBS/RPBS is a subsidisation program monitored by the HIC. Patients are classified into one of two categories, which determines the amount the patient contributes and the amount of subsidy paid by the government. General beneficiaries make a maximum patient contribution (A \$22.40 in 2002) per prescription item; concessional beneficiaries (primarily social security recipients) or veteran affairs (returned servicemen and women) categories purchase drugs at a concession rate (A \$3.60 in 2002). Additional “safety net” arrangements limit the total annual contribution that a family can make towards prescription costs for each of these categories of patient. Once these limits are reached, any PBS/RPBS prescriptions dispensed, are either free or with a much reduced co-payment for the remainder of the safety net period (Edmonds et al. 1993).

Pharmacists, rather than patients receive the reimbursement payment from the HIC when they report prescription information to the HIC, or they bear the unsubsidised cost of the medicine. Only, where a person does not have a Medicare card, is the onus on the patient to pay the full (non-subsidised) price for the prescription and personally claim a reimbursement from the HIC on provision of their Medicare number. These

arrangements have implications on the PBS/RPBS data set. When a patient pays the entire cost of the medication, there is no HIC record of the prescription. Prescription records for drugs costing less than the general patient co-payment will not be complete (only recorded for concessional beneficiaries and those who have reached safety net entitlements). There will be complete capture for more expensive drugs, as the government will have made a contribution in every case (Robertson et al. 2001).

Table 6.1 lists the PBS/RPBS anticonvulsant items selected. Only five of these anticonvulsants (phenobarbitone, phenytoin suspension, carbamazepine liquid, carbamazepine 50mg and lamotrigine 5mg) cost less than \$22.40, and so had limited capture. Some anticonvulsant medications were not selected (levetiracetam, oxcarbamazepine, and pregabalin) because at the time they were not PBS/RPBS listed medications. Benzodiazepines and acetazolamide prescriptions were excluded from selection because they were more likely to be prescribed as single agents for other conditions.

At the end of 2000, the Australian Federal Parliament passed the National Health Act Amendment - Improved Monitoring of Entitlement of Pharmaceutical Benefits. An important part of this legislation requires pharmacists in Australia to ask all consumers for their healthcare identification number (Medicare number or Veterans' Repatriation Health Card entitlement number) when they respectively present with a prescription for a PBS or RPBS subsidised medicine.

Table 6.1: “Reportable” anticonvulsant medications* supplied in Tasmania between 1st July 2001 and 30th June 2002

Generic name	Preparation
Methylphenobarbitone	Tablet
<i>Phenobarbitone</i>	<i>Tablet†</i>
Primidone	Tablet
<i>Carbamazepine</i>	<i>Tablet ‡</i>
Carbamazepine	Tablet (controlled-release)
<i>Carbamazepine</i>	<i>Liquid†</i>
Gabapentin	Tablet
<i>Lamotrigine</i>	<i>Tablet§</i>
<i>Phenytoin</i>	<i>Suspension†</i>
Phenytoin	Tablet
Phenytoin Sodium	Tablet
Sodium Valproate	Tablet
Sodium Valproate	Tablet (enteric-coated)
Sodium Valproate	Liquid
Sodium Valproate	Syrup
Topiramate	Tablet
Topiramate	Sprinkles
Ethosuximide	Tablet
Sulthiame	Tablet
Tiagibine	Tablet
Vigabatrin	Tablet

**All the anticonvulsant medications retail at more than \$A3.60 and there is a HIC record generated for all concession card patients receiving these drugs from a pharmacist. When medications retail at less than \$A22.40 there is no HIC record generated for general patients receiving these drugs from a pharmacist. †Denotes incomplete capture, ‡ and § denote incomplete capture only for 50mg and 5mg preparations respectively.*

This legislation meant that no government payment would be made to a pharmacist for a prescription unless an appropriate Medicare number was included with each claim.

Pharmacists were required to record a Medicare number for each PBS or RPBS script in their pharmacy dispensing software and to include the number with each claim for payment from the HIC. Where a person did not have a Medicare card, the person would need to pay full (non-subsidised) price for the prescription and claim a reimbursement from the HIC on provision of their Medicare number, subject to a check of their eligibility by the HIC. Special numbers were also established to cover emergencies and other situations where consumers were eligible but could not produce a Medicare card.

Until these legislation changes, prescriptions recorded by the HIC could not be attributed to individual patients. These changes also enabled non-identifying cross-matched prescription data to be obtained on age, gender, postcode region, date of dispensing, the category of recipient (general, concessional, doctors emergency bag, safety net, or veteran affairs) and category of prescriber.

Recruitment of participants

The target sample frame involved all those persons who have been supplied at least one prescription for an anticonvulsant medication in Tasmania above the 'reportable' PBS/RPBS threshold during the twelve month period July 1st 2001 to June 30th 2002. To be eligible, participants must have a listed postcode in Tasmania when collecting their prescription during this period.

Under privacy legislation, the release of information concerning the affairs of a person receiving benefits under the PBS/RPBS is prohibited except in exceptional circumstances. Therefore, each HIC sample patient was given a unique identifying number to enable the invitation and the tracking of response to be conducted anonymously from my study team. This meant my study team could not have access to HIC-held names and addresses linked to their uniquely generated ID number until those patients agreed to participate in the Register. Patients were sent a package of information from the HIC explaining the reasons for approaching them, outlining the aims of the study and inviting them to enrol on the Register on 20th November 2002. A second mail invitation was sent to those invited patients who had failed to respond within three

months of my initial invitation (19th February 2003), unless I had received a 'return to sender' notification or information that they had deceased. Those patients who did not respond to the second mail-out, within three months of its dispatch were classified as mail non-responders.

A mail invitation letter asked potential participants to agree to participate in a longitudinal disease cohort - The Tasmanian Epilepsy Register. In addition, as anticonvulsant medications can be prescribed for other medical conditions, invited HIC patients were also asked to disclose '*are you taking antiepileptic medications for blank spells, seizures or epilepsy*', so that their disease status could be recorded.

Once they had accepted an invitation, Register patients were contacted by telephone and written consent obtained after discussion with the study team. The telephone interviewing centre (private outbound telephone call-centre) was then given the names, telephone contact details and best times for contact so that the baseline interviews could be conducted. The HIC patients may refuse Register enrolment, or withdraw from participation after initially agreeing. They may indicate this to the study team or the HIC anonymously (from the study team) by mail or directly by telephone.

Methods used to maximise participation

To maximize recruitment, a promotional campaign was carried out prior to the HIC mail invitations. This involved presentations through established health professional and community organizations involved in the management and advocacy of epilepsy in the

state. The organizations included the regional Divisions of General Practice, hospital general physicians, paediatricians, neurologists and the Epilepsy Association of Tasmania in the three main regional centres Hobart, Launceston and Burnie. Presentations were also conducted with the three pharmacist representative organizations of the Pharmaceutical Guild of Tasmania, the Tasmanian Branch of the Pharmacist Society of Australia, and the Society of Hospital Pharmacists. A poster and information pamphlets were displayed and made available in prominent locations at all pharmacies, general practices, hospital neurology outpatient clinics and Epilepsy Association of Tasmania regional offices in the State. In addition, a media campaign was undertaken with a media release, a prime time news story on the Australian national television broadcaster, a news item and talkback session on the state radio station, media releases through the main state and regional newspapers and an item in each of the health professional and epilepsy association newsletter networks.

Data collection, management and storage

The HIC had sole access and administration of national prescription data until eligible patients consented to participate in the Register. The names and addresses of participants consenting to be involved in the Register were saved and transferred to the centre involved in conducting the baseline interviewing of participants involving diagnosis, risk factors, health service utilization, and co-morbid conditions (data not included). When all the baseline questionnaires were completed, a designated person maintained sole responsibility for collating, checking completeness, data entry, and storage of all data in preparation for analysis. Upon obtaining questionnaire data, at the interviewing centre, all identifying information was removed from the medical data and questionnaires.

Statistical Analysis

Recruitment through the HIC allowed us to obtain non-identifying demographic and treatment information for HIC patients on; age, gender, postcode region, socioeconomic status (SES) derived from postcode, prescribing doctor type and all other prescribed medications. To assess the representativeness of my responder sample, variations in my HIC mail invitation between responders versus non-responders were analyzed for these variables with a χ^2 test for differences between proportions. A test for trend in the proportion responding across levels of the characteristic (age, SES) was also conducted by fitting a univariable log binomial model and fitting the characteristic as a linear predictor.

Socioeconomic index for area (SEIFA)

The Socioeconomic Index For Area (SEIFA) 2001 was developed by the Australian Bureau of Statistics and using data derived from the 2001 Census of Population and Housing. It provides a range of measures to rank geographic areas based on their relative social and economic wellbeing (Trewin 2001). In 2001, there were four indexes, each summarizing a different aspect of the socio-economic conditions in an area. This report utilizes the Index of Relative Socio-Economic Advantage/Disadvantage. This is derived from attributes such as low income, low educational attainment, high unemployment, jobs in relatively unskilled occupations and variables that reflect disadvantage rather than measure specific aspects (e.g., Indigenous and Separated/Divorced). High scores on the Index of Relative Socio-Economic Advantage Disadvantage occur when the area has few families of low income and few people with little training and in unskilled occupations.

In 2001, Tasmania was the most disadvantaged state with a fewer proportion of residents in the higher SEIFA quintiles compared to all other Australian states. Therefore, for this analysis, the SEIFA index values were partitioned into quintiles that were approximately equal in size across the Tasmanian population.

Ethical approvals

Approval was obtained for the recruitment, baseline interviews, data storage and analysis from the Southern Tasmania Health and Medical Human Research Ethics Committee.

Approval was also obtained for recruitment through the Health Insurance Commission Medicare-PBS/RPBS database from the Health Insurance Commission Ethics Committee and the Department of Veterans' Affairs Human Research Ethics Committee.

Participants were asked to sign an Informed Consent Statement to participate in the Register. This statement explained the nature and content of the Register, the nature of their participation, issues relating to confidentiality and privacy, and voluntary participation in potential future studies.

6.3 Results

Patient recruitment and participation

Figure 6.2 summarizes the recruitment process and patient participation onto the Tasmanian Epilepsy Register from the Australian national prescription database. A total of 7,737 persons received 'reportable' prescriptions for anticonvulsant medications in Tasmania between July 1st 2001 and June 30th 2002, of which 7,541 had a listed Tasmanian address and were sent an invitation letter from the HIC. However, I received information that 48 had deceased and 247 were no longer resident at the address listed with the HIC from the time of sampling through the recruitment process (30th June 2002 to 31st May 2003). Therefore, 7246 were available to participate in the Register. Only 4.8% (372/7737) of persons had received RPBS prescriptions. Data on the specific dispensed anticonvulsant and doctor provider type was missing from the HIC database in 6.2% (470/7541) of persons for which all were 'general' patients without a 'safety net'. A total of 1957 patients responded to mailout 1 and 1418 responded to mailout 2. The overall eligible mail invitation response rate was 44.8% (3375/7541). Following the six month recruitment process, 1180 were enrolled on the Tasmanian Epilepsy Register, giving an overall participation rate of 34.9% (1180/3375). However, only half of all respondents indicated they were taking anticonvulsants for epilepsy and the participation rate amongst this group was considerably higher at 78.3% (1180/1507).

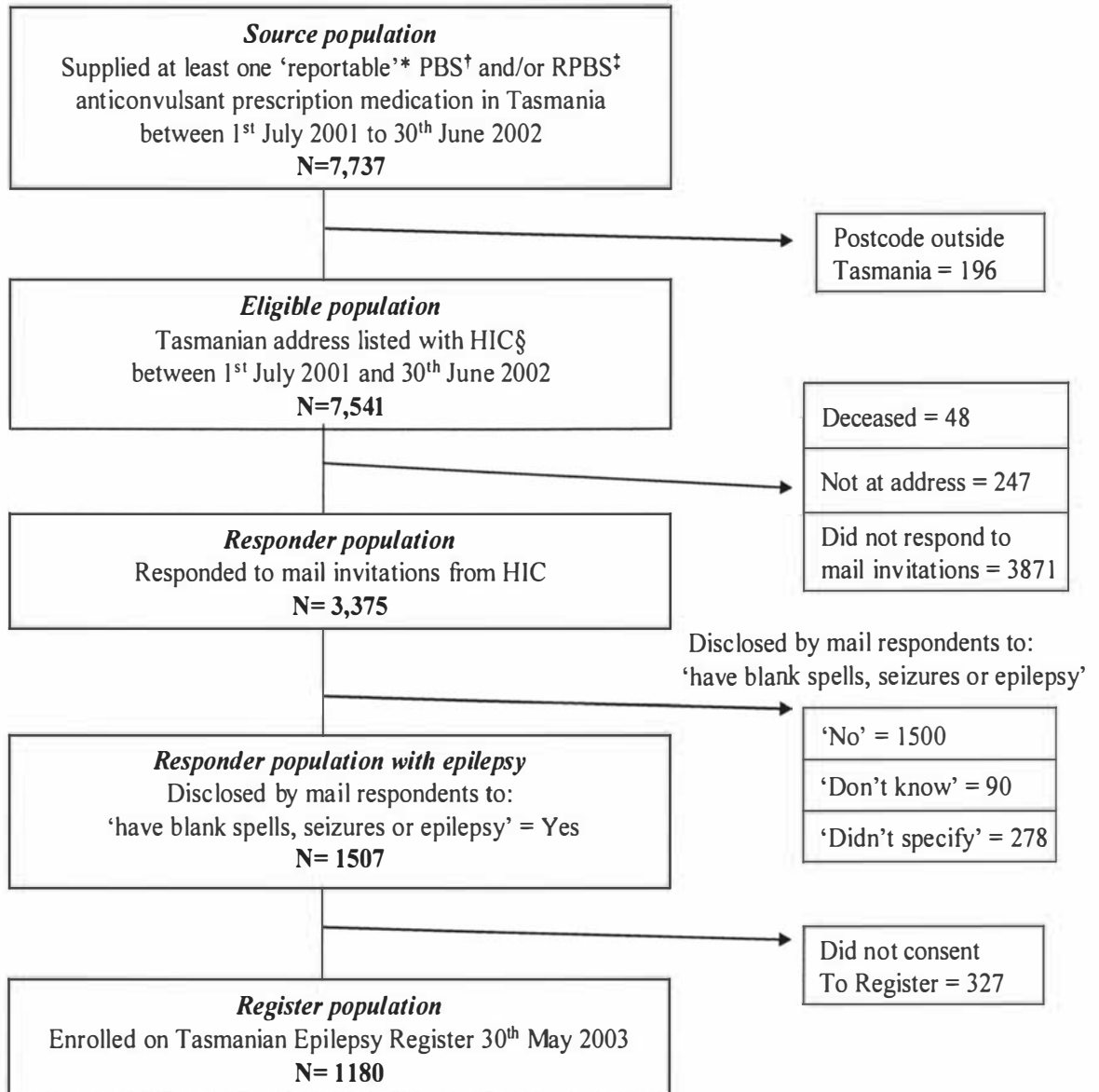
The 7071 patients for which HIC data were available had records corresponding to 13,033 prescriptions (data not shown). The majority of anticonvulsant prescriptions (82.4%, 10734/13033) from the HIC sample and enrolling on the epilepsy Register

(82.1%, 2354/2866) had been obtained from a general practitioner. In the preceding 12 months, Register participants were more likely to obtain their prescriptions exclusively from their general practitioner (70.9%) or from combined sources (19.1%) rather than from other sources (Table 6.2).

Non-responder bias

Table 6.3 shows the demographic features of the Tasmanian population, mail responders, non-responders and epilepsy Register participants. Patients taking anticonvulsant were more likely to respond with increasing age (trend $p < 0.001$), or when from a higher socio-economic quintile (linear trend $p < 0.001$) with over-representation if female almost reaching significance ($p = 0.053$). In addition, patients taking anticonvulsants were more likely to respond to my invitation if their prescription was obtained from a neurologist and less likely to respond if their prescription was obtained from a psychiatrist ($p = 0.007$). No regional differences in response were found.

Figure 6.2: Summary of patient recruitment and participation onto the Tasmanian Epilepsy Register



* 'Reportable' anticonvulsant prescriptions: see Table 1 for listed medications in 2002

† PBS = Pharmaceutical Benefits Schedule

‡ RPBS = Repatriation Benefits Schedule

§ HIC = Health Insurance Commission (Federal Government Agency that monitors healthcare entitlements including the Australian national prescription database)

Table 6.2: Comparison of HIC sample versus Register participants for anticonvulsant provider type in Tasmania between July 1st 2001 and June 30th 2002

Provider type	HIC Sample		Register	
	(n= 7541)	%	(n=1180)	%
Surgical specialist	91	1.2	1	0.1
General practitioner*	5420	72.1	837	70.9
General Physician	186	2.6	12	1.0
Neurologist	115	1.5	17	1.4
Paediatrician	162	2.3	49	4.2
Psychiatrist	254	3.5	6	0.5
Combination	843	10.7	225	19.1
Not known	470	6.1	33	2.8
Total	7541	100.0	1180	100.0

**includes qualified medical practitioners not in specialty training*

6.4 Discussion

The main aim of this study was to enrol a representative population cohort of community-treated epilepsy cases. This recruitment design is relevant for researchers in countries with centralized prescription databases, and who are intending to conduct studies with large sample sizes e.g. when estimating the prevalence of epilepsy sub-types, co-morbid conditions, syndrome-focused case-control studies, or longitudinal cohort studies. I deliberately chose not to extensively target patients receiving anticonvulsants from neurologists, paediatricians and general physicians, outside my mail recruitment campaign. This was to ensure my sample was not disproportionately enriched by hospital-treated cases, and to demonstrate the effectiveness and efficiency of this recruitment design, independent of doctor referral.

Table 6.3: Demographic features by age, gender, region and socio-economic status of the Tasmanian population, Register participants, responders and non-responders

	Tasmania		Register		Responder*		Non-Responder†		Responder vs. non-responder p value
	(n=472,672)	%	(n=1180)	%	(n=3375)	%	(n=4166)	%	
Age									
0-9	63717	13.5%	36	3.1%	51	1.5%	71	1.7%	
10-19	68096	14.4%	113	9.6%	172	5.0%	233	5.7%	
20-29	56153	11.9%	115	9.7%	218	6.4%	433	10.5%	
30-39	64730	13.7%	136	11.5%	327	9.6%	623	15.1%	
40-49	70829	15.0%	233	19.7%	536	15.9%	727	17.5%	
50-59	60386	12.8%	256	21.7%	688	20.4%	681	16.3%	
60-69	41233	8.7%	161	13.6%	546	16.2%	497	11.9%	
70-79	30747	6.5%	95	8.1%	490	14.5%	445	10.7%	
80+	16781	3.6%	35	3.0%	347	10.3%	456	10.9%	p <0.001 [§]
Gender									
Female	232768	49.2%	574	48.6%	1763	52.2%	2083	50.0%	
Male	239904	50.8%	606	51.4%	1612	47.8%	2083	50.0%	p =0.053 [#]
Region									
Mersey-Lyell	106309	22.5%	274	23.2%	753	22.3%	965	23.2%	
Northern	134701	28.5%	322	27.3%	871	25.8%	1024	24.6%	
Southern	231662	49.0%	584	49.5%	1751	51.9%	2177	52.3%	p=0.414 [#]
SES‡									
1 – low	104859	22.2%	257	21.8%	701	20.8%	1054	25.3%	
2 – low/moderate	92058	19.4%	233	19.7%	701	20.8%	884	21.2%	
3 - medium	91397	19.3%	234	19.8%	605	17.9%	714	17.2%	
4 - moderate/high	90750	19.2%	233	19.7%	673	19.9%	764	18.3%	
5 - high	93608	19.8%	216	18.3%	678	19.9%	715	17.2%	
Missing			7	0.6%	25	0.7%	35	0.8%	p<0.001 [§]

* Responders include 1180 finally enrolled on Register, †Non-responders include: 48 'deceased' and 247 'not at address', ‡SES = Socioeconomic index for area (SEIFA) quintile

§χ² test for trend, #χ² test for differences between proportions

General practice and anticonvulsant prescription data for case ascertainment are often linked in studies of epilepsy prevalence (Keranen et al. 1989, Oun et al. 2003). This is not surprising considering that general practitioners are often the first point of contact, as well as the ‘gatekeepers’ for further access of health services, including prescriptions, and specialist referral (MacDonald et al. 2000, Wright et al. 2000). ‘The General Practice Research Database’ (GPRD) in the United Kingdom, originally established to prospectively track prescribing practice and adverse events, is probably the database most analogous to my population cohort (Wallace et al. 1998a). This database has provided important patient population morbidity studies in epilepsy as it provides a source of continuous data on the diagnosis and treatment of illness in general practice as all individuals registered can be traced efficiently (Goodridge and Shorvon 1983). Hence, my choice in recruitment using the Australian National Prescription Database was primarily because it was likely to reflect community-treated disease, but unlike the GPRD which hold anonymous records, allowed us to re-identify cases for longitudinal cohort studies by directly communicating with individuals and their families.

The HIC prescription database only includes persons subsidized through the PBS and RPBS scheme above a ‘reportable’ retail price. In February 2002, all the anticonvulsant medications had a retail price more than the ‘safety net’ or ‘concessional’ patient price threshold and only the infrequently prescribed barbiturate anticonvulsants and preparations for patients with swallowing difficulties and young children (typically less than eight years of age) retailed below the ‘general’ patient price threshold. With less ‘general’ patients in Tasmania than other Australian states (Trewin 2001), and low dose

tablet preparations usually used in dose titration (rather than dose end-point), I expect the HIC sample frame is a comprehensive anticonvulsant treatment database for all 'concession' card holders and, with maybe the exception of very young children on single liquid preparations, the majority of remaining 'general' patients.

I chose the sample period to coincide with the implementation of 'Improved Monitoring of Entitlements' legislative changes, on July 1st 2001 that would enable my recruitment strategy through the HIC. Medication, demographic and doctor provider type information was complete on 94% (7071/7541) of the HIC prescription database during the time of my recruitment study, which compares favourably with the 90% accuracy of the GPRD (Wallace H et al. 1998a). As is commonly the case in mail surveys, I found older, and people from higher socio-economic areas to be over-represented among responders to my mail invitations (Groves et al. 2001).

Although more representative than specialist sources, epilepsy diagnosis statistics generated from general practice are less likely to be accurate without prior referral for specialist assessment, with general practitioners reporting diagnostic uncertainty especially in neurological disease (MacDonald et al. 2000). Hence, health systems with high referral practice and early access to specialist services are likely to have less diagnostic false positives and false negatives in epidemiological research, when sampling is from general practice sources. Studies have consistently suggested high access to tertiary health services in the United Kingdom (Cockerell et al. 1995, Goodridge and Shorvon 1983), with 76.2% of persons seen at some time by a neurologist or

paediatrician, 15.6% seen by another hospital specialist and in only 8.2% was hospital referral not undertaken (Goodridge and Shorvon 1983). However, half of these referred patients attend mainly for a short early diagnostic period and are subsequently managed by their general practitioner. Therefore, although only 20.5% of my register cohort is currently partly or exclusively managed by a medical specialist, it is conceivable that the pattern of high tertiary access at initial diagnosis found in other developed countries (Giuliani et al. 1992, Rutgers 1986) may also be present in Tasmania.

I acknowledge that anticonvulsant treatment may not be universal for patients who have a diagnosis of epilepsy, particularly in developing countries where fewer patients are on regular treatment (Coleman et al. 2002, Wang et al. 2003). However, in a number of communities, anticonvulsant medications have been demonstrated to have widespread use and penetration in treating epilepsy (Bharucha et al. 1988, Olafsson and Hauser 1999). Every person identified as having epilepsy in a door-to-door community survey in Australia had been prescribed anticonvulsant medications at some time in their lifetime, with virtually all of the one-third “off medication on survey day” seizure free in the preceding year (Beran et al. 1982). Although this level of treatment uptake for clinically active disease is unlikely to be universal (Zeilinski 1974a), particularly in some ethnic groups (Haerer et al. 1986), high lifetime access to anticonvulsant treatment for epilepsy, has also been demonstrated in a number of other communities (da Mota Gomes et al. 2002, Forsgren 1992, Rocca et al. 2001), suggesting that these circumstances are not unique and that my recruitment methods may have more general applicability.

Although lack of treatment with anticonvulsant medications does not necessarily imply inactive disease (Oun et al. 2003, White and Buckley 1981), patient identification by antiepileptic drug prescriptions, can also include the mild and sometimes inactive cases often not generated in tertiary-based recruitment (Giuliani et al. 1992). The HIC sample method only targets doctor-diagnosed ‘screened’ cases. With epilepsy prevalence expected to be less than 1% (Sander and Shorvon 1996), it ensured that I would generate a sufficient number of cases (necessary for future studies) to accurately estimate the demographic distribution of epilepsy and prevalence of seizure types and important epilepsy subtypes (e.g. idiopathic generalized epilepsy) rather than only the more heterogeneous diagnostic category ‘epilepsy’.

When a single medical source is used, anticonvulsant prescriptions or general practitioners records may be the most efficacious ascertainment source, compared to other medical sources (hospital, specialist, EEG). A study in Italy identified most cases (82%) equally from either anticonvulsant medications or family doctors (Maremmanni et al. 1991). Anticonvulsant prescription recruitment is also an efficient method for yielding cases compared to door-to-door surveys. For example, in Zambia a survey conducted to generate cases for a similarly intended population-based disease registry required 55,000 individuals to be screened to yield around 800 cases (Birbeck and Kalichi 2004), while another house-to-house survey in Ecuador employed more than 275 people to screen a population of 75,000 over three years and recruit about 1200 lifetime cases (Placencia et al. 1992b). In contrast, my study employed a 0.4 full-time equivalent (FTE) research assistant supervised by a 0.5 FTE Research Fellow for one year to screen

a population of about 8,000 anticonvulsant prescription users over six months, yielding about 1200 'active' cases, from a source population of around half a million Tasmanians.

Given increasing time constraints on general practitioners, I did not want recruitment to be directly reliant on their case records or referral. In a study using repeat prescription data to ascertain cases over six months in nine general practices in Belfast, one in four cases had not attended their general practitioner or hospital outpatient department despite repeat prescriptions for anticonvulsants. Despite non-attendance for doctor consultation (but not for prescription uptake) half these patients had one or more seizures in the preceding twelve months, suggesting that important active disease would have been unavailable for observation if recruitment had been reliant on direct doctor contact (McCluggage et al. 1986). General practice has a service rather than research priority, it is not surprising then that it has been demonstrated to be less than an ideal direct source for data collection due to problems with validity and completeness (MacDonald et al. 2000). Therefore, anticonvulsant prescription recruitment, although secondary to medical practitioner diagnosis and treatment, has the advantage that it does not rely on medical contact for denominator enumeration, invitation and patient participation.

Anticonvulsant medications are not exclusively prescribed for the treatment of epilepsy i.e. they lack disease treatment specificity. They are also used to treat bipolar affective disorder, migraine, and chronic pain conditions. In Australia, doctors prescribing medications are not required to indicate what condition is being treated on a prescription. This means that my invited source population included disease groups other than my

target population of treated epilepsy. Anticonvulsant treatment for conditions other than epilepsy in my study (44.4%) was one and a half to four times higher than that estimated in other prevalence studies involving prescription recruitment (Beghi et al. 1991, de la Court et al. 1996, Lambie et al. 1981). Given these widely variable reported disease treatment proportions, rather than employing an empirical correction factor, as suggested (de la Court et al. 1996), I excluded ineligible diseases by patient self-report whether anticonvulsants were prescribed for “blank spells, seizures or epilepsy’. Coupled with my two mail-out invitation design, this allowed me to adjust for the effect of any disease-related non-response bias in subsequent prevalence study estimates (see Chapter Seven) using imputation methods. Imputation assumes a linear trend in prevalence with each subsequent contact, allowing the disease prevalence in non-responders to be extrapolated by linear regression (Drane 1991, Drane et al. 1993).

Although a number of studies have utilized anticonvulsant prescriptions to conduct epidemiological studies on epilepsy (Giuliani et al. 1992, Lambie et al. 1981, Lammers et al. 1996), there is limited comparable information related to case prescription sources. Considering only the first prescription identified in a four month period for patients receiving anticonvulsant drugs in New Zealand, 22.5% (333/1479) of patients received their prescriptions from a specialist rather than general practitioner sources, although specialist prescribing rates were almost twice as high for children (Lambie et al. 1981). A Dutch survey of patients with epilepsy regarding treatment and supervision, found that almost half (48%) received their anticonvulsant drugs exclusively from a neurologist with a further 16% receiving them in combination with their GP (Rutgers 1986). However,

both these studies suggest that the medical practitioner writing anticonvulsant drug prescriptions is most likely to also be responsible for disease supervision and follow-up. With 70.9% of my register cases receiving their anticonvulsant prescriptions exclusively from their general practitioner, and 19.1% receiving them in part from a medical specialist, in the preceding twelve months it would suggest that my cohort represents community-treated disease. Therefore, my subsequent prevalence estimates for seizure types, specific syndromes and co-morbid conditions associated with epilepsy should provide valid community-based prevalence estimates.

Chapter Seven: The prevalence and distribution of treated epilepsy - A community-based study in Tasmania, Australia

7.1 Introduction

I demonstrated in the previous chapter, that in Australia, the national prescription database is representative of community-treated epilepsy, and can provide an effective and efficient method for large-scale patient recruitment for epidemiological research. In this chapter, utilizing this database along with a three-mail-contact design, I now estimate the prevalence of treated epilepsy in Tasmania, and its distribution by age-group, gender, region and socio-economic status.

Studying the distribution and determinants of disease in population-based surveys, rather than on atypical clinically-based samples, provides useful information on the population burden of disease, and the common etiological factors (Rose 1995). Previous population studies in Australia, New Zealand and Oceania have estimated the lifetime prevalence of epilepsy to be in the range of 3.4-7.5 per 1000 (Beran et al. 1982, Lambie et al. 1981, Stanhope et al. 1972) with active treated epilepsy to be about 4-5 per 1000 (Beran et al. 1982, Lambie et al. 1981). Case ascertainment, diagnosis and classification methods vary between these studies, hindering any meaningful direct comparisons (Sander and Shorvon 1987). Furthermore, with the exception of the New Zealand study (Lambie et al. 1981), these studies have all had insufficient power to include analyses by age, gender, region or socioeconomic status.

Even outside of this region there is limited knowledge on regional (CDC 1994, Placencia et al. 1992c) or socio-economic (Cornaggia et al. 1990, Pond et al. 1960) differences in epilepsy prevalence. Such comparative studies are important as they provide information on the burden of the condition, both at the population level and in specific sub-populations, and may also indicate etiological factors acting at the population-level.

7.2 Methods

The design and methods of patient recruitment have been described previously in detail (see Chapter Six) and will only be outlined briefly here.

Mail invitations

As outlined in Chapter Six, mail invitations were sent on 20th November 2002 and 19th February 2003, unless I had received a ‘return to sender’ notification or information that they had deceased. In addition, a third anonymous HIC mail contact was sent to antiepileptic drug (AED) prescribers of non-responders who did not respond to the second mail-out, on the 20th Feb 2004. This letter requested the treating doctor to provide the medical indication for AED treatment (epilepsy or other) and to advocate study participation.

Period prevalence of treated epilepsy

Prevalent cases of epilepsy were identified from all individuals supplied at least one prescription for an AED in Tasmania above the ‘reportable’ retail price threshold during the twelve month period from July 1st 2001 to June 30th 2002 (Table 6.1). Patients must

be alive and have a postcode listed in Tasmania at sometime during this time frame and indicate (either by self-reported mail invitation or from their treating doctor) that AEDs were prescribed for epilepsy. For the purposes of disease response, mail respondents were classified as having epilepsy when they affirmed to “*have blank spells seizures or epilepsy*” (mailout one and mailout two) or when the treating doctor affirmed a mail non-responder “*had been prescribed anticonvulsant medications for epilepsy*” (Mailout three). Mail respondents were classified as not having epilepsy when they affirmed to “*don't have blank spells, seizures of epilepsy*”. Those mail respondents who answered “*don't know*” [] or “*didn't specify*” [] were omitted from the analysis.

A validation study of this question's ability to confirm a diagnosis of epilepsy in a random sample of 293 of my self-reported mail respondents was undertaken using my modified diagnostic questionnaire from Chapter Five administered by a final year trainee neurologist with the responses interpreted by myself using my standardised diagnostic guidelines (see Appendix 22). In addition, when questionnaire diagnosis was ‘uncertain’ I interviewed the patient/witness further by telephone. For the privacy reasons outlined in Chapter Six, I was unable to assess the disease status of question negative respondents.

For these 293 respondents: none reported they were taking AEDs for indications other than epilepsy; epilepsy status remained uncertain even after further interview in only 4 (1.4%); a false positive diagnosis of epilepsy was reached in 23 (7.8%) (1 single seizure, 3 migraine, 9 psychogenic, 10 syncope); and a true positive diagnosis was confirmed in the remaining 266 (90.8%). Including the ‘uncertain’ category as false positives gave a

PPV of 0.91, whereas when these 4 cases were excluded the PPV was 0.92. Although, it would have been useful, for reasons of validity, to administer the diagnostic questionnaire to respondents who answered ‘no’, ‘don’t know’ or ‘didn’t specify’ to this disease confirmation questionnaire, this was not possible as this group of patients did not disclose their contact details to allow this. Therefore, the false negative and true negative rate of self-identification by this question was unable to be estimated.

In order to correct observed prevalence estimates for non-response bias, the method proposed by Drane was used (Drane et al. 1993) to determine imputed prevalence. This has demonstrated that, when an exponential decay in prevalence with each subsequent contact is observed, the true prevalence can be estimated by fitting a regression model to the observed prevalence at each mail contact and summing over all extrapolated mail contacts (see Figure 7.1). Confidence intervals for each imputed Tasmanian demographic prevalence estimate (age-group, gender, region and socio-economic status) were obtained by converting the corresponding confidence interval endpoints of each imputed sample estimate into prevalence estimates over Tasmania.

Disease prevalence was imputed for respondents who ‘didn’t know’ (don’t know if have blank spells, seizures or epilepsy) or ‘didn’t specify’ (didn’t specify if have blank spells, seizures or epilepsy) and also for non-respondents. To study the effect of misclassifying ‘don’t know’ and ‘didn’t specify’ as not having epilepsy rather than as disease non-respondents, I performed two sensitivity analyses. In the first sensitivity analysis, the “don’t know” category was included and classified as not having epilepsy. In the second

sensitivity analysis, both “don’t know” and “didn’t specify” were included and classified as not having epilepsy. Mail non-respondents were omitted from all analyses.

Association between demographic characteristics and prevalence of treated epilepsy

An approximately exponential decay in response rate with each mailing within each demographic subgroup was observed allowing an estimate of the distribution of treated epilepsy by five-year age group, gender, region (south, north, northwest) and socioeconomic status (SEIFA). I calculated univariate prevalence ratios (PR) to compare differences within variable categories by fitting a log binomial model to test for trend in prevalence for age and SIEFA, and to assess whether prevalence is associated with region and gender, after adjusting for the increased confidence intervals obtained using Drane’s imputation method. A univariate analysis was conducted as my final estimates for total prevalence, and its distribution by age, gender, region and SES yielded imputed rather than actual cases which do not enable a multivariate approach. All analyses were performed using Stata Version 9.

Antiepileptic drug polytherapy

For patients responding to my survey and indicating treatment for epilepsy, the percentage and estimated prevalence of patients prescribed concurrent AED was represented.

7.3 Results

A total of 4072 persons responded to the three mail contacts, giving an overall disease response rate of 54.0%. If the ineligible (n=311) are excluded the response rate is 56.3%

(4072/7230). Table 7.1 shows the breakdown of the responses to the three HIC mail invitations. Among responders there was evidence of a diminishing epilepsy prevalence with response time (mailout one: 990/7541=13.13%; mailout two: 517/7541=6.86% mailout three 267/7541=3.54%) with the 1774 (23.5%) indicating treatment for epilepsy, representing 86.0% of total imputed cases (n=2063) in Tasmania.

Table 7.2 shows the results of several prevalence sensitivity analyses. The prevalence of epilepsy was estimated to be 4.36 per 1000 persons in the Tasmanian population with 95% confidence interval (CI) 4.34 to 4.39. These estimates are independent of the definition of non-responders. However, the crude epilepsy prevalence is reduced by 3% to 7.61 per 1000 (CI 7.35, 7.86) or 11% to 6.95 per 1000 (CI 6.71, 7.20), according to the sensitivity analysis. Table 7.2 shows that the prevalence of epilepsy would be overestimated by 80% at 7.83 per 1000 without my correction for non-response bias.

I examined the association between age and prevalence of epilepsy using fractional polynomials and found that the data was best fitted to a log binomial model by transforming age to $1/\sqrt{\text{age}}$. Figure 7.2 displays the non-linear relationship between prevalence of epilepsy and increasing age.

Figure 7.1: Prevalence of epilepsy by imputation methods

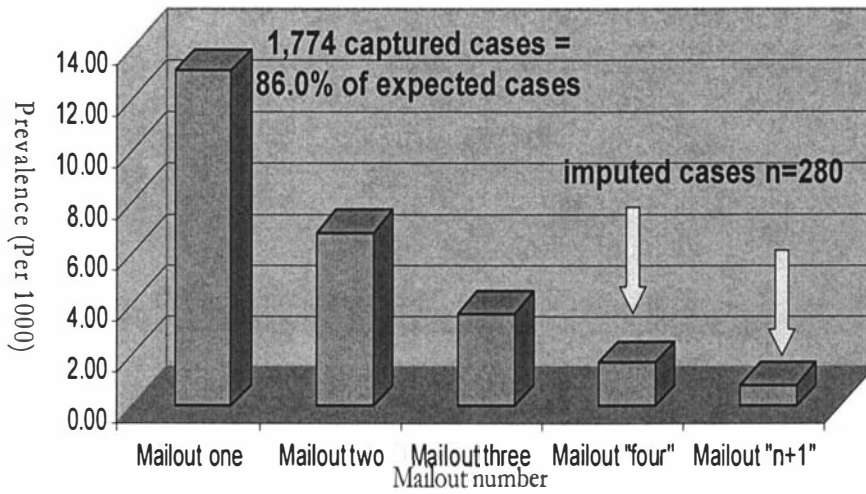
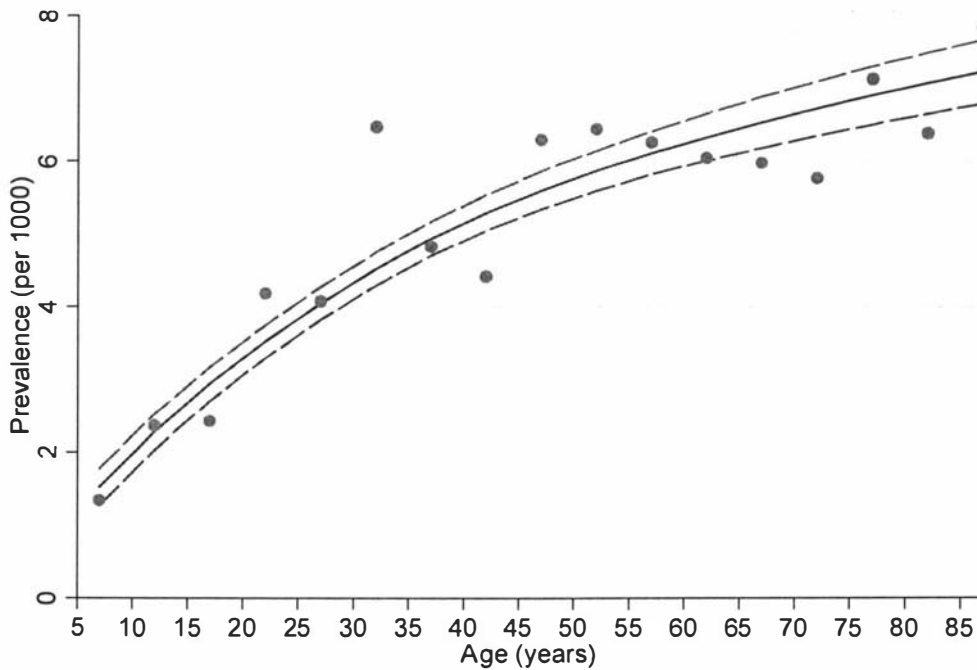


Figure 7.2: The prevalence* of treated epilepsy in Tasmania by five-year-age-groups



* Imputed prevalence reported. Age-sex standardisation to the World Standard or Australian Standard Population did not alter my results appreciably and so the Tasmanian figures are represented. For the purposes of disease response, mail respondents were classified as having epilepsy when they affirmed to "have blank spells seizures or epilepsy" and classified as not having epilepsy when they affirmed to "don't have blank spells, seizures or epilepsy". Disease prevalence was imputed from total disease non-respondents which comprise mail respondents who 'didn't know', 'didn't specify' and all mail non-respondents

Table 7.3 shows the estimated prevalence of treated epilepsy in Tasmania by twenty year age-group, gender, region and SEIFA. The unadjusted figures are shown, as age-sex standardisation to the World Standard Population or Australian Standard Population did not alter my results appreciably. Adjusted treated epilepsy prevalence was 8% lower (95% CI 6% to 38%) in women than men, similar in the three geographic regions and not associated with SEIFA ($p=0.50$). Finally, Table 7.4 shows the observed percentage and estimated prevalence (by imputation) of patients prescribed concurrent AED amongst those responding to my mail invitation indicating treatment for “blank spells, seizures or epilepsy”. More than two concurrent AED for epilepsy were taken by 142 (8.0%) of patients with an estimated prevalence of 0.34 per 1000 (CI 0.26 to 0.42) on this level of polytherapy in Tasmania.

7.4 Discussion

There have only been a few studies measuring the overall prevalence of epilepsy in Australia, New Zealand or the Oceania Region (Beran et al. 1982, Lambie et al. 1981, Stanhope et al. 1972). None of these studies have described prevalence patterns by gender, age-group, regional or socioeconomic status, and there are relatively few studies that have done so elsewhere in the world. Although, my epilepsy prevalence estimates may be influenced by factors that affect a person acquiring a diagnostic label for treatment purposes, AED prescription data provides a useful prevalence measure in communities characterized by high access to health services (Beran et al. 1982). Therefore, the representativeness of my sample of community-treated epilepsy and

greater confidence in the precision of my estimates with imputation correction, suggests that my findings have important clinical and public health implications.

Lack of community-based sampling has been a major criticism of most case ascertainment methods in previous epidemiological research into epilepsy (Sander and Shorvon 1996). Previous studies have suggested that the medical practitioner writing AED prescriptions is also most likely to be responsible for disease supervision and follow-up (Lambie et al. 1981, Rutgers 1986). If this is true, with 70.9% of epilepsy patients receiving their AED prescriptions exclusively from their general practitioner and 19.1% receiving them in part from a medical specialist in the preceding twelve months, this suggests that my cohort represents community-treated disease (D'Souza et al. 2007d).

Table 7.1: Response to the Health Insurance Commission mail invitations

	Mailout one		Mailout two		Mailout three		TOTAL	
	(n=7541)	%	(n=5448)	%	(n=3871)	%	n	%
Responders	1957	26.00%	1418	26.00%	697	18.01%	4072	54.00%
Have blank spells, seizures or epilepsy	990	13.10%	517	9.50%	267	6.90%	1774	23.52%
Don't have blank spells, seizures, epilepsy	796	10.60%	704	12.90%	338	8.73%	1838	24.37%
Don't know if have blank spells, seizures or epilepsy	49	0.60%	41	0.80%	19	0.49%	109	1.45%
Didn't specify if have blank spells, seizures or epilepsy	122	1.60%	156	2.90%	73	1.89%	351	4.65%
Ineligible	136	1.80%	159	2.90%	16	0.41%	311	4.12%
Deceased	21	0.30%	27	0.50%	10	0.26%	58	0.77%
Not at address	115	1.50%	132	2.40%	5	0.13%	252	3.34%
Non responders	5448	72.20%	3871	71.10%	3159	81.61%	3159	41.89%

Table 7.2: The effects on crude and imputed prevalence estimates of various methods of classifying mail respondents who answered “don’t know” or “didn’t specify” their epilepsy status

	Imputed prevalence per 1000			Crude prevalence per 1000		
	estimated cases	estimated prevalence	95% confidence interval	estimated cases	Estimated Prevalence	95% confidence interval
Result*	2063	4.36	(4.34 - 4.39)	3703	7.83	(7.58 - 8.10)
Sensitivity analysis one†	2063	4.36	(4.34 - 4.39)	3595	7.61	(7.35 - 7.86)
Sensitivity analysis two‡	2063	4.36	(4.34 - 4.39)	3286	6.95	(6.71 - 7.20)

* For the purposes of disease response, mail respondents were classified as having epilepsy when they affirmed to “have blank spells seizures or epilepsy” (mailout one and mailout two) or when the treating doctor affirmed a mail non-responder “had been prescribed anticonvulsant medications for epilepsy” (Mailout three). Mail respondents were classified as not having epilepsy when they affirmed to “don't have blank spells, seizures of epilepsy”. Those mail respondents who answered “don't know” [] or “didn't specify” [] were omitted from the analysis. Disease prevalence was imputed for respondents who 'didn't know' (don't know if have blank spells, seizures or epilepsy) or 'didn't specify' (didn't specify if have blank spells, seizures or epilepsy) and also for non-respondents. To study the effect of misclassifying 'don't know' and 'didn't specify' as not having epilepsy rather than as disease non-respondents, I performed two sensitivity analyses. In the first sensitivity analysis, the “don't know” category was included and classified as not having epilepsy. In the second sensitivity analysis, both “don't know” and “didn't specify” were included and classified as not having epilepsy. Mail non-respondents were omitted from all analyses.

Table 7.3: Estimated prevalence* of treated epilepsy in Tasmania by age-group, gender, region and SEIFA†

	Tasmanian Population†	Estimated Cases*	Estimated Prevalence §	Prevalence Ratio		p value
				Estimate	(95% CI)	
Age group (years)						
1-19	131813	215	1.63	1.00		
20-39	120883	586	4.85	2.97	(2.54, 3.47)	
40-59	131215	757	5.77	3.54	(3.04, 4.11)	
60+	88761	623	7.02	4.30	(3.69, 5.02)	p< 0.001#
Gender						
Male	232768	1059	4.55	1.00		
Female	239904	1003	4.18	0.92	(0.84, 1.00)	p=0.05
Region						
North-western	106309	478	4.50	1.00		
Northern	134701	550	4.08	0.91	(0.80, 1.03)	p=0.141
Southern	231662	1035	4.47	0.99	(0.89, 1.11)	p=0.908
SEIFA						
1 – low	104859	452	4.31	1.00		
2 – low/moderate	92058	446	4.84	1.12	(0.99, 1.28)	
3 – moderate	91397	354	3.87	0.90	(0.78, 1.03)	
4 - moderate/high	90750	429	4.73	1.10	(0.96, 1.25)	
5 – high	93608	378	4.04	0.94	(0.82, 1.07)	p=0.99#

* Imputed prevalence reported. Age-sex standardisation to the World Standard or Australian Standard Population did not alter my results appreciably and so the Tasmanian figures are represented. For the purposes of disease response, mail respondents were classified as having epilepsy when they affirmed to "have blank spells seizures or epilepsy" and classified as not having epilepsy when they affirmed to "don't have blank spells, seizures or epilepsy". Disease prevalence was imputed from total disease non-respondents which comprise mail respondents who 'didn't know', 'didn't specify' and all mail non-respondents. † As an indicator of socio-economic status, each patient's postcode of residence was scored into one of five ordered categories according to the Socioeconomic Index of Relative Advantage/Disadvantage (SEIFA) constructed by the Australian Bureau of Statistics (Trewin 2001). ‡ 472, 672 ((ABS) 2003). § Per 1000. # Test for linear trend using a log binomial model.

Table 7.4: Observed percentage and estimated prevalence of epilepsy treated with concurrent antiepileptic drug medications in Tasmania between July 1st 2001 and June 30th 2002

Number of concurrent AEDs	Observed Cases	Observed Percentage	Estimated Cases*	Estimated Prevalence†§	(95% CI)
One AED	1 139	64.2%	1368	2.90	(2.80 – 2.99)
Two AEDs	432	24.4%	519	1.10	(1.04 - 1.16)
More than two AEDs	142	8.0%	161	0.34	(0.26 - 0.42)
Missing data	61	3.4%	68	0.14	(0.09 - 0.20)
TOTAL	1774	100.0%	2116	4.48	(4.20 – 4.76)

* Imputed prevalence reported; † 472, 672 ((ABS) 2003); § Per 1000

AED = antiepileptic drugs

However, to be an ideal recruitment approach for prevalence estimation, AED prescription penetration for epilepsy treatment should have universality and validity (Kelsey et al. 1986). I acknowledge that disease non-disclosure and concealment may lower prevalence estimates. However, these problems are difficult to overcome irrespective of the recruitment method used, including household surveys (Beran et al. 1985b, Zeilinski 1974a). I am also aware that AED initiation and withdrawal practices among local physicians and patients may affect prevalence estimates from prescription data (Lloyd Jones 1980, Oun et al. 2003). In Australia the typical practice is to commence AED treatment after the second unprovoked seizure, and this is reflected in the low number of patients (0.34%) found to have been treated after a single seizure in my validation study, a similar figure to that found in a Swedish study (Forsgren 1992). Therefore, patient recruitment by AED prescription appears to have yielded few false positive cases due to ‘early’ treatment.

However, the lowest reported utilization rates of AED treatment usually arise from developing countries where attempts to obtain treatments are difficult because of lack of finances and/or drug supplies, resulting in few patients on regular treatment (Coleman et al. 2002). Nevertheless, in a number of communities, AEDs have been demonstrated to have widespread use and penetration in treating epilepsy, making them potentially a good target for identifying cases for clinical epidemiological research (Bharucha et al. 1988, Olafsson and Hauser 1999). Every person identified as having epilepsy in a door-to-door community survey in Australia had been prescribed AEDs at some time in their lifetime, with virtually all of the one-third of patients “off medication on survey day” being seizure

free in the preceding year (Beran et al. 1982). Although this level of treatment uptake for clinically active disease is unlikely to be universal (Zeilinski 1974a), particularly in some ethnic groups (Haerer et al. 1986), high lifetime access to AED treatment for epilepsy, has also been demonstrated in a number of other communities (Cockerell et al. 1995, Rocca et al. 2001), suggesting that case ascertainment sensitivity from AED prescription is not unique to Australia and that my recruitment methods may have more general applicability.

I also acknowledge that the estimation of prevalence rates from studies using AEDs prescriptions may overestimate the number of epilepsy cases, because epilepsy medications are sometimes prescribed for misdiagnosed epilepsy (Forsgren 1992, Keranen 1987) or for other diseases such as a migraine, depression, mood stabilization and chronic pain conditions (Lammers et al. 1996). Therefore, I used response to the question '*are you taking antiepileptic medications for blank spells, seizures or epilepsy?*' to confirm epilepsy status among mail respondents that had 'screened positive' to a doctor-diagnosed medical condition treated with an AED. Although this may not be a sensitive screening tool for epilepsy in household surveys, my aim was high PPV (0.92) for capturing patients with epilepsy. With similar false positive cases in my validation study among mail respondents to an Italian study (7.8% vs. 7%) (Maremmanni et al. 1991), I expect my AED estimate to be a useful measure of clinically active epilepsy prevalence (Wallace et al. 1998a).

Although the overall disease response rate of 54.0% (4072/7541) could be considered low, the heterogeneous nature of my target population meant that the 1774 indicating treatment for epilepsy, represents 86.0% of total imputed cases (n=2063) in Tasmania. Given the high PPV from my validation study (Chapter Five), negligible differential misclassification bias between self-reported and doctor-reported epilepsy status was assumed (Sackett 1979), allowing us to combine classification sources in a three contact exponential decay prevalence imputation approach (Drane et al. 1993). This approach enables disease status inference in remaining mail non-respondents improving the precision and confidence of my estimates. Without this correction for non-response bias, the prevalence of epilepsy would have been overestimated by 80%.

Useful insights into epilepsy treatment in Tasmania are obtained through the HIC AED prescription data. At 8.0%, the percentage of patients receiving more than two concurrent AEDs for epilepsy responding to my mail survey, is at the high end of polytherapy seen in most other developed countries (Forsgren 1992, Giuliani et al. 1992). Although not always possible to avoid, AED polytherapy is currently only recommended for inadequately controlled epilepsy when patients fail serial monotherapy and dual therapy (French 1994). Previous studies have suggested that significantly more patients prescribed AEDs, or when diagnosed and managed by doctors other than neurologists or paediatricians, are on multiple AEDs compared with those treated by private specialists or hospital doctors (Giuliani et al. 1992, Lambie et al. 1981). Therefore, the relatively high percentage of patients on multiple AED may either reflect increased prevalence of

severe epilepsy (Olafsson and Hauser 1999) or inadequate epilepsy management in Tasmania.

My estimated treated epilepsy prevalence of 4.36 per 1000 is consistent with a number of previous studies that have derived prevalence from AED prescription (Giuliani et al. 1992, Wallace H et al. 1998a), primary care (Cockerell et al. 1995), or household survey sources (Beran et al. 1982). Prevalence was 8% lower in women than men. While a few studies have found higher epilepsy prevalence in females than males (Nicoletti et al. 1999), and some have found no gender differences (Bondestam et al. 1990, CDC 1994), the majority are consistent with my findings, with greater prevalence in males compared to females (Hauser et al. 1991), at all age groups (Haerer et al. 1986). The explanations for these gender differences still remain largely unknown.

At present, our knowledge of socioeconomic differences in epilepsy prevalence is limited and conflicting (Cornaggia et al. 1990, Pond et al. 1960). The SEIFA index utilized in this study is comprised of variables relating to income, education, occupation, wealth and living conditions with the highest weighting being given to the first three variables (Trewin 2001). As SEIFA reflects the socio-economic wellbeing of an area, rather than of an individual, it is possible for a relatively advantaged person to be resident in an area which may have a low index score. SEIFA also has a varying impact on health service uptake, and potentially AED prescription treatment, with SEIFA 1 having higher general practice uptake in metropolitan and lower in rural Australian settings (Turrell et al. 2003). Therefore, one explanation for my finding of no association in treated epilepsy

prevalence and SEIFA is that it is real and does not reflect access to general practice services. Alternatively, it may be due to misclassification of individual socioeconomic status or confounding by area of residence.

In this study no differences in treated epilepsy prevalence were found between the three main geographic regions of Tasmania. Higher urban prevalence has been noted in two previous studies (Gudmundsson 1966, Olafsson and Hauser 1999), but more commonly, studies have found higher prevalence in rural compared to urban settings (Bondestam et al. 1990, Placencia et al. 1992c, Rwiza et al. 1992). Although, it has been speculated that these contrary findings may be due to greater access to health services in the urban setting at the treatment (Olafsson and Hauser 1999) or primary prevention level (Rwiza et al. 1992), no clear etiological reasons for these differences have been identified.

Epilepsy is often considered a disease of younger age, and the highest prevalence rates occur in children in a number of developing countries (Bondestam et al. 1990). In earlier studies, this higher childhood pattern was also seen in developed countries (Kurland 1959). However, recent studies have reported a reversed pattern with prevalence rates being lowest in children less than 14 years (Hauser et al. 1991, Wallace et al. 1998a) and highest in elderly people over 65 years of age (Cockerell et al. 1995, Wallace et al. 1998a) in developed countries. Consistent with these latter studies, I also found the lowest prevalence rates in children and highest in the elderly. Although, lower sampling of liquid AED preparations in children less than eight years, probably partly explains the lower prevalence rates seen in this age they persist beyond the age that these issues would

continue to have an impact. My findings suggest that incidence may be lower in the younger age group, or that the illness treatment duration maybe is more short-lived, compared to adults and the elderly (Olafsson et al. 2005). If correct, with demographers predicting a dramatically greater elderly population in the future, these findings have important implications for health service planning in developed countries.

Chapter Eight: The prevalence and distribution of the Idiopathic Generalized Epilepsies and their seizures in Tasmania, Australia.

8.1 Introduction

In this chapter, I estimate the prevalence and distribution of the Idiopathic Generalised Epilepsies and their seizures in Tasmania. This is performed by administering the modified diagnostic epilepsy questionnaire validated in Chapter Five to the community-based epilepsy cohort recruited in Chapter Six, and using my estimate of the prevalence and distribution of epilepsy imputed in Chapter Seven.

As discussed in Chapter Three, although we have reasonable estimates of the overall prevalence of epilepsy for most countries, we still lack knowledge of the prevalence and distribution of ‘more specific forms of epilepsy’, outside a hospital setting (Bauer 1994, Eadie 1996, Osservatorio Regionale per l'Epilessia (OREp) 1996). In fact, only a single study has been performed in an unselected age group general practice setting to classify patient’s epilepsy syndromes (Manford et al. 1997). However, even this study classified participants indirectly from medical records, which not surprisingly lead to diagnostic imprecision (Bodensteiner et al. 1988), particularly for the specific epilepsy syndromes and categories described by the ILAE (Kellinghaus et al. 2004, Manford et al. 1997, Oka et al. 2006, Olafsson and Hauser 1999, Osservatorio Regionale per l'Epilessia (OREp) 1996).

Hence by using a recruitment design and diagnostic methods focusing on epilepsy syndrome classification, this chapter provides the first population-based prevalence estimates of IGE directly from patient's self-report of their symptoms and the observation of these events from a witness. Furthermore, by conducting this research in the more homogenous genetic milieu of Tasmania and focusing on the most important group of genetically determined epilepsies, both the clinical importance and potential public health impact should be made more relevant.

8.2 Methods

The design and methods of patient recruitment have been described previously in detail in Chapter Six.

Diagnostic epilepsy interviews

I used the modified diagnostic epilepsy questionnaire validated in Chapter Five to classify patient's seizure types, seizure onset-types and idiopathic generalized epilepsy using standardised written guidelines (see Appendix 23). When possible, both the patient and a witness were questioned by the interviewer. A witness interview without a patient interview was performed for patients less than 13 years of age, or when an intellectual or language disability did not allow direct telephone interviewing. Questionnaires were administered by telephone interviewing by a team of non-medical interviewers using computer-assisted-telephone-interviewing (CATI).

Classification of seizures, epilepsy and the Idiopathic Generalised Epilepsies

Seizures and syndromes of patients and affected relatives (when required as outlined below) were classified according to the International League Against Epilepsy Classification (Engel 2001, ILAE 1981, ILAE 1989). When clinical information was inconclusive, a patient's epilepsy type was classified as 'uncertain epilepsy', 'uncertain partial or generalized epilepsy', or Idiopathic Generalised Epilepsy not otherwise specified, depending at which level diagnostic uncertainty occurred.

For many participants, clinical information was sufficiently detailed and clear to allow unambiguous classification of seizure and syndrome type into one of the Idiopathic Generalised Epilepsy Syndromes: Myoclonic Epilepsy of Infancy (MEI), Epilepsy with Myoclonic Astatic Seizures (MAE); Epilepsy with Myoclonic Absences (EMA); Childhood Absence Epilepsy (CAE), Juvenile Absence Epilepsy (JAE), Juvenile Myoclonic Epilepsy (JME) and Idiopathic Generalised Epilepsy not otherwise specified (IGEU) (Engel 2001). Generalised Epilepsy with Febrile Seizures Plus (GEFS+) (Engel 2001, Wallace et al. 1998b), and Jeavons's Syndrome (JS) (Panayiotopoulos 2005), were classified as IGEU.

Some IGE sub-syndromes are ambiguous. These 'ambiguous' cases were dealt with as follows: CAE typically presents between ages 4 and 8 years with multiple daily absences, whereas JAE presents in adolescence with infrequent absences. CAE was diagnosed when age at onset was 8 years or less, regardless of seizure frequency. When age at onset was between 9 and 11 years, the frequency of absence seizures was used to distinguish

between CAE and JAE. Patients with absences beginning at age 12 years or older were classified as JAE regardless of seizure frequency. JAE and JME were distinguished by the more frequent defining seizure type (absence vs. myoclonus) or, when frequency was equal or uncertain, with the seizure type of earliest onset age. When one defining seizure type (myoclonus vs. absence) occurred in isolation and the other always occurred immediately before a GTCS, then the independently occurring seizure type defined the syndrome. When an affected first degree relative was identified with seizures their seizure types were also evaluated and in patients for whom frequency, and independence of seizure type was equal, the first degree relatives syndrome type was used to assist in categorising patient's IGE syndrome.

Patients with 'IGE not otherwise specified' were categorized as such when, for one or more reasons, they did not fit into existing IGE categories. This included: 1) atypical age at onset; 2) atypical seizure type constellations e.g. Jeavons's Syndrome (Panayiotopoulos 2005) and Generalised Epilepsy with Febrile Seizures Plus with exclusively generalized seizure types (Engel 2001, Wallace et al. 1998b); 3) onset after age 30 years; 4) unclear age at onset; or 5) atypical seizure types e.g. ; subjects with GTCS only. Where GTCS occurred with questionable absences or myoclonic seizures only the definite seizure types were used for syndrome classification.

Statistical analysis

Age was recorded at the time of enrolment onto the TER. To assess the representativeness of my interview cohort, demographic variations between TER

participants versus interview responders were analyzed with a χ^2 test for differences between proportions (Armitage et al 2002). A test for trend in the proportion responding across levels of the characteristic (age, SES) was also conducted by fitting a univariable log binomial model and fitting the characteristic as a linear predictor (Armitage et al 2002). Prevalence estimates for Tasmania were calculated from the product of the corresponding imputed prevalence estimate (see Chapter Seven) and the observed interview cohort percentage for that variable.

8.3 Results

Study participants

On 31st May 2003, 1180 participants were initially enrolled on the Tasmanian Epilepsy Register. Of this original cohort, 97 were ineligible (28, deceased, 69 withdrew before interview) leaving 1083 eligible for this study. Of these 1083: 124 were unable to be contacted (moved from contact address, untraced at contact address, at contact address and agreed to be interviewed but did not complete interviewing), and 959/1083 (88.6%) completed the diagnostic telephone interviewing (including 34 deceased and 2 who withdrew after interview, and 4 were taking AEDs not for epilepsy). Of the 959 TER participants completing diagnostic telephone interviews, 209 involved a witness only, 367 a participant only, and 383 involved a participant and a witness.

Non-response bias

Table 8.1 compares the demographic features by age, gender, region and SES of the TER participants (n=1180) versus the diagnostic telephone interviewing respondents (n=955)

excluding the 4 taking AEDs for indications other than epilepsy. No differences between register and interview samples were found for these variables ($p>0.05$).

Table 8.1: Demographic features by age, gender, region and SES of the Tasmanian Epilepsy Register and diagnostic telephone interviewing respondents

	Register		Interview		Register vs. Interview
	(n=1180)	%	(n= 955)	%	p value
Age*					
0-19	149	12.7%	141	14.8%	p=0.37
20-39	251	21.2%	193	20.2%	
40-59	489	41.4%	392	41.0%	
60+	291	24.7%	229	24.0%	
Gender†					
Female	574	48.6%	475	49.7%	p=0.62
Male	606	51.4%	480	50.3%	
Region†					
Mersey-Lyell	274	23.2%	227	23.8%	p=0.62
Northern	322	27.3%	233	24.4%	p=0.19
Southern	584	49.5%	480	50.3%	p=0.47
SES*					
1.Low	257	21.8%	203	21.3%	p=0.87
2. Low/moderate	233	19.7%	196	20.5%	
3. Moderate	234	19.8%	177	18.5%	
4. Moderate/high	233	19.7%	180	18.8%	
5. High	216	18.3%	183	19.2%	

* χ^2 test for trend; † χ^2 test for differences between proportions (two-sided)

Frequency of generalised seizures, epilepsy syndromes and Idiopathic Generalised Epilepsy

Table 8.2 shows the frequency of broad epilepsy syndromes diagnosed. Excluding patients without epilepsy (n=92), partial epilepsy was classified in two thirds and generalised epilepsy in slightly more than one-fifth of those interviewed.

Table 8.2: Frequency of broad epilepsy syndromes by diagnostic telephone interviewing of Tasmanian Epilepsy Register participants (n=955)

	N	%	N	%
Total			863*	100%
Uncertain epilepsy			31	3.59%
Uncertain partial or generalised epilepsy			72	8.34%
Partial epilepsy			573	66.40%
Generalised epilepsy [†]			187	21.67%
Idiopathic generalised epilepsy	175	20.28%		
Symptomatic generalised epilepsy	12	1.39%		

Excludes 92 patients 'without epilepsy' (including 4 patients not taking antiepileptic drugs for 'blank spell, seizures or epilepsy')

Table 8.3: Frequency of Idiopathic Generalised Epilepsy Syndromes and generalised seizures by diagnostic telephone interviewing of Tasmanian Epilepsy Register participants (n=955)

	N	Epilepsy %	IGE* %
		(n=863) [†]	(n=175)
Idiopathic Syndromes			
Myoclonic epilepsy of infancy	0	0.00%	0.00%
Epilepsy with myoclonic astatic seizures	3	0.35%	1.71%
Epilepsy with myoclonic absences	3	0.35%	1.71%
Childhood absence epilepsy	49	5.68%	28.00%
Juvenile absence epilepsy	43	4.98%	24.57%
Juvenile myoclonic epilepsy	48	5.56%	27.43%
Unspecified [‡]	30	3.48%	17.14%
Generalised seizure types			
Tonic-Clonic	147	17.03%	84.00%
Absence	118	13.67%	67.43%
Myoclonic	83	9.62%	47.43%
Atonic	14	1.62%	8.00%
Astatic	8	0.93%	4.57%
Tonic	0	0.00%	0.00%

**Idiopathic Generalised Epilepsy: †955 patients on Tasmanian Epilepsy Register less 92 diagnosed as 'not having epilepsy' on interview but including 31 with 'uncertain epilepsy'; ‡ Includes 3 patients with Generalised Epilepsy with Febrile Seizures Plus*

Table 8.3 shows the frequency of IGE syndromes and generalised seizure types. A number of syndromes are infrequently observed (myoclonic epilepsy of infancy, epilepsy with myoclonic atstatic seizures, and epilepsy with myoclonic absences). Tonic-clonic seizures (17.03%) and the absence epilepsies combined (11.01%) are the most common IGE seizure types and syndromes respectively.

The prevalence and distribution of IGE and their associated generalised seizures in Tasmania, Australia

Tables 8.4, 8.5.1, 8.5.2 and 8.5.3 show the estimated prevalence and distribution (by age, gender, region and SES) of IGE, absence seizures, myoclonic seizures and generalised tonic clonic seizures respectively in Tasmania Australia. Excluding those patients without epilepsy, the estimated prevalence of IGE was 0.89 per 1000. IGE prevalence was highest between the ages of 20-39 years (see Figure 8.1) and in females, but similar between Tasmanian regions and socio-economic groups. Onset of IGE after 30 years was rare (n=3, see Figure 8.2).

For generalised seizures, tonic-clonic seizures had the highest prevalence (0.74 per 1000), followed by absence seizures (0.60 per 1000) and myoclonic seizures (0.42 per 1000). Absence and tonic clonic seizures prevalence both peaked between the ages of 20-39 years and fell to be lowest in the oldest age group for absence seizures but remained relatively constant after the age of forty years for tonic-clonic seizures. Similarly, myoclonic seizure prevalence also remained constant after the age of forty years (see Figure 8.3). The prevalence of all generalised seizure types was highest in females and

lowest in southern Tasmania (see Tables 8.4, 8.5.1, 8.5.2 and 8.5.3 and Figure 8.4). No socioeconomic differences in prevalence were found for any generalised seizures.

Figure 8.1: The prevalence of Idiopathic Generalised epilepsy by age-group (n=175)

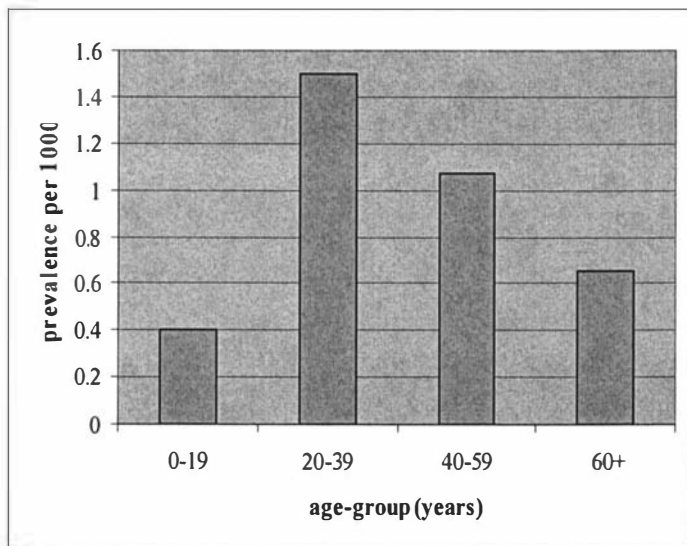
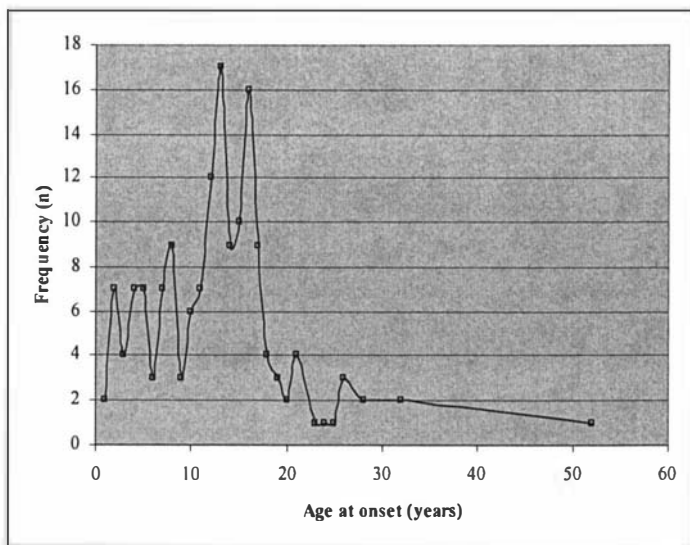


Figure 8.2: Idiopathic Generalised Epilepsy by age at onset (n=159*)



*excluding those where age of onset not specified (n=16)

Figure 8.3: The prevalence of IGE (n=175) and generalised seizure types by age-group (n=348)

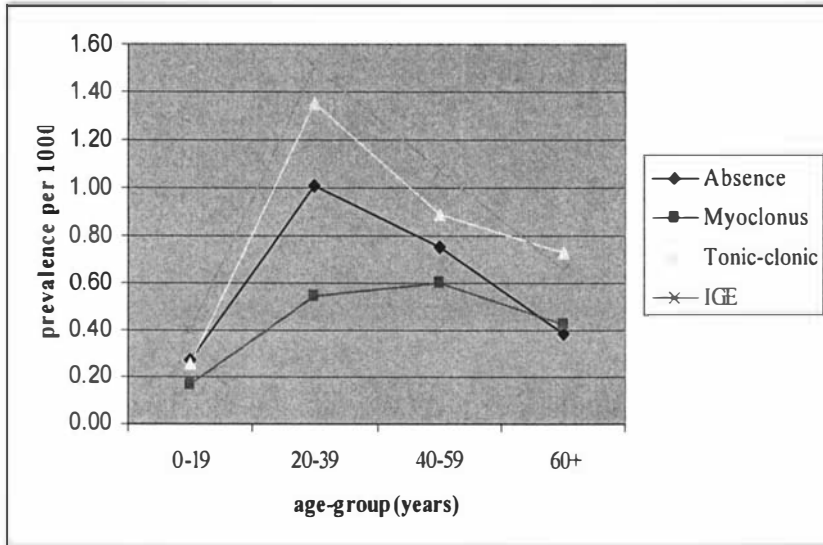


Figure 8.4: The prevalence of IGE and generalised seizure types by region

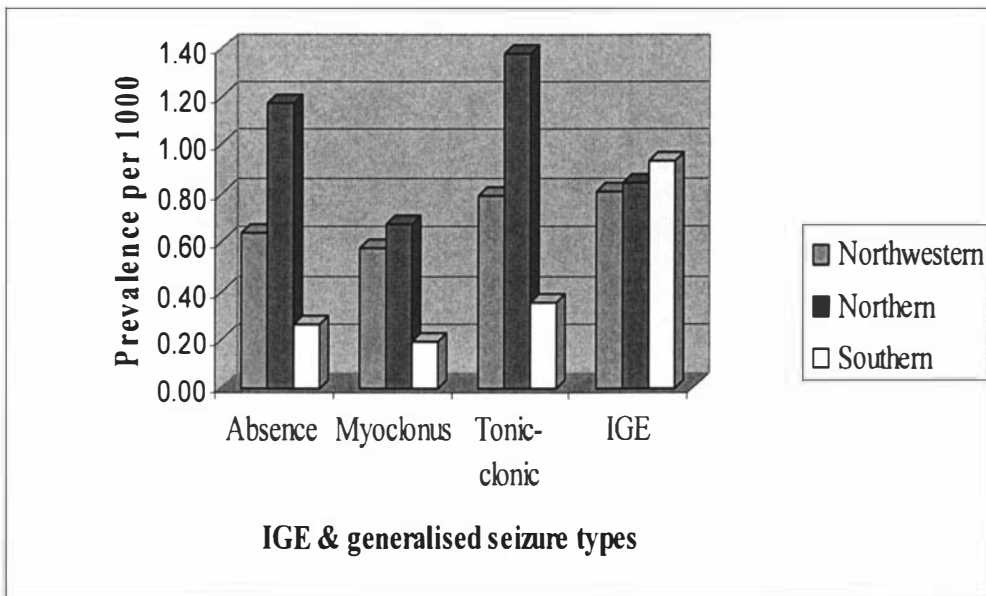


Table 8.4: Estimated prevalence and distribution of Idiopathic Generalised Epilepsy by age, gender, region and SES in Tasmania, Australia

	Tasmanian Population‡	Epilepsy Estimated Cases*	Epilepsy Estimated Prevalence §	Epilepsy Interview Population†	IGE Estimated Cases	IGE Estimated Percentage	IGE Estimated Prevalence#	(95% CI)
TOTAL	472672	2063	4.36	863	175	20.28%	0.89	(0.77-1.00)
Age group (years)								
0-19	131813	215	1.63	146	36	24.66%	0.40	(0.29-0.52)
20-39	120883	586	4.85	187	58	31.02%	1.50	(1.18-1.82)
40-59	131215	757	5.77	345	64	18.55%	1.07	(0.83-1.31)
60+	88761	623	7.02	183	17	9.29%	0.65	(0.36-0.95)
Gender								
Male	232768	1059	4.55	432	71	16.44%	0.75	(0.59-0.91)
Female	239904	1003	4.18	431	104	24.13%	1.01	(0.84-1.18)
Region								
Northern	106309	478	4.50	211	38	18.01%	0.81	(0.58-1.04)
North-western	134701	550	4.08	213	44	20.66%	0.84	(0.62-1.07)
Southern	231662	1035	4.47	426	89	20.89%	0.93	(0.76-1.11)
SES‡								
1. Low	104859	452	4.31	203	35	17.24%	0.74	(0.52-0.97)
2. Low/moderate	92058	446	4.84	196	34	17.35%	0.84	(0.58-1.10)
3. Moderate	91397	354	3.87	177	38	21.47%	0.83	(0.60-1.07)
4. Moderate/high	90750	429	4.73	180	29	16.11%	0.76	(0.51-1.02)
5. High	93608	378	4.04	183	35	19.13%	0.77	(0.54-1.00)

‡ 472, 672 ((ABS) 2003); *Imputed prevalence reported; § Per 1000; † 955 patients on Tasmanian Epilepsy Register less 92 diagnosed as 'not having epilepsy' on interview but including 31 with 'uncertain epilepsy'; # Calculated from the product of the imputed prevalence and the estimated percentage for that variable; ‡ SES = Socioeconomic index for area (SEIFA) quintile; IGE = Idiopathic Generalised Epilepsy; BMEI = Benign Myoclonic Epilepsy of Infancy; MAE = Epilepsy with Myoclonic Astatic Seizures; EMA = Epilepsy with myoclonic absences; CAE = Childhood Absence Epilepsy; JAE = Juvenile Absence Epilepsy; JME = Juvenile Myoclonic Epilepsy; Unspecified = Idiopathic Generalised Epilepsy Not Otherwise Specified

Table 8.5.1: Estimated prevalence and distribution of absence seizures by age, gender, region and SES in Tasmania, Australia

	Tasmanian Population‡	Epilepsy Estimated Cases*	Epilepsy Estimated Prevalence §	Epilepsy Interview Population†	Absence Estimated Cases	Absence Estimated Percentage	Absence Estimated Prevalence#	(95% CI)
TOTAL	472672	2063	4.36	863	118	13.67%	0.60	(0.50-0.70)
Age group (years)								
0-19	131813	215	1.63	146	24	16.44%	0.27	(0.17-0.37)
20-39	120883	586	4.85	187	39	20.86%	1.01	(0.73-1.29)
40-59	131215	757	5.77	345	45	13.04%	0.75	(0.55-0.96)
60+	88761	623	7.02	183	10	5.46%	0.38	(0.15-0.16)
Gender								
Male	232768	1059	4.55	432	50	11.57%	0.53	(0.39-0.66)
Female	239904	1003	4.18	431	68	15.78%	0.66	(0.52-0.80)
Region								
North-western	106309	478	4.50	211	30	14.22%	0.64	(0.43-0.85)
Northern	134701	550	4.08	213	61	28.64%	1.17	(0.92-1.42)
Southern	231662	1035	4.47	426	25	5.87%	0.26	(0.16-0.36)
SES‡								
1.Low	104859	452	4.31	203	26	12.81%	0.55	(0.35-0.75)
2. Low/moderate	92058	446	4.84	196	20	10.20%	0.49	(0.29-0.70)
3. Moderate	91397	354	3.87	177	26	14.69%	0.57	(0.37-0.77)
4. Moderate/high	90750	429	4.73	180	21	11.67%	0.55	(0.33-0.77)
5. High	93608	378	4.04	183	22	12.02%	0.49	(0.30-0.68)

‡ 472, 672 ((ABS) 2003); *Imputed prevalence reported; § Per 1000; † 955 patients on Tasmanian Epilepsy Register less 92 diagnosed as 'not having epilepsy' on interview but including 31 with 'uncertain epilepsy'; # Calculated from the product of the imputed prevalence and the estimated percentage for that variable; ‡ SES = Socioeconomic index for area (SEIFA) quintile; IGE = Idiopathic Generalised Epilepsy; BMEI = Benign Myoclonic Epilepsy of Infancy; MAE = Epilepsy with Myoclonic Astatic Seizures; EMA = Epilepsy with myoclonic absences; CAE = Childhood Absence Epilepsy; JAE = Juvenile Absence Epilepsy; JME = Juvenile Myoclonic Epilepsy; Unspecified = Idiopathic Generalised Epilepsy Not Otherwise Specified

Table 8.5.2: Estimated prevalence and distribution of myoclonic seizures by age, gender region and SES in Tasmania, Australia

	Tasmanian Population‡	Epilepsy Estimated Cases*	Epilepsy Estimated Prevalence §	Epilepsy Interview Population†	Myoclonic Estimated Cases	Myoclonic Estimated Percentage	Myoclonic Estimated Prevalence#	(95% CI)
TOTAL	472672	2063	4.36	863	83	9.62%	0.42	(0.33-0.51)
Age group (years)								
0-19	131813	215	1.63	146	15	10.27%	0.17	(0.09-0.25)
20-39	120883	586	4.85	187	21	11.23%	0.54	(0.33-0.76)
40-59	131215	757	5.77	345	36	10.43%	0.60	(0.42-0.79)
60+	88761	623	7.02	183	11	6.01%	0.42	(0.18-0.66)
Gender								
Male	232768	1059	4.55	432	30	6.94%	0.32	(0.21-0.43)
Female	239904	1003	4.18	431	53	12.30%	0.51	(0.38-0.64)
Region								
North-western	106309	478	4.50	211	27	12.80%	0.58	(0.37-0.78)
Northern	134701	550	4.08	213	35	16.43%	0.67	(0.47-0.87)
Southern	231662	1035	4.47	426	18	4.23%	0.19	(0.10-0.27)
SES‡								
1. Low	104859	452	4.31	203	17	8.37%	0.36	(0.20-0.53)
2. Low/moderate	92058	446	4.84	196	18	9.18%	0.44	(0.25-0.64)
3. Moderate	91397	354	3.87	177	16	9.04%	0.35	(0.19-0.51)
4. Moderate/high	90750	429	4.73	180	11	6.11%	0.29	(0.12-0.45)
5. High	93608	378	4.04	183	19	10.38%	0.42	(0.24-0.60)

‡ 472, 672 ((ABS) 2003); *Imputed prevalence reported; § Per 1000; † 955 patients on Tasmanian Epilepsy Register less 92 diagnosed as 'not having epilepsy' on interview but including 31 with 'uncertain epilepsy'; # Calculated from the product of the imputed prevalence and the estimated percentage for that variable; ‡ SES = Socioeconomic index for area (SEIFA) quintile; IGE = Idiopathic Generalised Epilepsy; BMEI = Benign Myoclonic Epilepsy of Infancy; MAE = Epilepsy with Myoclonic Astatic Seizures; EMA = Epilepsy with myoclonic absences; CAE = Childhood Absence Epilepsy; JAE = Juvenile Absence Epilepsy; JME = Juvenile Myoclonic Epilepsy; Unspecified = Idiopathic Generalised Epilepsy Not Otherwise Specified

Table 8.5.3: Estimated prevalence and distribution of tonic-clonic seizures by age, gender, region and SEIFA in Tasmania, Australia

	Tasmanian Population‡	Epilepsy Estimated Cases*	Epilepsy Estimated Prevalence §	Epilepsy Interview Population†	Tonic-clonic Estimated Cases	Tonic-clonic Estimated Percentage	Tonic-clonic Estimated Prevalence#	(95% CI)
TOTAL	472672	2063	4.36	863	147	17.03%	0.74	(0.63-0.85)
Age group (years)								
0-19	131813	215	1.63	146	23	15.75%	0.26	(0.16-0.35)
20-39	120883	586	4.85	187	52	27.81%	1.35	(1.04-1.66)
40-59	131215	757	5.77	345	53	15.36%	0.89	(0.67-1.11)
60+	88761	623	7.02	183	19	10.38%	0.73	(0.42-1.04)
Gender								
Male	232768	1059	4.55	432	58	13.43%	0.61	(0.46-0.76)
Female	239904	1003	4.18	431	89	20.65%	0.86	(0.70-1.02)
Region								
North-western	106309	478	4.50	211	37	17.54%	0.79	(0.56-1.02)
Northern	134701	550	4.08	213	72	33.80%	1.38	(1.12-1.64)
Southern	231662	1035	4.47	426	34	7.98%	0.36	(0.24-0.47)
SES‡								
1. Low	104859	452	4.31	203	29	14.29%	0.62	(0.41-0.82)
2. Low/moderate	92058	446	4.84	196	29	14.80%	0.72	(0.48-0.96)
3. Moderate	91397	354	3.87	177	32	18.08%	0.70	(0.48-0.92)
4. Moderate/high	90750	429	4.73	180	23	12.78%	0.60	(0.37-0.83)
5. High	93608	378	4.04	183	30	16.39%	0.66	(0.45-0.88)

‡ 472, 672 ((ABS) 2003); *Imputed prevalence reported; § Per 1000; † 955 patients on Tasmanian Epilepsy Register less 92 diagnosed as 'not having epilepsy' on interview but including 31 with 'uncertain epilepsy'; # Calculated from the product of the imputed prevalence and the estimated percentage for that variable; ‡ SES = Socioeconomic index for area (SEIFA) quintile; IGE = Idiopathic Generalised Epilepsy; BMEI = Benign Myoclonic Epilepsy of Infancy; MAE = Epilepsy with Myoclonic Astatic Seizures; EMA = Epilepsy with myoclonic absences; CAE = Childhood Absence Epilepsy; JAE = Juvenile Absence Epilepsy; JME = Juvenile Myoclonic Epilepsy; Unspecified = Idiopathic Generalised Epilepsy Not Otherwise Specified

8.4 Discussion

This is the first study to estimate the prevalence of ‘more specific forms of epilepsy’ directly by administering standardised seizure interviews and interpretative guidelines in a community-based study population, thereby improving the validity of these findings. Partial epilepsy was classified in two thirds and generalised epilepsy in slightly more than one-fifth, with IGE observed in 20.3% and the absence epilepsies representing the most common IGE syndromes. IGE prevalence beyond childhood was more common, related to refractory childhood and adolescent disease rather than older-onset cases, and characterised by myoclonic and tonic-clonic. Generalised seizures but not IGE were less prevalent in southern Tasmania. These findings suggest that IGE is a common group of epilepsies with important aetiological and prognostic determinants occurring at the seizure rather than syndrome level of classification.

My aim was to focus recruitment on community-treated rather than hospital-treated epilepsy as under-reporting of idiopathic epilepsy, generalised seizures and syndromes (in particular absence seizures and epilepsy) may be reduced by up to a half when hospital-based recruitment is the sole method of case ascertainment (Cardozo and Patel 1976, Gudmundsson 1966, Loiseau et al. 1991, Osuntokun and Odeku 1970, Stanhope et al. 1972). For example, a French study found that uptake could be twice as high when “community-based” private specialists were available compared to hospital-based neurological services for generalized epilepsy (42.1% vs. 20.1%), IGE (35.8% vs. 16.2%) and all IGE sub-syndromes especially childhood absence (Loiseau et al. 1991). In addition, a study of school aged children found a similar frequency of IGE in new onset

(incident) clinic patients as a community population (27.8% vs. 30.8%) (Cavazzuti 1980). However, this was not the case for the more refractory localisation or symptomatic generalized epilepsies (Cavazzuti 1980, Loiseau et al. 1991). Therefore, in addition to treating severe disease, hospital services often reflect issues of health care access (Cardozo and Patel 1976, Osuntokun and Odeku 1970) with incomplete disease enumeration being especially problematic when disease referral is low (Abo Melha and Al-Rajeh 1987, Granieri et al. 1983).

Thus, although my sample does not include untreated sources, as would be the case from direct household recruitment, it represents one of the few studies performed outside a hospital setting (Manford et al. 1997). Nevertheless, countries such as Australia with better access to primary and specialist services and high uptake of AEDs for ‘active’ disease (Beran et al. 1982) are more likely to ascertain a wider spectrum of idiopathic epilepsy from health service utilisation recruitment (Cardozo and Patel 1976, Gudmundsson 1966, Osuntokun and Odeku 1970), but there is still likely to be substantial underascertainment, which can be better avoided with a community-based study of the type that I have conducted.

I could also be criticised for diagnosing epilepsy, seizures and syndromes by interview rather than more typically by an epilepsy specialist’s clinical assessment (Debrock et al. 2000, Meneghini et al. 1991, Osuntokun et al. 1982, Placencia et al. 1992b, Tekle-Haimanot et al. 1990a). However, my modified questionnaire administered by CATI and interpreted by standardized diagnostic guidelines, was in close agreement with an

epilepsy specialist's clinical assessment in diagnosing the main seizure types, presence of epilepsy, seizure-onset types, and IGE (see Chapter Five). In addition, this diagnostic mode is more cost-effective than personal interviews and almost certainly led to the high completion rate (88.6%) seen in this study (Rowan and Hyman 1976) thereby increasing the validity of these findings.

A number of previous studies have tended to classify all generalized convulsive seizures as generalized-onset epilepsy elevating these estimates and consequently deflating estimates of partial-onset epilepsy (Haerer et al. 1986). This is the likely reason for the relatively high estimates of generalized epilepsy noted in some previous studies (Granieri et al. 1983, Li et al. 1985, Wang et al. 1983) compared to the two-thirds with partial epilepsy and slightly more than one-fifth with generalised epilepsy classified in this study.

Although generalized epilepsy has been seen with similar frequency in those above and below 20 years of age (Joshi et al. 1977), most studies suggest it is higher in the younger age group (Danesi 1985, Gastaut et al. 1975, Joshi et al. 1977), being generally about 30% (Alving 1979, Danesi 1985, Eadie 1996, Kramer et al. 1998, Oka et al. 1995). However, in this study IGE prevalence beyond childhood was more common, related almost exclusively to refractory cases persisting into adulthood rather than late onset disease, and was more often characterised by myoclonic and tonic-clonic rather than absence seizures. The lower prevalence of IGE in childhood relative to other ages is unexplained but may also relate to lower childhood prevalence estimates reported in other

developed countries (Hauser et al 1991, Wallace et al 1998a), or reduced sampling of liquid AED preparations (as described in Chapter Six) in children with a limited disease duration (Olaffason et al 2005).

Although one study found only 6.6% of epilepsy cases to have IGE (Oun et al. 2003) and another study reported a prevalence of 10.8% (Manford et al. 1997) these relatively low estimates are likely to be due to a higher proportion of unclassifiable epilepsy in these studies with the latter study diagnosing syndromes from secondary medical record sources rather than from those directly experiencing (patients) or observing (witnesses) seizures, as in this study. In adults, with these two exceptions, the proportion of patients with idiopathic generalized epilepsy is remarkably consistent across studies, ranging from 17.5% to 23.9% (Alving 1979, Danesi 1985, Eadie 1996, Osservatorio Regionale per l'Epilessia (OREp)) and is consistent with the 20.3% observed overall in this study.

Although JME is often considered the most common IGE syndrome (Olafsson and Hauser 1999), my findings suggest that the absence epilepsies are the most common. In fact, in previous studies the estimated prevalences of specific IGE syndromes had relatively wide confidence intervals (Alving 1979, Eadie 1996, Juul-Jensen and Foldspang 1983, Oka et al. 1995, Oka et al. 2006, Viani et al. 1988) with the exception of lower observed frequencies for JAE (0.2% to 1.6%) and higher frequencies for EMA (11.1%) these previous studies are therefore consistent with my findings. As discussed in Chapters Two, Three and Four the reasons for these differences are most likely to be due to widespread variations in ascertainment, diagnosis and classification between studies.

Similar to the estimate of 13.7% in this study, previous studies have observed absence seizures in 1% to 17.8% % of total cases (Alving 1978, Alving 1979, Aziz H et al. 1994, Billinghamurst et al. 1973, Danesi 1985, Gastaut et al. 1975, Granieri et al. 1983, Joensen 1986, Joshi et al. 1977, Juul-Jensen 1964, Loiseau et al. 1991, Tekle-Haimanot 1984, Viani et al. 1988). Although these studies suggest that these seizures typically peak in younger patients (Danesi 1985, Gastaut et al. 1975, Joshi et al. 1977), particularly the 5-10 year age group (Rajeh et al. 1990) my observations suggest this peak occurs in the age-group immediately following childhood (see Figure 8.3), with the highest retrospective onset of disease in adolescence (see Figure 8.2).

Given the reasonable diagnostic validity for classifying generalised non-convulsive seizures demonstrated by interview (see Table 5.3), it is more likely that previous studies have underestimated their presence. This may be due to a tendency to misdiagnosis, particularly for absence seizures (Nicoletti et al. 1999), up to almost one-third of cases (Leibowitz and Alter 1968), as a result of questionnaire sensitivity (Rajeh et al. 2001, Rajeh et al. 1993), concealment by the patient (Rocca et al. 2001), and classifying seizures exclusively as tonic-clonic seizures from the predominant seizure type rather than all seizures types independently (Brewis et al. 1966, Forsgren 1992, Keranen et al. 1989, Olafsson and Hauser 1999). Hence, the findings for IGE present beyond childhood relating to refractory childhood onset disease, characterised by myoclonic and tonic-clonic seizures, are likely to be accurate, and have important prognostic implications that

deserve further investigation (Berkovic et al. 1987, Loiseau et al. 2002, Malafosse et al. 1994)

Although phenotypic concordance of IGE sub-syndromes among first degree relatives is about one third (Group 1993, Ottman R et al. 1998b), these studies all show overlap of sub-syndromes within families, suggesting that although these epilepsies are genetically closely related, the absence epilepsies are more closely related than the myoclonic epilepsies (Winawer et al. 2003). This is not surprising, as the presence of specific seizure types and their expression drives both the diagnosis of IGE and its sub-syndromes (Loiseau et al. 2002). The total number of individual generalized seizure types that make up the IGE phenotype present in this study (absence n=118, myoclonic n=83, tonic-clonic seizures n= 147) enabled me to also explore their demographic distribution. Hence, although the regional differences observed in generalized seizure types, but not IGE, is not easily explained, it is consistent with the hypothesis that the underlying etiological factors for IGE act at a seizure rather than a syndrome level of classification, i.e. that classifying epilepsy cases by syndrome yields more homogeneous groups than classifying cases by the type seizure.

Chapter Nine: Conclusions

9.1 Introduction

Better understanding of the demographic distribution of epilepsy and the prevalence of ‘more specific forms of epilepsy’ in community-based settings would improve our understanding of this disorder at the population level. By adaptation of the diagnostic cascade design originally established to measure the overall prevalence of epilepsy in developing countries, this thesis provides the first community-based estimates of the prevalence of the most common clinical group of epilepsies presumed to have a genetic basis – The Idiopathic Generalised Epilepsies (IGE) - by patient and witness interview.

9.2 Summary of major findings

Validation

Diagnostic questionnaires administered by CATI and interpreted by standardized diagnostic guidelines, are in close agreement with an epilepsy specialist’s clinical assessment in diagnosing the main seizure types, presence of epilepsy, seizure-onset types, and IGE. These instruments are less useful (as is clinical judgment) for diagnosing partial epilepsy syndromes beyond the broad syndrome level or aetiology. However, diagnosis still remained less than ideal for discriminating the onset-type of generalized convulsive seizures. These deficiencies relate more to under-recognition of individual generalized non-convulsive seizures rather than misinterpretation of partial seizures.

Recruitment

Recruitment through the HIC national prescription database provides a representative population cohort of community-treated epilepsy cases. This recruitment design does not appear to produce samples that are disproportionately enriched by hospital-treated cases, and demonstrated effective and efficient enrolment, independent of doctor referral for epidemiologic case-based recruitment of epilepsy, particularly when ‘more specific forms of epilepsy’, co-morbid diseases associated with epilepsy and longitudinal cohort studies are required.

Prevalence and distribution of epilepsy

The estimated treated epilepsy prevalence in Tasmania was 4.36 per 1000, with the percentage of patients receiving more than two concurrent AEDs for epilepsy at the high end of polytherapy seen in most other developed countries at 8.0% (Fosgren 1992, Giuliani et al 1992). Treated prevalence was 8% lower in women than men, age-group rates lowest in children and highest in the elderly. However, no differences in treated epilepsy prevalence were found between the three main geographic regions of Tasmania or by socio-economic status categorised by postcode of residence.

Prevalence and distribution of generalised seizures and IGE

Partial epilepsy was classified in two-thirds and generalised epilepsy in slightly more than one-fifth of patients, with IGE being observed in 20.3% and the absence epilepsies representing the most common IGE syndromes. IGE was more common beyond childhood, related to refractory childhood and adolescent disease rather than older-onset

cases, and characterised more often by myoclonic and tonic-clonic seizures. Generalised seizures, but not IGE were less prevalent in southern Tasmania.

9.3 Limitations of the data

Validation

Although useful, further ‘splitting’ of the IGE syndromes into their subtypes (e.g. childhood absence epilepsy) was not possible as this would have involved too few numbers to draw meaningful conclusions. In addition, at the time of formulation of the written guidelines my limited clinical experience (three years specialist epilepsy training) was by no means definitive (Bodensteiner et al 1988). However, by formalization of this clinical diagnostic process using the expertise of my more senior epilepsy specialist colleagues (D’Souza et al 2007b), it was hoped this would lead to more transparent and testable future refinements. Diagnoses were reached without the use of EEG recordings as these would not always be possible when conducting epidemiological studies in resource-constrained communities (Senanayake 1993). Nevertheless, as the evidence suggested that an eye-witness account of the patient’s seizures was more critical to diagnosis (Reutens et al 1992, Senanayake 1993), I focused on maximising this part of the diagnostic process.

Recruitment

The HIC prescription database only included persons above a ‘reportable’ retail price threshold, and does not detect undiagnosed and untreated disease. This is likely to hinder this recruitment design in developing countries and those with poor access to healthcare

(e.g. ethnic, indigenous, rural/remote communities) (Haerer et al 1986). However, at the time of study all the anticonvulsant medications had a retail price more than this threshold, in Australia and only the infrequently prescribed barbiturate anticonvulsants and preparations for patients with swallowing difficulties and young children (typically less than eight years of age) retailed below the 'general' patient price threshold. Therefore, the HIC sample frame is a comprehensive AED database, with the exception of very young children on single liquid preparations (D'Souza et al 2007c).

Although more representative than specialist sources, epilepsy diagnosis statistics generated from general practice are less likely to be accurate in the absence of confirmation by specialist assessment, with general practitioners reporting diagnostic uncertainty especially in neurological disease (MacDonald et al 2000) (hence my subsequent use of a diagnostic questionnaire for this purpose).

AEDs may not be universal for patients who have a diagnosis of epilepsy, and may underestimate prevalence, particularly in developing countries where fewer patients are on regular treatment (Coleman et al 2002). However, in a number of communities, including Australia (Beran et al 1982), AEDs have been demonstrated to have widespread use and market penetration in treating epilepsy (Bharucha et al 1988, Olafsson and Hauser 1999). Although this Australian study suggests no lifetime AED treatment gap for epilepsy, this seems likely to be an underestimate (Beran et al 1982). The situation in Australia is more likely to resemble countries with similar universal primary and tertiary

healthcare access such as Sweden or the UK where AED under-ascertainment of 8-25% has been observed (Forsgren 1992, Cockerell et al. 1995).

In addition, AEDs are not exclusively prescribed for the treatment of epilepsy, i.e. they lack disease treatment specificity. They are also used to treat bipolar affective disorder, migraine, and chronic pain conditions. In Australia, as doctors prescribing medications are not required to indicate what condition is being treated on a prescription, this means that my invited source population included disease groups other than my target population of treated epilepsy. Rather than employing an empirical correction factor, as has been suggested previously (de la Court et al 1996) ineligible diseases were excluded by patient self-report as to whether AEDs were prescribed for ‘blank spells, seizures or epilepsy’ and this question was found to have high positive predictive value using the diagnostic questionnaire from Chapter Five. However, as mail respondents who replied ‘no’ to this question declined further study participation, measurement of the false negative rate and true negative rate of this question was not able to be estimated. This would have allowed calculation of the sensitivity and specificity, potential margins for error in our prevalence finding (Plancencia et al 1992b), and improve the ultimate validity of our results.

Prevalence and distribution of epilepsy

My epilepsy prevalence estimates may be influenced by factors that affect a person acquiring a diagnostic label for treatment purposes. However, AED prescription data

provides a useful prevalence measure in communities, such as Australia, characterized by high access to health services (Beran et al 1982).

AED initiation and withdrawal practices among local physicians and patients may affect prevalence estimates from prescription data (Forsgren 1992, Oun et al 2003). In Australia the typical practice is to commence AED treatment after the second unprovoked seizure and this was reflected in the low number of patients that were found to have been treated after a single seizure (see Chapter Seven). Therefore, patient recruitment by AED prescription also appears to have yielded few false positive cases due to 'early' treatment.

Although the overall response rate to my prevalence survey using the HIC mail invitation may be considered low (54%) the heterogeneous nature of the prescription population meant that the 1774 indicating treatment for epilepsy represented 86.0% of total epilepsy cases (imputed) in Tasmania. Given the high PPV from my validity study, negligible differential misclassification bias between self-reported and doctor-reported epilepsy status could be assumed, allowing a three contact exponential decay prevalence imputation approach (Drane et al 1993). This approach enables the inference of disease status in remaining mail non-respondents improving the precision of prevalence estimates (Drane 1991).

SEIFA is a relatively imprecise measure of the socioeconomic status of an individual as it reflects the socio-economic wellbeing of an area, rather than of an individual, making it possible for a relatively advantaged person to be resident in an area which may have a

low index score (Trewin 2001). Although, lower sampling of liquid AED preparations in children less than eight years, probably partly explains the lower prevalence rates seen in childhood they persist beyond the age that these issues would continue to have an impact.

Prevalence and distribution of generalised seizures and IGE

The sample does not include untreated sources, as would be the case from direct household recruitment (Schoenberg 1982) however it represents one of the few studies performed outside a hospital setting (Manford et al 1997). Nevertheless, countries such as Australia with better access to primary and specialist services and high uptake of AEDs for 'active' disease are more likely to ascertain a wider spectrum of idiopathic epilepsy from health service utilisation recruitment (Beran et al 1982).

Assessment of epilepsy, seizures and syndrome diagnosis was by interview rather than more typically by an epilepsy specialist's clinical assessment (Plancencia et al 1992b). However, the modified questionnaire administered by CATI and interpreted by standardized diagnostic guidelines was in close agreement with an epilepsy specialist's clinical assessment in diagnosing the main seizure types, presence of epilepsy, seizure-onset types, and IGE.

9.4 Implications

Validation

Generalised seizures and IGE can be classified primarily with historical data when interpreted with written guidelines, facilitating their study in large scale population

studies by questionnaire. Further improvements in discriminating the individual non-convulsive generalized seizure types (without appreciable loss of validity) and a more quantitative approach to questionnaire interpretation would further enhance the utility of these field instruments for epilepsy syndrome-based population research. This could be through the development of new written questions (particularly for absence seizures), novel diagnostic instruments (e.g. video questionnaire sequences of specific seizure symptoms) or an analysis weighting the importance of individual questionnaire responses to determine diagnostic ‘best fit’ for ‘more specific forms of epilepsy’ such as IGE.

Recruitment

The recruitment design outlined in this thesis is relevant for researchers in countries with centralized prescription databases, and who are intending to conduct studies with large sample sizes, e.g. when estimating the prevalence of epilepsy sub-types, co-morbid conditions, syndrome-focused case-control studies, or longitudinal cohort studies. AED recruitment is also an efficient method for yielding cases compared to door-to-door surveys (Birbeck and Kalichi 2004, Plancencia et al 1992b), although secondary to medical practitioner diagnosis and treatment, it also has the advantage that it does not rely on medical contact for denominator enumeration, invitation and patient participation.

Other neurological diseases where this form of prescription recruitment could be utilized are Multiple Sclerosis, Parkinson’s disease, Myasthenia Gravis and Dementia. The Australian National Prescription Database has the advantage that it allows potential re-identification of cases for longitudinal cohort studies by indirect communication with

individuals and their families by anonymous contact through the HIC. Alternatively, my Tasmanian Epilepsy Register Cohort could be expanded to recruit cases longitudinally (e.g to explore incident treated cases), nationally (to compare and combine case in other Australian states) or to study/compare other AED disease groups (e.g. the effects on pregnant woman takings AEDs for psychiatric conditions).

With appropriate consideration of individual privacy, linking HIC prescription database with other government-funded services i.e. track AEDs with diagnostic investigations (MRI, EEG), providers with epilepsy expertise and hospital services (e.g. injuries) would be a highly useful research instrument. This would require legislative change to enable this kind of data linkage. Improving specific disease identification at the prescribing stage would enhance monitoring and research of medically treated diseases (although this may be difficult as it could expose non-indication pharmacological treatment by doctors).

Further validation of the HIC AED prescription database (with respect to disease sensitivity and specificity for epilepsy) would enhance the precision of my prevalence estimates. However, this would be difficult to perform given that the restrictions on privacy and confidentiality for those on the database does not allow access to false negatives and true negatives to allow sensitivity and specificity calculations.

Prevalence and distribution of epilepsy

The estimated treated epilepsy prevalence in Tasmania is consistent with a number of previous studies that have derived prevalence from AED prescription (Giuliani et al 1992,

Wallace et al 1998a), primary care (Cockerell et al 1995), or household survey sources (Beran et al 1982). However, the relatively high percentage of patients on multiple AED may either reflect increased prevalence of severe epilepsy or inadequate epilepsy management in Tasmania and requires further evaluation. Despite its consistency in many studies, the explanations for the higher male prevalence still remain largely unknown. One explanation of the lack of association between treated epilepsy prevalence and SEIFA is that it is real and does not reflect access to general practice services. Alternatively, it may be due to misclassification of individual socioeconomic status or confounding by area of residence.

The observed age-group differences suggest that incidence may be lower in the younger age group, or that the illness treatment duration is more short-lived, compared to adults and the elderly (Olafsson et al 2005). If correct, with demographers predicting a dramatically greater elderly population in the future, these findings have important implications for health service planning in developed countries. This would need to involve increased education and awareness of elderly epilepsy presentation, diagnosis and management in primary care, general physicians and geriatricians. Along with studies to better understand the aetiology of epilepsy in the elderly so that preventable causes may be addressed. Although it would require considerable resources an age-specific incidence study focusing on children and/or the elderly could explore this important public health issue further. By enrolling a prospective cohort, better understanding (mortality, response to treatment and disease remission) of the prognosis of epilepsy, or 'more specific forms of epilepsy e.g. IGE could be gained.

9.5 Concluding remarks

IGE and generalised seizure types are common and constitute an important public health issue, with their underlying etiological and prognostic factors acting at a seizure rather than a syndrome level of classification.

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Appendices

Appendix 1: Screening questions for epilepsy used in the WHO screening questionnaire for neurological diseases

- a. For subjects of 7 years of age and older:
 - 1. Have you ever lost consciousness?
 - 2. Have you ever had episodes where you lost contact with your surroundings?
 - 3. Have you ever had any shaking of your arms and legs which you could not control?

- b. For children under 7 years of age:
 - 1. Has this child ever lost consciousness?
 - 2. Does this child have episodes characterized by vagueness and unawareness of surroundings?
 - 3. Have you ever seen this child shaking and unable to control the arms or legs?

Questionnaire of 15 or 16 questions used for screening for neurological diseases in epidemiological surveys.

Appendix 2: Criteria for the definition of tonic-clonic seizures, used in epilepsy studies in rural areas of Africa, Asia, and South America (Sander and Shorvon 1987)

- i. Loss of consciousness from 1-30 min
- ii. Tonic phase
- iii. Clonic phase
- iv. Sphincteric disturbance
- v. Tongue biting
- vi. Fall
- vii. Injury due to fall
- viii. Postictal muscle soreness
- ix. Postictal drowsiness, sleep, or confusion
- x. Transient postictal focal paralysis

A tonic-clonic convulsion is considered to have definitely occurred if criteria i-iii are present with any two of criteria iv-x

Appendix 3: Operational definitions of seizures used in Ecuador study

A. Epileptic Seizure

1. Simple Partial Seizure (SPS)

Attacks occur without loss of consciousness or amnesia and one or more of the following criteria occur;

- i. Focal jerking or tonic, tonic clonic, clonic movements (face/extremities/head)
- ii. Head turning
- iii. Paralysis of a limb
- iv. Hallucinations/optical illusions (metamorphopsia, teleopsia, polyopsia)
- v. Speech alterations (aphasia, dysarthria)
- vi. Parasthesias, numbness in face/limbs
- vii. Olfactory/gustatory hallucinations
- viii. Auditory Hallucinations/illusions
- ix. Dismnesic phenomena (déjà vu, etc)
- x. Vegetative (epigastric sensations, etc)
- xi. Affective symptoms (fear, weeping, etc)

2. SPS evolving to Complex Partial Seizures (CPS)

If any of the above criteria is/are followed by impairment of consciousness without a generalized convulsion

3. CPS

If the attacks take the form of loss of consciousness without generalized convulsions, but with any of the following symptoms/signs:

- i. Duration of attack from 30s to several minutes
- ii. Postictal headache and/or sleep, and/or post/transictal confusion
- iii. Impairment of consciousness only or with at least one of the following:
 - a. Non-propositive automatisms: facial (swallowing, grimacing), fiddling movements (fingers, hands, etc)
 - b. Propositive automatisms (gestural, walking, vocalization)

4. Generalised Absence

If the attacks take the form of a brief loss of consciousness with amnesia only and the following signs occur:

- i. Onset between 5 and 15 years
- ii. Usually less than 30s
- iii. Without movements, except slight blinking or head jerking
- iv. Without fall
- v. Without postictal headache or sleep
- vi. Family history of similar attacks
- vii. Occur especially when drowsy

5. Alteration of Consciousness of undefined Classification

If there are criteria for both 3 (CPS) and 4 (generalised absence).

6. Generalised Tonic-Clonic Seizures (primarily and secondarily generalized)

If the attacks take the form of a generalized convulsion and the following criteria occur:

- i. Loss of consciousness 1-30 min
- ii. Bilateral tonic contracture, followed by iii
- iii. Bilateral clonic movements
- iv. Sphincteric incontinence
- v. Fall
- vi. Injury with fall
- vii. Tongue biting
- viii. Cyanosis/pallor
- ix. Postictal drowsiness, sleep, confusion, or headache, muscular aching
- x. Postictal unilateral limb weakness

If the attack is immediately preceded by any of the symptoms in 1 (SPS), 2 (SPS + CPS) or 3 (CPS), the diagnosis becomes that of a secondarily generalized convulsion.

7. Atonic attacks

If the attacks take the form of a non-orthostatic sudden fall with loss of tone without clonic movements, and with loss of consciousness and the following criteria occur:

- i. Brief consciousness loss (usually seconds)
- ii. Fall with injury
- iii. Confusion, headache, drowsiness postictally

8. Tonic Attacks

If the attacks take the form of a sudden fall with rigidity without clonic movements, and with loss of consciousness and the following criteria, the attacks are classified as tonic attacks:

- i. Brief (usually seconds)
- ii. Injury in the attack
- iii. Tongue biting
- iv. Confusion, headache, drowsiness postictally

9. Myoclonic Seizures

If the attacks take the form of brief jerks and if any of the following criteria occur:

- i. Jerks singly or in brief runs'
- ii. Worse on awakening or when falling asleep
- iii. Often in clusters

B. Febrile Convulsions

If the attacks occurred only or are occurring between the ages of 2 and 5 years and the following criteria are positive:

- i. The attacks only occur in the context of fever
- ii. Less than six attacks have occurred in total
- iii. The attacks have convulsive feature

C. Recurrent Attacks

- i. Single attacks: if the attacks occurred on only one occasion or the attacks occurred on more than one occasion but the interval between attacks was less than 48 hours
- ii. Recurrent attacks: if the attacks occurred on more than one occasion, and if the intervals between attacks were greater 48 hours.

Appendix 4: Original screening questionnaire as used during the clinic-based validation in the Ecuador Study

1. Have you ever lost consciousness?
2. Have you ever had attacks in which you loose contact with the surrounding?
3. Have you ever had attacks of shaking of the arms or legs which you could not control?
4. Have you ever had attacks in which you fall to the ground with loss of consciousness?
5. Have you ever had attacks in which you fall and bite your tongue?
6. Have you ever had attacks in which you fall and lose control of your bladder?
7. Have you ever had attacks in which you fall and become pale?
8. Have you ever had attacks in which you lose your memory for a short period of time?
9. Have you ever had attacks of strange behaviour and loss of memory?
10. Have you ever had brief attacks of shaking or trembling in one arm or leg or in the face?
11. Have you ever had attacks of tingling or numbness which move up your arm, leg or body?
12. Have you ever had attacks of jerkings which move up your arm, leg or body?
13. Have you ever had attacks in which you lose contact with the surroundings and experience a feeling of unreality or dreaminess?
14. Have you ever had attacks in which you lose contact with the surrounding and experience a sensation in which objects change shape or size?
15. Have you ever had attacks in which you lose contact with the surrounding and experience abnormal visions?
16. Have you ever had attacks in which you lose contact with the surrounding an experience abnormal sounds?
17. Have you ever had attacks in which you lose contact with the surrounding an experience abnormal smells?
18. Have you ever had attacks in which you behave momentarily in a confused fashion?
19. Have you ever had attacks of palpitation?
20. Have you ever been told that you have or had epilepsy or epileptic fits?

Appendix 5: Screening questionnaire as used during the large-scale survey in the community Ecuador study

1. Have you ever had attacks of shaking of the arms or legs which you could not control?
2. Have you ever had attacks in which you fall and become pale?
3. Have you ever lost consciousness?
4. Have you ever had attacks in which you fall with loss of consciousness?
5. Have you ever had attacks in which you fall and bite your tongue?
6. Have you ever had attacks in which you fall and lose control of your bladder?
7. Have you ever had attacks of shaking or trembling in one arm or leg or in the face?
8. Have you ever had attacks in which you lose contact with the surroundings and experience abnormal smells/sensations?
9. Have you ever had a diagnosis of epilepsy or epileptic fits?

Appendix 6: Additional questions used in Zambia to differentiate acute symptomatic seizures from epilepsy (Birbeck et al 2004)

Has such an attack occurred only once ever?

Did this/these attacks occur in a child (7 years or younger) 'only' during an illness with fever?

Did this/these attacks occur 'only' during an acute infection with malaria that resulted in hospital admission?

Asked only if screen positive (any positive response to these questions negates above and makes screen negative)

**Appendix 7: Screening Questions used in a study in rural south India
(Mani et al 1998)**

1. TCS

- (a) Have you ever lost consciousness? If yes
- (b) Were you then said to have had stiffness/jerking of arms and legs on both sides at that time?
- (c) Was there any fall, injury, froth, tongue bite with cut, or incontinence at that time?

2. SPS-Focal motor

When fully conscious, have you ever had repeated episodes of stiffness/jerking of eyelid, mouth, hand or leg on one side only?

3. CPS/Absence

Have you ever had repeated blank spells with

- (a) Staring look or other strange behaviour of which you were not aware?
OR
- (b) Sudden, dull look when you become quiet and unresponsive for a very short time only?

4. Myoclonic jerks

When awake, have you ever had very brief episodes of sudden jerking of arms, legs or head?

Yes/No/Do not know/Not recorded

Questions translated in local language and supplemented by actions

Questions 1 and 3 repeated for fever and hot-water bath
Grammar modified for children below 15 years of age

Appendix 8: Survey questionnaire used in West Bengal, India (Pal et al 1998)

How many children are there in the family between 2 and 18 years of age?

Has any one of them ever had these problems?:

1. Sudden jerking or shaking of arms, legs or face which the child could not stop themselves?
2. Suddenly fell over and lost consciousness?
3. Suddenly fell over and bit their tongue?
- 4.. Experienced any of the following: suddenly lost touch, didn't notice what was going around him, at this time experienced a bodily sensation eg smell which no one else did ?
5. Had khichuni, khach, mrigi or fit? Did anyone say that's what it was?

Appendix 9: Screening questionnaire on neurological symptoms used in Ethiopian Neuroepidemiology Study (Telke-Haimanot et al 1990)

Date	Interviewer	Peasants' Assoc	House No.	Filing No.	
<p>NEUROLOGICAL SYMPTOMS</p> <p>Is there anyone in the household who has or had the following symptoms?</p>					
		NO	YES	NAME (ID CODE)	Number of persons
Severe mental retardation					
Speech disturbance					
Unconsciousness fit, esp., with frothing, biting of tongue or incontinence of urine					
Sudden jerking movements					
Blindness					
Deafness					
Movement disorder of arm					
Movement disorder of leg					
Movement disorder of face					
Walking difficulty					
Numbness feet/hand					
Is there anyone in the household who has leprosy					
For someone with one of these symptoms please fill Questionnaire on neurological symptoms (Figure 3)					
Chronic disease but none of the above symptoms					

FIGURE 2. Questionnaire on neurological symptoms

Appendix 10: Detailed follow-up questionnaire for neurological interview used in Ethiopia (Telke-Haimanot et al 1990)

Name of person	AGE	SEX	Identity of Person	Date	Interviewer	Peasants' Assoc.	House No:	Filing No:

	YES	NO	AGE AT ONSET	SYMPTOMS		IN CASE OF SYMPTOMS	COMMENTS
				Acute	Gradual		
MENTAL DISABILITY						HEAD CIRCUMFRANCE NORMAL <input type="checkbox"/> SMALL <input type="checkbox"/> BIG <input type="checkbox"/> URINARY INCONTINENCE NO <input type="checkbox"/> YES <input type="checkbox"/>	
SPEECH DISTURBANCE						SPEAKS NOT <input type="checkbox"/> A FEW WORDS <input type="checkbox"/> SLURS <input type="checkbox"/> STAMMERS <input type="checkbox"/> STRANGE SPEAKING <input type="checkbox"/>	
UNCONSCIOUS FITS						IF THE PERSON HAS HAD UNCONSCIOUSNESS FITS AND/OR OCCASIONAL SUDDEN JERKY MOVEMENTS, PLEASE COMPLETE THE EPILEPSY FORMS	
SUDDEN JERKY MOVEMENTS	R	L					
BLINDNESS	R	L					
DEAFNESS	R	L					
MOVEMENT DISTURBANCE : ARM	R	L				PARALYSIS <input type="checkbox"/> SHAKING/STRANGE MOVEMENTS <input type="checkbox"/> DEFORMED JOINT SPINE <input type="checkbox"/>	
"_ " : LEG	R	L				<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
"_ " : HEAD/FACE	R	L					
WALKING DIFFICULTY	R	L				CAN NOT WALK <input type="checkbox"/> WALKS WITH AID <input type="checkbox"/> WITHOUT AID BUT WITH DIFFICULTY <input type="checkbox"/> WITH SLIGHT DIFFICULTY <input type="checkbox"/>	
NUMBNESS ARM/HAND	R	L				LEPROSY	
"_ " LEG/FOOT	R	L				YES <input type="checkbox"/> NO <input type="checkbox"/>	

SAME DISEASE/SYMPOM IN RELATIVES: NO <input type="checkbox"/> YES <input type="checkbox"/> IF YES; NAME:
TRAUMA BEFORE ONSET OF SYMPTOMS: : NO <input type="checkbox"/> YES <input type="checkbox"/> IF YES; HEAD <input type="checkbox"/> SPINE <input type="checkbox"/> OTHER
DELIVERY OF THE AFFECTED INDIVIDUAL: HOME <input type="checkbox"/> HOSPITAL <input type="checkbox"/> HEALTH CARE <input type="checkbox"/> KNOWN COMPLICATION: KNOWN COMPLICATION: NO <input type="checkbox"/> YES <input type="checkbox"/>
HISTORY OF EXCESSIV ALCOHOL INTAKE NO <input type="checkbox"/> YES <input type="checkbox"/>
HISTORY OF DIABETES MELLITUS NO <input type="checkbox"/> YES <input type="checkbox"/>

Appendix 11: English version of screening instrument used in the Sicilian Neuro-epidemiology Survey (SNES)

1. Have you (has the child) ever had episode of unconsciousness – that is, not understanding, not hearing, not seeing what was happening around you (him/her), an later not remembering what had happened during the loss of consciousness?

*1=Yes (more than once) *2 = Yes (once) 3 = Never
4 = Don't know 5 = No answer 8 = Not applicable

2. Have you (has the child) ever had uncontrolled movements of your (his/her) legs or arms?

*1=Yes 2 = No 3 = Don't know 4 = No answer 8 = Not applicable

3. Has the child ever stared into space blinking and rolling his/her eyes for a short time?

*1=Yes (more than once) *2 = Yes (once) 3 = Never
4 = Don't know 5 = No answer 8 = Not applicable

4. Has there been serious changes in the way you speak?

*1=Yes 2 = No 3 = Don't know 4 = No answer 8 = Not applicable

5. Has your face, or any part of it, ever been paralysed for more than 24 hours

*1=Yes 2 = No 3 = Don't know 4 = No answer 8 = Not applicable

6. Has your mouth ever drooped for more than 24 hours?

*1=Yes 2 = No 3 = Don't know 4 = No answer 8 = Not applicable

7. Have you ever suffered from paralysis in your arms or legs for more than 24 hours

*1=Yes 2 = No 3 = Don't know 4 = No answer 8 = Not applicable

8. Have you ever had, from more than 24 hours (or less time but more than once), tingling, pain, burning, or loss of feeling in your arms and legs, without anything having happened to you immediately before?

*1=Yes 2 = No 3 = Don't know 4 = No answer 8 = Not applicable

8.1 If yes: Did this occur between May and November 1987

*1=Yes 2 = No 3 = Don't know 8 = Not applicable

9. Have you ever had rigidity or slowness in movement?

*1=Yes 2 = No 3 = Don't know 4 = No answer 8 = Not applicable

10. Have you ever had tremors of your head, arms, or legs that lasted more than 1 day?

*1=Yes 2 = No 3 = Don't know 4 = No answer 8 = Not applicable

Each subject is screened as positive if at least one selected answer is positive (the responses indicated by an "*" in the table. The only exception is for question 8, where each must have a selected answer indicated by an "*" in order for the subject to be screened as positive. In the actual survey, self-reported previous diagnoses of the study diseases were also considered as part of the screening

Appendix 12: English version of LIMOGES epilepsy screening questionnaire used in Tropical countries

SCREENING

For the questions: S1 to S5 (Yes = 1; No = 2; Unknown = 9)

Does the subject have a history of:

S1) Loss of consciousness and / or loss of bladder control and / or foam at the mouth ?
/ ___ /

S2) Absence(s) or sudden lapse(s) of consciousness during a short time ? / ___ /

S3) Involuntary clonic movements or muscular jerks of arm(s) and / or leg(s)
(convulsions) / ___ /
that start suddenly and stop within minutes ?

S4) Does the subject sometimes experience sudden and brief bodily sensations, see or hear things that are not there, or smell strange odours ? / ___ /

S5) Did someone tell the subject that he / she had epilepsy or that he / she already had epileptic fits ? / ___ /

If at least one answer is yes, the subject must be examined by the medical team

S6) To conclude, should the subject be examined by the medical team ? (Yes = 1; No = 2) / ___ /

EPILEPSY CONFIRMATION

EC1) Description of the attack(s) (symptoms), which could be an epileptic seizure:

EC2) Could the attack(s) be related to a particular situation or a medical condition * ?
(Yes = 1; No = 2; Unknown = 9) / ___ /

EC3) If yes, specify:

EC4) Was at least one of these attacks an epileptic seizure ? (Yes = 1; No = 2; Unknown = 9) / ___ /

EC5) If not, what was the probable diagnosis

EC6) If yes, has only one epileptic seizure occurred ? (Yes = 1; No = 2) /___/

*** Examples of particular situations or medical conditions:
Febrile convulsions; seizures occurring only during a metabolic or a toxic condition;
caused by alcohol; anti-malaria drugs; eclampsia ...**

NATURAL HISTORY OF THE SEIZURE DISORDER

N1) Has the subject had any seizure in the last 5 years ? (Yes = 1; No = 2; Unknown = 9)
/___/

N2) Age at the first seizure ? /___/
(During the first 10 days of life = 1; Between 10 days and 6 months = 2;
Between 6 months and 2 years = 3; Between 2 years and 6 years = 4;
Between 6 years and 12 years = 5; Between 12 years and 20 years = 6;
Between 20 years and 40 years = 7; Over 40 years = 8; unknown = 9)

For the questions N3 to N14: (Yes = 1; No = 2; Unknown = 9)

Does the subject have a history of:

N3) Generalized tonic and clonic seizures ? /___/

N4) Generalized myoclonic seizures ? /___/

N5) Generalized atonic seizures ? /___/

N6) Absences ? /___/

N7) Other generalized seizures ? /___/

N8) If yes, specify :

N9) Simple partial seizures ? /___/

N10) Complex partial seizures ? /___/

N11) Partial seizures with a secondary generalization ? /___/

N12) Another type of seizure (difficult to classify) ? /___/

N13) Status epilepticus ? /___/

N14) Several types of seizures ? /___/

If several types of seizures: (questions N15 to N17)

*(Generalized tonic or clonic seizures = 1; Generalized myoclonic seizures = 2;
Generalized atonic seizures = 3; Absences = 4; Simple partial seizures = 5;
Complex partial seizures = 6; Seizures with a secondary generalization = 7; Other
= 9)*

N15) Type of the first seizure ? /___/

N16) Type of the most recent seizures ? /___/

N17) Type of the most frequent seizures ? /___/

N18) Age at the beginning of the second type of seizures ? /___/

*(During the first 10 days of life = 1; Between 10 days and 6 months = 2;
Between 6 months and 2 years = 3; Between 2 years and 6 years = 4;
Between 6 years and 12 years = 5; Between 12 years and 20 years = 6;
Between 20 years and 40 years = 7; Over 40 years = 8; unknown = 9)*

Precipitating Factors: (Yes = 1; No = 2; Unknown = 9)

N19) Emotion ? /___/

N20) Alcohol ? /___/

N21) Sleep ? /___/

N22) Lack of sleep ? /___/

N23) Flashing lights (sun on water or through foliage, television screen or disco) ?
/___/

N24) Hyperventilation ? /___/

N25) Menstruation ? /___/

N26) Stopping the anti-epileptic drugs ? /___//

N27) Other drugs or toxic agents ? /___/

N28) If yes, specify

N29) Do the seizures occur within one hour of awakening ? /___/

N30) If one or several other precipitating factor(s) exist(s), specify:

**Appendix 13: Screening Questions for epilepsy used in the Copenh County study
(Baumann et al 1977)**

- 1a Has anyone in the family, that is, you, your -----, etc., ever had
- Seizures?
 - Convulsions?
 - Epileptic attacks or epilepsy?
 - Fits?
 - Falling out spells?
 - Repeated spells or blackouts with fainting?
 - Repeated spells when they would stare, be confused, or unable to respond to anyone for a few moments?
 - Repeated spells when they were absent-minded or out-of-touch, drooled, or had unusual body movements or jerks?
 - Repeated short spells when they would behave strangely or abnormally?
- 1b. Who was this?
- 1c. Anyone else?
- 2a. Did anyone in the family ever have fever convulsions in early childhood, that is, before the age of six?
- 2b. Who was this? (Anyone else?)
- 2c. How many fever convulsions did ----- have?

If any subpart of question 1a was answered in the affirmative, the person to whom the response pertained was screened positive (as in epilepsy suspect and was designated for a brief neurologic examination and history. Any person reported, from questions 2a through 2c, to have had more than one fever convulsion before the age of six would also be screened positive.

Appendix 14: Initial questionnaire sent home with all schoolchildren attending public or private schools in Clay County, Kentucky (Rose et al 1973)

CHILD HEALTH SURVEY											
CHILD'S FULL NAME						CHILD'S BIRTHDATE <i>Month Day Year</i>			AGE		
COUNTY OF RESIDENCE						SCHOOL					
GRADE <i>(Circle One)</i> Kindergarten 1 2 3 4 5 6 7 8 9 10 11 12											
MAILING ADDRESS											
MOTHER'S FULL NAME						MOTHER'S MAIDEN NAME					
MOTHER'S BIRTHDATE <i>Month Day Year</i>			IS CHILD LIVING WITH MOTHER? <input type="checkbox"/> YES <input type="checkbox"/> NO - Who does the child live with now?								

Please give us a minute of your time to answer the following questions concerning your child.

1. Has this child ever had an epileptic fit, spell, convulsion, blackout, seizure, fever fit, worm fit, or other type of passing out spell?
 Yes No Cannot be certain

2. Indicate the person who completed question No. 1.
 Parent Guardian Nurse Other

3. Indicate the person(s) who helped complete question No. 1.
 Parent Guardian Nurse Other

Appendix 15: Mail questionnaire to assess prevalence of doctor-diagnosed epilepsy in Sydney, Australia (Beran et al 1982)

We would like you to answer the questions below about epilepsy

To help you to do this we have given you a simple definition of “Epilepsy”, and the grounds upon which a person will be considered to have Epilepsy.

This questionnaire has been numbered so that we know who has not returned a completed form. You can be assured that the information given will be kept confidential and you do not need to give your name if you do not want to.

DEFINITION: - The person with Epilepsy has short periods when they black out and may or may not fall down. People often call these periods “turns”, “fits”, “convulsions” or “seizures”. During a “fit” one may have jerky movements, do things one cannot control, or be aware of things one cannot explain.

Other conditions may be mistakenly called Epilepsy and therefore to be considered to have epilepsy you should have had at least 3 “fits” that were diagnosed by a doctor.

QUESTIONS: - please fill in appropriate box or tick the correct answer below: -

1. How many people are there in your household?
2. Do any of these people have epilepsy?
3. If “YES” – how many?
4. Of those who had Epilepsy how many were prescribed drugs?
5. Of those prescribed drugs how many are still taking these drugs?

Appendix 16: Screening questionnaire used in Pakistani study (Aziz et al. 1994)

1. Have you ever lost consciousness?
2. Did you fall?
3. Did you injure yourself?
4. Have you ever had episodes in which you lost contact with your surroundings?
5. Have you ever had uncontrollable shaking of your arms and legs?
6. Have you ever lost control of your bowels or bladder?

Appendix 17: International Classification of Epileptic Seizures (ICES) simplified version

- 1.0 Partial seizures
 - 1.1.0 Simple partial seizures (consciousness not impaired)
 - 1.1.1 With motor signs
 - 1.1.2 With somatosensory or special sensory symptoms
 - 1.1.3 With autonomic symptoms or signs
 - 1.1.4 With psychic symptoms
 - 1.2.0 Complex partial seizures (consciousness impaired)
 - 1.2.1 Simple partial onset followed by impairment of consciousness
 - 1.2.2 With impairment of consciousness at onset
 - 1.3.0 Partial seizures evolving to secondarily generalised seizures
 - 1.3.1 Simple partial seizures evolving to generalised seizures
 - 1.3.2 Complex partial seizure evolving to generalised seizures
 - 1.3.3 Simple partial seizure evolving to complex partial seizures evolving to generalised seizures
- 2.0 Generalised seizures (convulsive or non-convulsive)
 - 2.1 Absence seizures
 - 2.1.1 Typical absence seizures
 - 2.1.2 Atypical absence seizures
 - 2.2 Myoclonic seizures
 - 2.3 Clonic seizures
 - 2.4 Tonic seizures
 - 2.5 Tonic clonic seizures
 - 2.6 Atonic (astatic) seizures
- 3.0 Unclassified epileptic seizures

Appendix 18: The 1989 International Classification of the Epilepsies and Epilepsy Syndromes (ICEES)

1.0 Localisation-related epilepsies and syndromes

- 1.1 Idiopathic
 - 1.1.1 Localisation-related idiopathic benign childhood epilepsy with centrotemporal spikes
 - 1.1.2 Localisation-related idiopathic childhood epilepsy with occipital paroxysms
 - 1.1.3 Primary reading epilepsy

- 1.2 Symptomatic
 - 1.2.1 Chronic progressive epilepsia partialis continua of childhood
 - 1.2.2 Syndromes characterised by seizures with specific modes of precipitation
 - 1.2.3.1 Temporal
 - 1.2.3.2 Frontal
 - 1.2.3.3 Parietal
 - 1.2.3.4 Occipital

- 1.3. Cryptogenic
 - 1.3.3.1 Temporal
 - 1.3.3.2 Frontal
 - 1.3.3.3 Parietal
 - 1.3.3.4 Occipital

2.0 Generalised epilepsies and syndromes

- 2.1.0 Idiopathic age-related onset
 - 2.1.1 Benign myoclonic epilepsy of infancy
 - 2.1.2 Childhood absence epilepsy, juvenile absence epilepsy
 - 2.1.3 Juvenile myoclonic epilepsy
 - 2.1.4 Epilepsies with generalised tonic-clonic seizures on awakening
 - 2.1.5 Syndromes characterised by seizures with specific modes of precipitation
 - 2.1.6 Other idiopathic generalised epilepsies

- 2.2.0 Cryptogenic or symptomatic (in order of age)
 - 2.2.1 West syndrome
 - 2.2.2 Lennox-Gastaut syndrome
 - 2.2.3 Epilepsy with myoclonic atonic seizures
 - 2.2.4 Epilepsy with myoclonic absences

- 2.3.0 Symptomatic
 - 2.3.1 Non-specific aetiology
 - 2.3.1.1 Early myoclonic encephalopathy
 - 2.3.1.2 Early infantile epileptic encephalopathy with suppression burst
 - 2.3.1.3 Other symptomatic generalised epilepsies
 - 2.3.2 Epilepsies due to specific neurological diseases

3.0 Epilepsies undetermined whether focal or generalised

- 3.1.0 with both generalised and focal seizures
 - 3.1.1 Neonatal seizures
 - 3.1.2 Severe myoclonic epilepsy of infancy
 - 3.1.3 Epilepsy with continuous spike waves during slow wave sleep
 - 3.1.4 Acquired epileptic aphasia (Landau Kleffner Syndrome)
 - 3.1.5 Other undetermined epilepsies
 - 3.2.0 Without unequivocal focal or generalised features

4.0 Special Syndromes

- 4.1 Situation related epilepsies
 - 4.1.1 Febrile convulsions
 - 4.1.2 Isolated seizures or status epilepticus
 - 4.1.3 Seizures due to a toxic or metabolic event

**Appendix 19: The Semi-Structured Seizure Classification Interview
(Ottman et al 1990)**

DIAGNOSTIC INTERVIEW

NAME: _____ _____ _____

 first name middle last name

FAMILY #: _____

SUBJECT #: _____

INFORMANT #: _____ [000 IF SELF

DATE OF BIRTH: _____ / _____ / _____

 month day year

TIME BEGAN: _____ : _____ AM PM

ADMINISTERED: 1 = by phone 2 = in person

TODAY'S DATE: _____ / _____ / _____

 month day year

INTRODUCTION TO RESPONDENT:

I am interviewing you because _____ may have had seizures at some time during [your/his/her] life. Some of the questions may not apply to [you/him/her] but I need to ask them of everyone who is interviewed. Thank you for agreeing to participate.

Part IA: SEIZURE AND ETIOLOGY SCREEN

Q1. Has anyone ever told you that when [you/he/she] [were/was] a small child [you/he/she] had a convulsion because of a high fever?

- Yes..... 1
- No..... 0 (GO TO Q2)
- Don't know..... 9 (GO TO Q2)
- Not asked..... 8

- A. How many seizures did [you/he/she] have because of a high fever? _____
[DK=-1; NOT ASKED=-8]
- B. How old [were/was] [you/he/she] [the first time]? _____
[DK=-1; NOT ASKED=-8; UP TO AGE 1=01] age
- C. **[IF SUBJECT HAD MORE THAN ONE FEBRILE SZ.]...**
How old [were/was] [you/he/she] the last time? _____
age

Q2. [Other than the seizure[s] [you/he/she] had as a small child because of a high fever [have you ever had/(has/did)(he/she) ever (had/have)] any of the following...**[ASK ALL OF A-H]**

	YES	POSSIBLE	NO	DON'T KNOW	NOT ASKED
A. epilepsy or a seizure disorder?	1	2	0	9	8
B. a seizure or convulsion that wasn't caused by epilepsy?	1	2	0	9	8
C. uncontrolled movements of part or all of [your/his/her] body such as twitching, jerking, shaking or going limp?	1	2	0	9	8
D. [IF SUBJECT HAS EPILEPSY, ASK...] a change in [your/his/her] mental state or awareness of [your/his/her] surroundings? [IF SUBJECT DOES NOT HAVE EPILEPSY, ASK...] a change in [your/his/her] mental state or awareness of [your/his/her] surroundings for no apparent reason?	1	2	0	9	8
E. [IF INTERVIEWING A PARENT...] , [When he/she was a small child], [Does/did] [he/she] seem to daydream or stare into space more than other children?	1	2	0	9	8
F. Shortly after [you/he/she] [wake(s)/woke] up, either in the morning or after a nap, [have/has] [you/he/she] ever noticed unusual movements such as dropping things or things suddenly "flying" from [your/his/her] hands or uncontrollable <u>jerking</u> or <u>clumsiness</u> ?	1	2	0	9	8
G. I'm also interested in [your/his/her] responses to certain types of lighting. Have [you/he/she] ever been bothered by or noticed any unusual feelings when exposed to strobe lights, video games, light shining through trees, or light reflecting off of snow or ice?	1	2	0	9	8
H. any other type of repeated unusual spells?	1	2	0	9	8

[IF YES OR POSSIBLE TO ANY OF Q2 A-H, SAY THE FOLLOWING AND THEN GO TO Q3...

"I'm going to ask you in detail about [each of] the event(s) you just told me [you/he/she] [have/has] experienced, but first I need to ask you some questions about [your/his/her] general medical history."

[IF NO TO Q2 A-H...

1. IF SUBJECT IS 16 YEARS OLD (NOW OR AT DEATH), SKIP TO Q6 PAGE 9 AND ASK ALCOHOL QUESTIONS, THEN TERMINATE INTERVIEW

2. IF SUBJECT IS <16 YEARS OLD (NOW OR AT DEATH), SKIP TO Q11 PAGE 39 AND THEN TERMINATE INTERVIEW.]

Q3. A. [Other than the seizures [you/he/she] had because of a high fever], how many [seizures/of these events] would you say [you/he/she] [have/has] had in [your/his/her] lifetime? Would you say ...

One.....	1
Two.....	2
Three.....	3
Four or more.....	4
Don't know.....	9
Not asked.....	8

B. How old [were/was] [you/he/she] when [you/he/she] had the [first] [seizure/of these events] [that wasn't caused by a high fever]? _____ age _____
[DK=-1; NOT ASKED=-8]

Part IB: DETAILED RISK FACTOR HISTORY

We are interested in certain aspects of [your/his/her] medical history that are sometimes related to seizures. We need to ask these questions of everyone so we might have to ask you to repeat some of the things you already told us.

Q1. Before [your/his/her] [first] seizure [that wasn't caused by a high fever] did [you/he/she] ever have a serious head injury?

- Yes..... 1
- No..... 0 (GO TO Q2)
- Don't know..... 9 (GO TO Q2)
- Not asked..... 8

A. How many serious head injuries [have/has/did] [you/he/she] [had/have]?
[DK=-1; NOT ASKED=-8] _____
[IF MORE THAN ONE] I'd like to ask some questions about each of these serious head injuries -
Let's start with the earliest one.

No. of injury: _____
[ENTER 0 IF NO HEAD INJURIES]

B. How old [were/was] [you/he/she] when it happened? _____
[DK=-1; NOT ASKED=-8] age

C. What happened to cause the injury? **[RECORD VERBATIM]**

D. Did [you/he/she] lose consciousness, even for a short time, because of the injury?

- Yes..... 1
- No..... 0 (GO TO F)
- Don't know..... 9 (GO TO F)
- Not asked..... 8

E. How long [were/was] [you/he/she] unconscious? Would you say...

- Less than a minute... 1
- 1-15 minutes..... 2
- 16-30 minutes..... 3
- More than 30 min.... 4
- Don't know..... 9
- Not asked..... 8

F. Were you told that [you/he/she] had a skull fracture when [you/he/she] had the injury?

- Yes..... 1
- No..... 0
- Don't know..... 9
- Not asked..... 8

- G. Did [you/he/she] spend the night in a hospital because of the head injury?
 Yes..... 1
 No..... 0 (GO TO J)
 Don't know..... 9 (GO TO J)
 Not asked..... 8
- H. Would you say the **main reason** [you/he/she] spent the night in the hospital was...
 The head injury..... 1
 Other injuries..... 0
 Don't know..... 9
 Not asked..... 8
- I. How long [were/was] [you/he/she] in the hospital?
[RECORD VERBATIM AND THEN CODE]
 Overnight..... 1
 Less than 1 week..... 2
 1 week or more..... 3
 Don't know..... 9
 Not asked..... 8
- J. Did [you/he/she] have a seizure within 7 days after the injury?
 Yes..... 1
 No..... 0
 Don't know..... 9
 Not asked..... 8

[IF SUBJECT HAS HAD ADDITIONAL HEAD INJURIES, FILL OUT ADDITIONAL HEAD INJURY FORMS AND THEN GO TO Q2; OTHERWISE GO DIRECTLY TO Q2 ON THE NEXT PAGE]

Q2. Were you ever told that [you/he/she] had a stroke, that is, cerebral thrombosis or cerebral hemorrhage?

- Yes..... 1
- No..... 0 (GO TO Q3)
- Don't know..... 9 (GO TO Q3)
- Not asked..... 8

A. How many times did that happen to [you/him/her]? _____

B. How old [were/was] [you/he/she] when it happened [the first time]?

 Age

C. Did [you/he/she] have a seizure within seven days after [any of] the stroke[s]?

- Yes..... 1
- No..... 0
- Don't know..... 9
- Not asked..... 8

Q3. [Have/Has/Did] [you/he/she] ever [had/have] a brain tumor?

- Yes..... 1
- No..... 0 (GO TO Q4)
- Don't know..... 9 (GO TO Q4)
- Not asked..... 8

A. How old [were/was] [you/he/she] when [you/he/she] first found out about it?

 Age

B. Were you told that [any of] [your/his/her] seizure[s] [were/was] caused by the brain tumor?

- Yes..... 1
- No..... 0
- Don't know..... 9
- Not asked..... 8

Q4. [Have/Has/Did] [you/he/she] ever [had/have] brain surgery?

- Yes..... 1
- No..... 0 (GO TO Q5)
- Don't know..... 9 (GO TO Q5)
- Not asked..... 8

A. What was the reason for the surgery?

- Treatment for epilepsy..... 1
- Brain tumor..... 2

Head injury.....	3
Stroke, hemorrhage, blood clot.....	4
Hydrocephalus (shunt operation for water on the brain)....	5
Other	6
(specify)	
Don't know.....	9
Not asked.....	8

B. How old [were/was] [you/he/she] when [you/he/she] had the surgery?

age

C. Did [you/he/she] have any seizures **before** the surgery?

Yes.....	1
No.....	0
Don't know.....	9
Not asked.....	8

D. Did [you/he/she] have a seizure within seven days **after** the surgery?

Yes.....	1
No.....	0
Don't know.....	9
Not asked.....	8

Q5. [Have/Has/Did] [you/he/she] ever [had/have] an infection of the brain, such as spinal meningitis or encephalitis?

Yes.....	1
No.....	0 (GO TO Q6)
Don't know.....	9 (GO TO Q6)
Not asked.....	8

A. What type of infection did [you/he/she] have? **[RECORD VERBATIM]**

B. How old [were/was] [you/he/she] when [you/he/she] first had it?

age

C. Did [you/he/she] have a seizure **while** [you/he/she] had the infection?

Yes.....	1
No.....	0
Don't know.....	9
Not asked.....	8

[GO TO Q10 PAGE 12 IF SUBJECT IS 15 YEARS OLD NOW OR AT AGE OF DEATH]

The next questions are about drinking alcohol, such as beer; wine including champagne or wine coolers; liquors such as whiskey, rum, gin, vodka, bourbon, scotch, or liqueurs; and also any other type of alcohol.

- | | |
|--|--|
| Q6A. [Over the past 12 months/During the last year of his/her life], did [you/he/she] have at least 12 drinks of <u>any</u> kind of alcohol? | Yes..... 1 [GO TO Q7A]
No..... 0
Don't know..... 9
Not asked..... 8 |
| B. Was there ever any one year period in [your/his/her] entire life when [you/he/she] had at least 12 drinks of <u>any</u> kind of alcohol? | Yes..... 1 [GO TO Q8A]
No..... 0 [GO TO Q10]
Don't know..... 9 [GO TO Q10]
Not asked..... 8 |

People report drinking different amounts of alcohol in different patterns. The next few questions are about drinking beer, wine, liquor, or **any** kind of alcohol [**during the last 12 months/during the last 12 months of his/her life**].

- | | |
|---|---|
| Q7A. During the last 12 months [of his/her life], about how often did [you/he/she] USUALLY drink <u>any</u> alcohol? Would you say... | Every day..... 1
Not every day, but at least once a week..... 2
Less than once a week, but at least once a month..... 3
Less than once a month..... 4
Don't know..... 9
Not asked..... 8 |
|---|---|

- B. On the days when [you/he/she] drank alcohol in the last 12 months [of his/her life], about how many drinks did [you/he/she] USUALLY drink in a single day? Consider a "drink" to be a cocktail containing one ounce of hard liquor, or one 12-oz. beer, or one 6-oz. glass of wine.

_____ # of drinks

- C. You just told me how much and how often [you/he/she] drank in the last 12 months [of his/her life]. For how long [have/has/did] [you/he/she] [been] drink[ing] about this amount with this frequency? **[RECORD VERBATIM, THEN CODE]**

_____ week(s)
_____ month(s)
_____ year(s)

- D. During the last 12 months [of his/her life], about how often did [you/he/she] have five or more drinks of any type of alcohol in a single day? Would you say...

Every day.....	1
Not every day, but at least once a week.....	2
Less than once a week, but at least once a month.....	3
Less than once a month.....	4
Not at all.....	5

	Don't know.....	9
	Not asked.....	8
E.	[Has/Was] there ever [been] a time in [your/his/her] life when [you/he/she] drank more than [you/he/she] did during the last 12 months [of his/her life]?	Yes..... 1 No..... 0 [GO TO Q9] Don't know..... 9 [GO TO Q9] Not asked..... 8
Q8A.	In [your/his/her] entire life, when [you/he/she] drank the <u>most</u> , about how often did [you/he/she] USUALLY drink <u>any</u> beer, wine, or liquor? Would you say...	Every day..... 1 Not every day, but at least once a week..... 2 Less than once a week, but at least once a month..... 3 Less than once a month..... 4 Don't know..... 9 Not asked..... 8
B.	During that time when [you/he/she] drank the most, about how many drinks did [you/he/she] USUALLY drink in a single day? (Please include all types of alcohol if [you/he/she] usually drank more than one type of alcohol on a TYPICAL day). Consider a "drink" to be a cocktail containing one ounce of hard liquor, or one 12-oz. beer, or one 6-oz. glass of wine.	<u> </u> <u> </u> # of drinks
C.	During that time when [you/he/she] drank the most, what was the LARGEST TOTAL # of drinks you can recall [him/her] drinking in a single day? (Please include all types of alcohol if [you/he/she] usually drank more than one type of alcohol on a TYPICAL day).	<u> </u> <u> </u> # of drinks
D.	About how often did [you/he/she] drink (amount in Q8C) in a single day? Would you say...	Every day..... 1 Not every day, but at least once a week..... 2 Less than once a week, but at least once a month..... 3 Less than once a month..... 4 Don't know..... 9 Not asked..... 8
E.	You just told me how much and how often [you/he/she] drank the most. About how old [were/was] [you/he/she] when [you/he/she] began drinking this way?	<u> </u> <u> </u> age

F. For how long did [you/he/she] drink this way?
[RECORD VERBATIM, THEN CODE]

_____ week(s)

_____ month(s)

_____ year(s)

**[IF NO TO SCREENING BOX Q'S 2A-H ON PAGE 2, SKIP TO Q11 PAGE 39 AND THEN
TERMINATE INTERVIEW]**

Q9. [Before [your/his/her] epilepsy started] did [you/he/she] ever have a seizure within 48 hours after drinking what you thought was a large quantity of alcohol? Yes..... 1
 No..... 0 (GO TO Q10)
 Don't know..... 9 (GO TO Q10)
 Not asked..... 8

A. How many times did [you/he/she] have a seizure after drinking a large quantity of alcohol? Would you say... One time..... 1
 Two times..... 2
 Three times 3
 Four or more times... 4
 Don't know..... 9
 Not asked..... 8

B. How old [were/was] [you/he/she] [when/the first time] [you/he/she] had a seizure after drinking a large quantity of alcohol? _____
 age
 [DK=-1;NOT ASKED=-8]

C. How many drinks did [you/he/she] have before [you/he/she] had the seizure [the first time]? _____
 # of drinks
 [DK=-1;NOT ASKED=-8]

D. How many hours after drinking the last drink did the seizure occur? _____
 Hours

**[IF NO TO SCREENING BOX Q'S 2A-H ON PAGE 2, SKIP TO Q11 PAGE 34 AND THEN TERMINATE INTERVIEW]
 [GO TO Q11 ON THE NEXT PAGE IF SUBJECT IS A FEMALE, 12 YEARS OF AGE NOW (OR AT DEATH), OR IF SUBJECT IS MALE]**

Q10. **IF SUBJECT [IS/WAS] FEMALE, 12 YEARS OF AGE:**
 [Have/Has/Was] [you/she] ever [been] pregnant? Yes.....1
 No.....0 (GOTOQ11)
 Not asked.....8

A. How many times [were you/was she] pregnant? _____

B. Did [you/she] ever have toxemia, preeclampsia, or eclampsia -- that is, a serious illness of pregnancy involving high blood pressure and protein in the urine? Yes.....1
 No.....0
 Don't know.....9 (GOTOQ11)
 Not asked.....8

C. How old [were/was] [you/she] when that happened? _____
 [DK = -1, NOT ASKED = -8] age

D. Did [you/she] have any seizures because of this illness? Yes.....1
 No.....0
 Don't know.....9
 Not asked.....8

Q11. [Have/Has/Did] [you/he/she] ever [had/have] any of the following?...

	Yes	No	DK	Not Asked	How old [were/was] [you/he/she] when it began?
A. AVM (arterial venous malformation)	1	0	9	8	_____
B. Cerebral Palsy	1	0	9	8	_____
C. Polio	1	0	9	8	_____
D. Multiple Sclerosis	1	0	9	8	_____
E. Tuberous Sclerosis	1	0	9	8	_____
F. Fragile X Syndrome	1	0	9	8	_____
G. Diabetes	1	0	9	8	_____
H. A coma for any reason? Please explain.	1	0	9	8	_____
I. [Have/Has/Did] [you/he/she] ever [had/have] any other medical problems you think we should know about? Please explain. [PROBE FOR SPECIFICS AND AGE AT ONSET FOR EACH PROBLEM]					

Now, I'd like to ask you specifically about the types of seizures [you/he/she] [have/has] had.

Part IIA: GRAND MAL SEIZURES

Q1. [Have/Has/Did] [you/he/she] ever [had/have] any big seizures or grand mal seizures where [you/he/she] lost consciousness and [your/his/her] whole body shook?

- Yes..... 1
- No..... 0 (GO TO IIB-PG.22)
- Don't know..... 9 (GO TO IIB-PG.22)
- Not asked..... 8

Q2. How many big seizures [have/has/did] [you/he/she] [had/have] in [your/his/her] lifetime? Would you say...

- One..... 1
- Two..... 2
- Three..... 3
- Four or more..... 4
- Don't know..... 9
- Not asked..... 8

Q3. How old [were/was] [you/he/she] when it happened [the first time]? _____
age

[IF ONLY ONE BIG SEIZURE, GO TO Q6]

Q4. In the [last year/year before death], about how many grand mal seizures [have/has/did] [you/he/she] [had/have]? Would you say...

- None..... 1
- One..... 2
- 2-6..... 3
- 6-12..... 4
- More than 12..... 5
- Don't Know..... 9
- Not asked..... 8

Q5. When did [you/he/she] have the last grand mal seizure?
[DK=99/9999 FOR MONTH AND YEAR; NOT ASKED=88/8888 FOR MONTH AND YEAR]

_____ / _____
month year

 Age

Q6. [Have/Did] [your/his/her] grand mal seizure[s] occur[ed]...

- Only** while [you/he/she] [were/was] **asleep**.....1 **(GO TO Q7)**
- Only** while [you/he/she] [were/was] **awake**.....2
- Both** while awake and during sleep.....3
- Don't know.....9
- Not asked.....8

A. [Of the grand mal seizures that (you/he/she) had while awake], [have/did] [they/it] [**usually**] [occurred/occur] shortly after waking up, either in the morning or after a nap?

- Yes..... 1
- No..... 0 **(GO TO Q7)**
- Don't know..... 9 **(GO TO Q7)**
- Not asked..... 8

B. How many minutes after waking up would you say the grand mal seizure(s) [usually] occurred?

- Would you say...
- Less than 15 min..... 1
 - 15-30 minutes..... 2
 - 31-45 minutes..... 3
 - 46-60 minutes..... 4
 - More than 60 min..... 5
 - Don't know..... 9
 - Not asked..... 8

Q7. In your own words, can you describe:

- A. How [you/he/she] [have/has] [usually] felt **before** the big seizure[s] started?
[RECORD VERBATIM] Anything else?

**[IF SUBJECT DOES NOT KNOW WHAT HAPPENS BEFORE BIG SEIZURES,
SKIP TO 7B ON THE NEXT PAGE]**

How long [did/does] [you/he/she] feel that way before the seizure[s] start[s/ed]?
Would you say...

- Less than 1 min..... 1
- 1-5 minutes..... 2
- 6-10 minutes..... 3
- More than 10 min..... 4
- Don't know..... 9
- Not asked..... 8

[ASK (2) IF SUBJECT REPORTS SELF OR SUBJECT BEING DIZZY OR LIGHT-HEADED; OTHERWISE GO TO B]

(2) What do you mean by [dizzy/light-headed]?
[RECORD VERBATIM]

Anything else?

- B. How [have/has/did] [you/he/she] [usually] [felt/feel] or what happen[s/ed] **during** the big seizure[s]? **[RECORD VERBATIM]** Anything else?
- C. How [have/has/did] [you/he/she] [felt/feel] or what happen[s/ed] afterwards?
[RECORD VERBATIM] Anything else?

Just to make sure we get the same information on everybody, let me ask a few specific questions...

Q8. A. Before the seizure[s] start[s/ed], [have/has/did] [you/he/she] [usually] [had/have] jerking, shaking, or uncontrolled body movements on only one side of the body?

- Yes..... 1
- No..... 0 (GO TO B)
- Don't know..... 9 (GO TO B)
- Not asked..... 8

[IF SUBJECT HAS HAD ONLY ONE BIG SEIZURE, GO TO (2)]

- (1) Is it always the **same** side? Yes..... 1
 No..... 0 [GO TO (3)]
 Don't know..... 9 [GO TO (3)]
 Not asked..... 8
- (2) Which side?
 Left side..... 1
 Right side..... 2
 One side but
 DK which side..... 3
 Not asked..... 8

(3) Which parts of the body [are/were] involved?
[RECORD VERBATIM]

(4) What [are/were] the movements like? **[RECORD VERBATIM]**

B. Before the seizure[s] start[s/ed], [do/does/did] [you/he/she] [usually] have numbness, tingling, or other unusual feelings on only one side of the body?

- Yes..... 1
- No..... 0 (GO TO C)
- Don't know..... 9 (GO TO C)
- Not asked..... 8

[IF SUBJECT HAS HAD ONLY ONE BIG SEIZURE, GO TO (2)]

- Is it always the **same** side? Yes..... 1
 No..... 0 [GO TO (3)]
 Don't know..... 9 [GO TO (3)]
 Not asked..... 8
- (2) Which side?
 Left side..... 1
 Right side..... 2
 One side but
 DK which side..... 3
 Not asked..... 8

(3) Which parts of the body [are/were] involved? **[RECORD VERBATIM]**

(4) What [are/were] the **feelings** like? **[RECORD VERBATIM]**

C. **Before** the seizure[s] start[s/ed] [do/does/did] [you/he/she] [usually] have jerking, twitching, or uncontrolled body movements on both sides of the body? **[PROBE FOR MYOCLONIC JERKS PRECEDING GRAND MAL SEIZURES]**

Yes..... 1
No..... 0 **(GO TO D)**
Don't know..... 9 **(GO TO D)**
Not asked..... 8

(1) Which parts of the body [are/were] involved?
[RECORD VERBATIM]

(2) What [are/were] the movements like? **[RECORD VERBATIM]**

D. **Before** the seizure[s] start[s/ed], [do/does/did] [you/he/she] [usually] have an unusual feeling in the stomach or chest?

Yes..... 1
No..... 0 **(GO TO E)**
Don't know..... 9 **(GO TO E)**
Not asked..... 8

(1) What [is/was] the feeling? **[RECORD VERBATIM]**

E. **Before** the seizure[s] start[s/ed], [do/does/did] [you/he/she] [usually] experience an unusual **taste** or **smell**?

Yes..... 1
No..... 0 **(GO TO F)**
Don't know..... 9 **(GO TO F)**
Not asked..... 8

(1) What [is/was] the taste or smell? **[RECORD VERBATIM]**

F. **Before** the seizure[s] start[s/ed], [do/does/did] [you/he/she] [usually] **hear** any unusual sounds, or have any change in your **hearing**?

Yes..... 1
No..... 0 **(GO TO G)**
Don't know..... 9 **(GO TO G)**
Not asked..... 8

(1) What [is/was] the sound or change in hearing? **[RECORD VERBATIM]**

G. **Before** the seizure[s] start[s/ed], [do/does/did] [you/he/she] [usually] see anything unusual, or have any change in your **vision**?

Yes..... 1
No..... 0 (GO TO H)
Don't know..... 9 (GO TO H)
Not asked..... 8

(1) What [did/do] [you/he/she] see or what was the change in vision?
[RECORD VERBATIM]

H. [Do/Does/Did] [you/he/she] [usually] have any other warning (or aura) that [a/the] big seizure [is/was] about to happen?

Yes..... 1
No..... 0 (GO TO Q9)
Don't Know..... 9 (GO TO Q9)
Not asked..... 8

(1) What [is/was] the warning or aura like? **[RECORD VERBATIM]**
Anything else?

Q9. A. **After** [a/the] seizure, [do/does/did] [you/he/she] [usually] feel **confused** or **mixed up**?

Yes..... 1
No..... 0 (GO TO B)
Don't know..... 9 (GO TO B)
Not asked..... 8

(1) How long [do/does/did] [you/he/she] feel that way? Would you say ...

Less than 1 min..... 1
1-5 minutes..... 2
More than 5 mins..... 3
Don't know..... 9
Not asked..... 8

B. [Do/Does/Did] [you/he/she] [usually] feel **sleepy or drowsy afterwards**?

Yes..... 1
No..... 0 (GO TO C)
Don't know..... 9 (GO TO C)
Not asked..... 8

(1) How long [do/does/did] [you/he/she] feel that way? Would you say ...

- Less than 1 min..... 1
- 1-5 mins..... 2
- More than 5 mins.... 3
- Don't know..... 9
- Not asked..... 8

C. **After** the seizure [has] ended, [do/does/did] [you/he/she] **remember** what happened during the seizure [your/his/her]self, or [do/does/did] [you/he/she] learn about it from someone else?

- Learn from someone else..... 1
- Remember..... 0
- Sometimes remember, sometimes don't.... 2
- Don't know..... 9
- Not asked..... 8

D. **After** the seizure, [do/has/did] [you/he/she] ever [have/had] **numbness or tingling** on part or all of **one side** of the body?

- Yes..... 1
- No..... 0 (GO TO E)
- Don't know..... 9 (GO TO E)
- Not asked..... 8

[IF SUBJECT HAS HAD ONLY ONE BIG SEIZURE, GO TO (2)]

(1) Is it always the **same side**? Yes..... 1
 No..... 0 (GO TO E)
 Don't know..... 9 (GO TO E)
 Not asked..... 8

(2) Which side? Left side..... 1
 Right side..... 2
 One side but
 DK which side..... 3
 Not asked..... 8

E. **Afterwards**, [do/has/did] [you/he/she] ever [have/had] **weakness** on part or all of **one side** of the body?

- Yes..... 1
- No..... 0 (GO TO F)
- Don't know..... 9 (GO TO F)
- Not asked..... 8

[IF SUBJECT HAS HAD ONLY ONE BIG SEIZURE, GO TO (2)]

(1) Is it always the **same side**? Yes..... 1

- | | | |
|-----------------|--------------------|-------------|
| | No..... | 0 (GO TO F) |
| | Don't know..... | 9 (GO TO F) |
| | Not asked..... | 8 |
| (2) Which side? | Left side..... | 1 |
| | Right side..... | 2 |
| One side, but | DK which side..... | 3 |
| | Not asked..... | 8 |

- F. Other than what I've asked, [have/has/did] [you/he/she] experience[d] any other problems **after** [the] big seizure[s]?
- | | | |
|--|-----------------|-------------|
| | Yes..... | 1 |
| | No..... | 0 (GO TO G) |
| | Don't know..... | 9 (GO TO G) |
| | Not asked..... | 8 |

- (1) What were the problems? [RECORD VERBATIM]

G. [IF SUBJECT HAS ANY WARNING/AURA INCLUDING UNILATERAL MOTOR SYMPTOMS OR ANY SENSORY SYMPTOMS...]

- H. [Do/Does/Did] [you/he/she] ever get the warning(s) of _____ that you described previously, **without** it leading to a grand mal seizure?
- | | | |
|--|-----------------|---|
| | Yes..... | 1 |
| | No..... | 0 |
| | Don't know..... | 9 |
| | Not asked..... | 8 |

[IF YES, BE SURE TO RECORD THIS AURA AS A SEPARATE SMALL SEIZURE IN PART IIB - NEXT PAGE]

Part IIB: SMALL SEIZURES

Now I'm going to ask you about each of the smaller seizures or events that you told me [you/he/she] [have/has] experienced.

Q1. [Have/Has/Did] [you/he/she] ever [had/have] any small spells [other than the grand mal seizures]? [EVEN IF PERSON ANSWERS NO OR DK TO THIS QUESTION, PROCEED WITH THE WHOLE SMALL SEIZURE SECTION IF THEY ANSWERED YES OR POSSIBLE TO Q2C-H IN THE SCREENING BOX (PAGE 2) OR Q9G ON PAGE 21]

- Yes..... 1
- No..... 0 (GOTO IIC-PG30)
- Don't know..... 9 (GOTO IIC-PG34)
- Not asked..... 8

I would like to determine how many different types of small spells [you/he/she] [have/has] had and get an accurate description of each type. I'm going to start by asking a series of questions about the small spell [you/he/she] had most recently or the one that you can describe the best. After we finish talking about that spell, we'll go back and discuss other spells [you/he/she] may have had.

A. When was the last time [you/he/she] had a small spell?
[DK=99/9999 FOR MONTH AND YEAR; NOT ASKED=88/8888 FOR MONTH AND YEAR]

_____ age

_____ / _____
month year

Q2. Thinking back to that most recent spell or to the one that you can describe the best, can you tell me in your own words ...

A. How [you/he/she] felt just **before** the spell started? **[RECORD VERBATIM]**

Anything else?

B. How did [you/he/she] feel, what happened, or what were you told [you/he/she] did **during** this spell? **[RECORD VERBATIM]**

Anything else?

C. How did [you/he/she] feel, what happened, or what were you told [you/he/she] did **afterwards**? **[RECORD VERBATIM]**

Anything else?

To make sure I've covered everything, I'd like to ask you some specific questions about the spell you just described to me.

Q3. Would you say this spell was longer, shorter, or about the same length as a TV commercial?

- Longer..... 1
- Shorter..... 2
- The same length..... 3
- Don't know..... 9
- Not asked..... 8

A. About how long would you say that was..

- Less than 15 sec..... 1
- 15-30 seconds..... 2
- 30 sec to 1 min..... 3
- 1-2 minutes..... 4
- More than 2 min..... 5
- Don't know..... 9
- Not asked..... 8

Q4. During this last spell, which of the following best describes [your/his/her] awareness of the surroundings?

- Fully aware..... 1
- Fully unaware..... 2
- Somewhat aware, but less aware than usual..... 3
- Don't know..... 9
- Not asked..... 8

A. During this spell, [were/was] [you/he/she] able to **function** as [you/he/she] normally [do/does/did]?

- Yes..... 1
- No..... 0
- Don't know..... 9
- Not asked..... 8

B. During this spell, [were/was] [you/he/she] able to **communicate** as [you/he/she] normally [do/does/did]?

- Yes..... 1
- No..... 0
- Don't know..... 9
- Not asked..... 8

- C. After the spell was over, did [you/he/she] remember what happened **during the spell [yourself/himself/herself]**, or did [you/he/she] learn about it from someone else?

Someone else..... 1
 Remember..... 0
 Don't know..... 9
 Not asked..... 8

[IF SUBJECT REMEMBERED WHAT HAPPENED DURING THE SPELL (WAS FULLY AWARE), SKIP TO Q5]

- D. [Have/Has/Did] [you/he/she] ever [had/have] a spell with similar symptoms except that [you/he/she] **remained fully aware** of the surroundings?

Yes..... 1
 No..... 0
 Don't know..... 9
 Not asked..... 8

[IF YES, BE SURE TO CONSIDER THIS A SEPARATE SEIZURE TYPE AND FILL OUT AN EXTRA SMALL SEIZURE FORM]

- Q5.** During this spell, did any parts of [your/his/her] body move uncontrollably?
[PROBE FOR FOCAL MOTOR ACTIVITY]

Yes..... 1
 No..... 0 (GO TO Q6)
 Don't know..... 9 (GO TO Q6)
 Not asked..... 8

- A. Which parts of the body were involved? **[RECORD VERBATIM]**

- B. What were the movements like? **[RECORD VERBATIM]**

- C. Was this on only **one side**? Yes..... 1
 No..... 0 (GO TO Q6)
 Don't know..... 9 (GO TO Q6)
 Not asked..... 8

- (1) Which side? Left side..... 1
 Right side..... 2
 One side,
 but DK which side.... 3
 Not asked..... 8

- (2) [Have/Has/Did] [you/he/she] ever [had/have] a similar spell with movements on the opposite side?

Yes..... 1
 No..... 0
 Don't know..... 9
 Not asked..... 8

Q6. During this spell, did any parts of [your/his/her] body jerk suddenly and unexpectedly?

Yes..... 1
No..... 0 (GO TO Q7)
Don't know..... 9 (GO TO Q7)
Not asked..... 8

A. Which parts of the body were involved? [RECORD VERBATIM]

B. What was the jerking like? [RECORD VERBATIM]

C. Was this on only one side? Yes..... 1
No..... 0 (GO TO D)
Don't know..... 9 (GO TO D)
Not asked..... 8

(1) Which side? Left side..... 1
Right side..... 2
One side,
but DK which side.... 3
Not asked..... 8

(2) [Have/Has/Did] [you/he/she] ever [had/have] a similar spell with jerking on the opposite side?
Yes..... 1
No..... 0
Don't know..... 9
Not asked..... 8

D. Would you say the jerking felt like an electric shock going through [your/his/her] body?

Yes..... 1
No..... 0
Don't know..... 9
Not asked..... 8

E. [Has/Did] this type of spell usually [occurred/occur] shortly after [you/he/she] [wake[s]/woke] up, either in the morning or after a nap?

Yes..... 1 (GO TO G)
No..... 0
Don't know..... 9
Not asked..... 8

F. [Does/Has/Did] this type of spell [occur[ed]] **only** when [you/he/she] [are/is/were/was] going to sleep?

Yes..... 1
No..... 0
Don't know..... 9
Not asked..... 8

G. Did this type of spell ever occur as a result of lights shining in [your/his/her] eyes -- for example, strobe lights, video games, reflections, or sun glare?

Yes..... 1
No..... 0
Don't know..... 9
Not asked..... 8

Q7. During this spell, did part of [your/his/her] body suddenly go limp, causing [you/him/her] to fall or drop things?

Yes..... 1
No..... 0 (GO TO D)
Don't know..... 9 (GO TO D)
Not asked..... 8

A. Which part of the body was involved? [RECORD VERBATIM]

B. What was the limpness like? [RECORD VERBATIM]

C. Was this on only **one side**?

Yes..... 1
No..... 0 (GO TO D)
Don't know..... 9 (GO TO D)
Not asked..... 8

(1) Which side?

Left side..... 1
Right side..... 2
One side,
but DK which side... 3
Not asked..... 8

(2) [Have/Has/Did] [you/he/she] ever [had/have] a similar spell where part of the body went limp on the opposite side?

Yes..... 1
No..... 0
Don't know..... 9
Not asked..... 8

D. [Other than during a grand mal seizure] During a spell like this did [your/his/her] **whole** body ever go limp? **[IF YES, RECORD VERBATIM DESCRIPTION AND PROBE FOR ATONIC SEIZURES]**

Q8. During this spell, did [you/he/she] behave in unusual ways such as smacking [your/his/her] lips, touching [your/his/her] clothes, or doing any other unusual things without intending to?

Yes..... 1
No..... 0 (GO TO Q9)
Don't know..... 9 (GO TO Q9)
Not asked..... 8

A. What did [you/he/she] do? **[RECORD VERBATIM]**

Q9. Did [your/his/her] eyelids flutter during this spell?

Yes..... 1
No..... 0
Don't know..... 9
Not asked..... 8

Q10. During this spell, did [you/he/she] have an unusual feeling in the stomach or chest?

Yes..... 1
No..... 0 (GO TO Q11)
Don't know..... 9 (GO TO Q11)
Not asked..... 8

(1) What was the feeling? **[RECORD VERBATIM]**

- Q11.** During this spell, did [you/he/she] experience an unusual **taste** or **smell**?
- Yes..... 1
 No..... 0 (GO TO Q12)
 Don't know..... 9 (GO TO Q12)
 Not asked..... 8

A. What was the taste or smell? **[RECORD VERBATIM]**

- Q12.** During this spell, did [you/he/she] **hear** any unusual sounds, or have any change in your **hearing**?
- Yes..... 1
 No..... 0 (GO TO Q13)
 Don't know..... 9 (GO TO Q13)
 Not asked..... 8

A. What was the sound or change in hearing? **[RECORD VERBATIM]**

- Q13.** During this spell, did [you/he/she] **see** anything unusual, or have any change in your **vision**?
- Yes..... 1
 No..... 0 (GO TO Q14)
 Don't know..... 9 (GO TO Q14)
 Not asked..... 8

A. What did [you/he/she] see or what was the change in vision? **[RECORD VERBATIM]**

- Q14.** **Afterwards**, did [you/he/she] feel confused or mixed up?
- Yes..... 1
 No..... 0 (GO TO B)
 Don't know..... 9 (GO TO B)
 Not asked..... 8

(1) How long did [you/he/she] feel that way? Would you say

- Less than 15 sec..... 1
 15-30 seconds..... 2
 30 sec to 1 min..... 3
 More than 1 minute.. 4
 Don't know..... 9
 Not asked..... 8

- B. Did [you/he/she] feel drowsy or sleepy **afterwards**?
- Yes..... 1
 No..... 0 (GO TO Q15)
 Don't know..... 9 (GO TO Q15)
 Not asked..... 8

(1) How long did [you/he/she] feel that way? Would you say .

- Less than 15 sec..... 1
- 15-30 seconds..... 2
- 30 sec to 1 min..... 3
- More than 1 min..... 4
- Don't know..... 9
- Not asked..... 8

Q15. About how many times in [your/his/her] life would you say [you/he/she] experienced spells like the one you just described? Would you say.

- One..... 1 (GO TO Q17)
- Two..... 2
- Three..... 3
- Four or more..... 4
- Don't know..... 9
- Not asked..... 8

Q16. How old [were/was] [you/he/she] the first time [you/he/she] had a spell like the one you just described?

Age

A. During the [past year/year prior to death], about how often did [you/he/she] have this type of spell? Would you say...

- Not at all..... 0 (GO TO C)
- At least once, but < 1/month. 1 (GO TO C)
- Once a month..... 2 (GO TO C)
- Twice a month..... 3 (GO TO C)
- 3-4 times a month..... 4 (GO TO C)
- More than 4 times a month.. 5
- Don't know..... 9 (GO TO C)
- Not asked..... 8

B. About how many times **per week** did [you/he/she] have this type of spell during the [past year/year prior to death]? _____

C. During the period of [your/his/her] life when [you/he/she] [were/was] having these spells most frequently, about how often did [you/he/she] have them?

- Less than once a month..... 1 (GO TO Q17)
- Once a month..... 2 (GO TO Q17)
- Twice a month..... 3 (GO TO Q17)
- 3-4 times a month..... 4 (GO TO Q17)
- More than 4 times a month.. 5
- Don't know..... 9 (GO TO Q17)
- Not asked..... 8

D. About how many times **per week** did [you/he/she] have this type of spell during the time of [your/his/her] life when [you/he/she] [were/was] having them most frequently? _____

E. How old [were/was] [you/he/she] during this time?
[RECORD VERBATIM AND CODE EARLIEST AGE] _____
Age

Q17. [Have/Has/Did] [you/he/she] ever [had/have] any other spells that were different from the one you just described?

[IF SUBJECT WAS REPORTED TO HAVE SIMILAR SPELLS BUT WITHOUT LOSS OF CONSCIOUSNESS, BE SURE TO CONSIDER THIS A SEPARATE SMALL SEIZURE TYPE]

Yes.....	1
No.....	0 (GO TO II-C)
Don't know.....	9 (GO TO II-C)
Not asked.....	8

Q18. How many other types of small spells [have/has/did] [you/he/she] [had/have]? _____

A. What do you call each of the other types?

1. _____ 3.
2. _____ 4.

[FILL OUT ANOTHER SMALL SEIZURE FORM FOR EACH ADDITIONAL TYPE OF SMALL SEIZURE; THEN CONTINUE TO II-C, NEXT PAGE]

[IF SUBJECT SAID YES TO >1 OF SCREENING BOX Q2C-H (PAGE 2) AND/OR Q9G PAGE 21, BE SURE A SMALL SEIZURE FORM HAS BEEN FILLED OUT FOR EACH TYPE]

Part IIC: WRAP-UP

Q1. [Have/Has/Did] [you/he/she] see a doctor because of the [seizure[s]/event[s]]?

Yes.....	1
No.....	0 (GO TO Q2)
Don't know.....	9 (GO TO Q2)
Not asked.....	8

A. How old [were/was] [you/he/she] the **first** time [you/he/she] saw a doctor because of the [seizure[s]/event[s]]? _____

age

(DK=-1; NOT ASKED=-8)

Q2. [Have/Has/Did] [you/he/she] ever talk[ed] to a doctor about what probably caused [your/his/her] [seizure(s)/event(s)]?

Yes..... 1
No..... 0 (GO TO Q3)
Don't know..... 9 (GO TO Q3)
Not asked..... 8

A. What did the doctor say was the cause? **[RECORD VERBATIM]**

- | | |
|---|-----------------------------------|
| 1. Head injury | 8. Toxic/poisoning |
| 2. Infection of brain or CNS such as spinal meningitis, encephalitis or polio | 9. Alcohol |
| 3. Stroke | 10. Drug withdrawal |
| 4. Brain Tumor | 11. Metabolic |
| 5. Birth Injury | 12. Other |
| 6. Fever | 13. Cause unknown or "idiopathic" |
| 7. Hypertensive/eclampsia | 99. Don't know |
| | 88. Not asked |

Q3. [Have/Has/Did] [you/he/she] ever [taken/take] medications for [your/his/her] seizure[s]?

Yes..... 1
No..... 0 (GO TO Q5)
Don't know..... 9 (GO TO Q5)
Not asked..... 8

A. How old [were/was] [you/he/she] when [you/he/she] first started taking medications for the seizure(s)?

Age _____

IF SUBJECT IS LIVING:

- B. [Are/Is] [you/he/she] still taking medications for the seizure(s) now?
- Yes..... 1 (GO TO Q4)
 - No..... 0 (GO TO C)
 - Don't know..... 9 (GO TO Q4)
 - Not asked..... 8

IF SUBJECT IS DECEASED:

Was [he/she] still taking medications for the seizure(s) at the time of [his/her] death?

- Yes..... 1 (GO TO Q4)
- No..... 0
- Don't know..... 9 (GO TO Q4)
- Not asked..... 8

- C. How old [were/was] [you/he/she] when [you/he/she] stopped taking them?
- _____
- Age

Q4. IF SUBJECT IS CURRENTLY TAKING ANTICONVULSANTS: Which medications [are/is] [you/he/she] taking? [RECORD VERBATIM]

Anything else? [PROBE: [Are/Is] [you/he/she] taking any of the following: Tegretol, Phenobarbital, Mysoline, Dilantin, Depakene, Depakote, Zarontin or Mebaral?]

IF SUBJECT FORMERLY TOOK ANTICONVULSANTS OR IS DECEASED: Which medications [were/was] [you/he/she] taking when [you/he/she] [stopped/died]? [RECORD VERBATIM]

Anything else? [PROBE: [Were/Was] [you/he/she] taking any of the following: Tegretol, Phenobarbital, Mysoline, Dilantin, Depakane, Depakote, Zarontin or Mebaral?]

Q5. [Have/Has/Did] [you/he/she] ever [had/have] an episode of continuous seizures lasting for 30 minutes or more, without recovering between seizures?

- Yes..... 1
- No..... 0 (GO TO Q6)
- Don't know..... 9 (GO TO Q6)
- Not asked..... 8

- A. How old [were/was] [you/he/she] when this happened? _____

B. Did [you/he/she] have to spend the night in a hospital because of this event?

Yes..... 1
No..... 0
Don't know..... 9
Not asked..... 8

Q6. [Have/Has/Did] [you/he/she] ever [had/have] a brainwave test, that is an EEG?

Yes..... 1
No..... 0 (GO TO Q7)
Don't know..... 9 (GO TO Q7)
Not asked..... 8

A. Where was the most recent EEG done?

Hospital

City

State

B. When was it? _____ / _____
(DK=99/9999; NOT ASKED=88/8888)month year

Q7. [Have/Has/Did] [you/he/she] ever [had/have] an MRI of the brain?

Yes..... 1
No..... 0 (GO TO Q8)
Don't know..... 9 (GO TO Q8)
Not asked..... 8

A. Where was the most recent MRI done?

Hospital

City

State

B. When was it? _____ / _____
(DK=99/9999; NOT ASKED=88/8888)month year

Q8. [Have/Has/Did] [you/he/she] ever [had/have] a CAT scan of the brain?

Yes..... 1
No..... 0 (GO TO Q9)
Don't know..... 9 (GO TO Q9)
Not asked..... 8

A. Where was the most recent CAT scan done?

Hospital

City

State

B. When was it? _____ / _____
(DK=99/9999; NOT ASKED=88/8888)month year

ASK Q9 ONLY IF SELF INTERVIEW, OR IF SUBJECT IS INFORMANT'S CHILD AND IS <18 YEARS OLD, OR IF SUBJECT IS DECEASED, OTHERWISE GO TO Q10

Q9. In order to make sure that our information is as accurate as possible, we would like to review medical records of our study participants. Would it be all right with you if we contact the doctor who would have the **most information** about [the seizure(s)/this problem]?

Yes.....	1
No.....	0 (GO TO Q16)
Not Asked.....	8

[IF YES, FILL OUT MEDREC REQUEST FORM AND THEN RETURN TO Q10]

Q10. Is there anything you would like to add? **[RECORD VERBATIM]**

[IF SELF INTERVIEW GO TO Q12]

Q11. How well do you know (subject's) medical history? Would you say

Very well.....	1
Reasonably well.....	2
Not very well.....	3
Not at all.....	4
Not asked.....	8

Thank you for your patience and participation!

[FOR OFFICE USE]

Q12. DID OTHER FAMILY MEMBERS CONTRIBUTE TO INTERVIEW?

YES..... 1

NO..... 0

IF YES, WHO CONTRIBUTED?

Name(s):

_____ subject number

_____ Subject number

Relationship(s) o subject: _____

INTERVIEWER IMPRESSIONS:

1. RESPONDENT'S UNDERSTANDING OF QUESTIONS

EXCELLENT..... 1

GOOD..... 2

ADEQUATE.....3

POOR..... 4

2. OTHER IMPRESSIONS

TIME ENDED: _____ : _____ AM PM

Appendix 20: The Unstructured Seizure Classification Interview (Reutens et al 1992)

1. How many different types of seizures do you think you have?
2. Please describe what happens in each type of seizure?
3. Do you have blank spells or spells in which you “switch off or go off the airwaves?”
4. Do you have spells in which you twitch or jerk, especially just after waking up?

For each seizure type:

- 1.0 Do the seizures follow each other in a particular pattern? Describe the pattern.
- 2.0 Do you have any warning before seizures occur? Describe the warning.
 - 2.1 If yes to 2.0: How long does the warning last?
 - 2.2 Does the warning ever occur on its own?
- 3.0 Do you “go blank” or lose awareness of your surroundings during the seizure?
 - 3.1 If yes to 3.0: For how long are you blank or “out of it?”
 - 3.2 Do you go completely blank (out of it altogether) or retain some awareness of your surroundings?
 - 3.3 Do you stop what you are doing or continue on automatically “like a robot?”
- 4.0 If No to 3.0: Without losing consciousness, have your legs given way?
 - 4.1 Without losing consciousness, have you dropped to the ground?
 - 4.2 Without losing consciousness, have your arms dropped or sagged?
 - 4.3 Without losing consciousness, have you dropped objects?
 - 4.4 Without losing consciousness, does your head drop or sag?
- 5.0 During a seizure, do you experience emotional changes or flashbacks? Describe them.
 - 5.1 During a seizure, do you experience a feeling of being in a dream or in an unusually strange or familiar place? Describe the feeling.
 - 5.2 If Yes to 5.0: During a seizure do you experience intense fear?
During a seizure do you experience rage or anger?
During a seizure do you experience euphoria, happiness, or pleasure?

- 5.3 If Yes to 5.2: How long do the emotional changes last?
- 5.4 If Yes to 5.0: During a seizure do you experience flashbacks or memories of past events (as though you are reliving the past)?
- 5.5 During a seizure do you experience the sense that everyday surroundings or objects are unfamiliar?

- 6.0 During a seizure do you see or hear things that aren't real? Describe the hallucination.
 - 6.1 If Yes to 6.0: Indicate type of hallucination (visual/auditory)
 - 6.2 How long do the hallucinations last?

- 7.0 During a seizure do you experience any unusual smells or tastes? Describe the smells or tastes.
 - 7.1 If yes to 7.0: Indicate type of hallucinations (olfactory/gustatory)
 - 7.2 How long do these hallucinations last?

- 8.0 During a seizure do you notice any pins and needles, electric shocks, tingling, or other changes in sensation? Describe the sensations.
 - 8.1 If yes to 8.0 Where does the change in sensation start and how does it spread?
 - 8.2 How long does the change in sensation last?

- 9.0 During a seizure do objects or sounds in the room appear distorted or altered? For example, do sounds seem nearer or farther away or objects seem shrunken or magnified? Describe the changes.
 - 8.3 If yes to 9.0: Indicate if auditory or visual.
 - 8.4 How long does it last?

- 10.0 During a seizure do you feel that everything is in slow motion or sped up? Describe the feeling.
- 11.0 During a seizure do you experience a funny feeling in your tummy?
- 12.0 During a seizure do you experience mouth watering or drooling?
- 13.0 During a seizure do you experience palpitations or a pounding heart?
- 14.0 During the seizure do the eyes roll back or tend to look in a particular direction?
 - 14.1 If yes to 14.0: Which direction do they turn?
 - 14.2 How long does it last?

- 15.0 During a seizure, does the head turn in a particular direction?
- 15.1 If yes to 15.0: Which direction does it turn?
- 15.2 How long does it last?
- 16.0 During a seizure, are the arms held stiff in a particular position? Describe what happens.
- 16.1 If yes to 16.0: Are both arms or is just one arm affected?
- 16.2 Are the arms bent or straight?
- 16.3 How long does it last?
- 17.0 During a seizure are the legs held stiff in a particular position? Describe what happens.
- 17.1 If yes to 17.0: Are both legs or is just one leg affected?
- 17.2 Are the legs bent or straight?
- 17.3 How long does it last?
- 18.0 During the seizure, does breathing stop or does the subject go blue?
- 19.0 Do any jerking or twitching movements of the face, arm or leg occur during the seizure?
- 19.1 If yes to 19.0: Which parts of the body do they affect (face or lips/arms/legs)?
- 19.2 Does the jerking affect both sides of the body at the same time or only one side at a time?
- 19.3 How long does the jerking last?
- 20.0 During a seizure, do the eyelids twitch or is there repeated blinking?
- 20.1 If yes to 20.0: How long does it last?
- 21.0 During a seizure, do any of the following things occur: smacking of the lips, licking of the lips, chewing, swallowing, laughing, picking at or fiddling with things, walking or making stepping or bicycling movements, speaking? Describe what happens.
- 22.0 Do you ever bite you tongue during a seizure?
- 23.0 Do you ever wet yourself during a seizure?
- 24.0 After a seizure are you confused or drowsy? Describe how you feel after a seizure.

24.1 If yes to 24.0: How long does the confusion or drowsiness last?

25.0 After a seizure, do you have a headache? Describe it.

25.1 If yes to 25.0: Is the headache on one side of the head or does it ache all over?

26.0 Do seizures have any longer lasting effects on vision, speech, sensation, or muscle power? Describe the changes.

26.1 If yes to 26.0: How long do these effects last?

SEIZURE TYPE =

EPILEPSY SYNDROME =

Appendix 21: Differences in non-convulsive seizure questions between the semi-structured seizure (Ottmans et al 1990) interview and the clinical seizure interview (Reutens et al 1992)

REUTEN'S QUESTIONNAIRE	OTTOMAN'S QUESTIONNAIRE
<p>Staring episodes (absence or complex partial seizures)</p> <p>1 Do you have blank spells or spells in which you "switch off or go off the airwaves?"</p> <p>2 Do you "go blank" or lose awareness of your surroundings during the seizure?</p> <ul style="list-style-type: none"> • For how long are you blank or "out of it?" • Do you go completely blank (out of it altogether) or retain some awareness of your surroundings? • Do you stop what you are doing or continue on automatically "like a robot?" <p>5. During the seizure do the eyes roll back or tend to look in a particular direction?</p> <ul style="list-style-type: none"> • Which direction do they turn? • How long does it last? 	<p>Staring episodes (absence or complex partial seizures)</p> <p>1. [Other than the seizure[s] [you/he/she] had as a small child because of a high fever [have you ever had/(has/did)(he/she) ever (had/have)] any of the following...</p> <ul style="list-style-type: none"> • [IF SUBJECT HAS EPILEPSY, ASK...] a change in [your/his/her] mental state or awareness of [your/his/her] surroundings? • [IF SUBJECT DOES NOT HAVE EPILEPSY, ASK...] • a change in [your/his/her] mental state or awareness of [your/his/her] surroundings for no apparent reason? • [IF INTERVIEWING A PARENT...], [When he/she was a small child], [Does/did] [he/she] seem to daydream or stare into space more than other children?
<p>Jerking episodes (myoclonic or clonic seizures)</p> <p>1. Do you have spells in which you twitch or jerk especially just after waking up?</p> <p>2. Do any jerking or twitching movements of the face, arm or leg occur during the seizure?</p> <ul style="list-style-type: none"> • Which parts of the body do they affect (face or lips/arms/legs)? • Does the jerking affect both sides of the • body at the same time or only one side at a time? • How long does the jerking last <p>3. During a seizure, do the eyelids twitch or is there repeated blinking?</p> <ul style="list-style-type: none"> • How long does it last? 	<p>Jerking episodes (myoclonic or clonic seizures)</p> <p>1. [Other than the seizure[s] [you/he/she] had as a small child because of a high fever [have you ever had/(has/did)(he/she) ever (had/have)] any of the following...</p> <ul style="list-style-type: none"> • [uncontrolled movements of part or all of [your/his/her] body such as twitching, jerking, shaking or going limp • Shortly after [you/he/she] [wake(s)/woke] up, either in the morning or after a nap, [have/has] [you/he/she] ever noticed unusual movements such as dropping things or things suddenly "flying" from [your/his/her] hands or uncontrollable jerking or clumsiness? <p>2. Before the seizure[s] start[s/ed], [have/has/did] [you/he/she] [usually] [had/have] jerking, shaking, or uncontrolled body movements on only one side of the body?</p>

	<ul style="list-style-type: none"> • Is it always the same side? • Which side? • Which parts of the body [are/were] involved? [RECORD VERBATIM] • What [are/were] the movements like? [RECORD VERBATIM] <p>3. Before the seizure[s] start[s/ed] [do/does/did] [you/he/she] [usually] have <u>jerking</u>, twitching, or uncontrolled body movements on <u>both sides</u> of the body? [PROBE FOR MYOCLONIC JERKS PRECEDING GRAND MAL SEIZURES]</p> <ul style="list-style-type: none"> • Which parts of the body [are/were] involved? [RECORD VERBATIM] • What [are/were] the movements like? [RECORD VERBATIM] <p>4. During this spell, did any parts of [your/his/her] body jerk suddenly and unexpectedly?</p> <p>5. [Has/Did] this type of spell usually [occurred/occur] shortly after [you/he/she] [wake[s]/woke] up, either in the morning or after a nap?</p> <p>6. [Does/Has/Did] this type of spell [occur[ed]] only when [you/he/she] [are/is/were/was] going to sleep?</p> <p>7. During this spell, did any parts of [your/his/her] body move uncontrollably? [PROBE FOR FOCAL MOTOR ACTIVITY]</p> <ul style="list-style-type: none"> • Which parts of the body were involved? [RECORD VERBATIM] What were the movements like? [RECORD VERBATIM] • Was this on only one side? • Which side? • [Have/Has/Did] [you/he/she] ever [had/have] a similar spell with movements on the opposite side? <p>8. During this spell, did any parts of [your/his/her] body jerk suddenly and unexpectedly?</p> <ul style="list-style-type: none"> • Which parts of the body were involved? [RECORD VERBATIM]
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	<ul style="list-style-type: none"> • What was the jerking like? [RECORD VERBATIM] • Was this on only one side? • Which side? • [Have/Has/Did] [you/he/she] ever [had/have] a similar spell with jerking on the opposite side? • Would you say the jerking felt like an electric shock going through [your/his/her] body? • [Has/Did] this type of spell usually [occurred/occur] shortly after [you/he/she] [wake[s]/woke] up, either in the morning or after a nap? • [Does/Has/Did] this type of spell [occur[ed]] only when [you/he/she] [are/is/were/was] going to sleep? • Did this type of spell ever occur as a result of lights shining in [your/his/her] eyes -- for example, strobe lights, video games, reflections, or sun glare? <p>9. Did [your/his/her] eyelids flutter during this spell?</p>
<p>Limp episodes (atonic seizures)</p>	<p>Limp episodes (atonic seizures)</p>
<ol style="list-style-type: none"> 1. Without losing consciousness, have your legs given way? 2. Without losing consciousness, have you dropped to the ground? 3. Without losing consciousness, have your arms dropped or sagged? 4. Without losing consciousness, have you dropped objects? 5. Without losing consciousness, does your head drop or sag? 	<ol style="list-style-type: none"> 1. During this spell, did part of [your/his/her] body suddenly go limp, causing [you/him/her] to fall or drop things? <ul style="list-style-type: none"> • Which part of the body was involved? [RECORD VERBATIM] • What was the limpness like? [RECORD VERBATIM] • Was this on only one side? • Which side? • [Have/Has/Did] [you/he/she] ever [had/have] a similar spell where part of the body went limp on the opposite side? 2. [Other than during a grand mal seizure] During a spell like this did [your/his/her] whole body ever go limp? [IF YES, RECORD VERBATIM DESCRIPTION AND PROBE FOR ATONIC SEIZURES]

Stiff episodes (tonic seizures)	Stiff episodes (tonic seizures)
<p>1. During a seizure, are the arms held stiff in a particular position? Describe what happens.</p> <ul style="list-style-type: none"> • Are both arms or is just one arm affected? • Are the arms bent or straight? • How long does it last? <p>2. During a seizure are the legs held stiff in a particular position? Describe what happens.</p> <ul style="list-style-type: none"> • Are both legs or is just one leg affected? • Are the legs bent or straight? • How long does it last? 	

Appendix 22: Standardised written guidelines used to classify seizures, broad epilepsy-onset types, and idiopathic generalized epilepsy from our modified diagnostic questionnaire.

Features more suggestive of syncope

- Context i.e. typical provoking circumstances e.g. phlebotomy, pain, prolonged standing
- Observed pallor, sweating or clamminess prior to, during or immediately after event
- Gradual evolution of warning symptoms; hot, light-headed, feeling like “going to faint”, blurred vision especially “graying out” or fading out” of vision, or weakness
- Brief loss of consciousness
- Rapid recovery with minimal post-ictal confusion
- No tongue biting, drooling or events during deep sleep

Features more suggestive of psychogenic non-epileptic seizures

- Prolonged duration of attack i.e. convulsive or motionless unresponsive component greater than ten minutes
- Prominent motor activity characterized by:
 - thrashing or flailing limbs movements
 - waxing and waning intensity of movements
 - side-to-side head movements
- Prolonged motionless, unresponsiveness (maybe aware of surroundings) greater than ten minutes
- Eyes closed during all events
- Crying
- Multiple different attacks

Absence seizures

- Age of onset (major < 15 years; minor < 40 years)
- Brief, usually less than 30 seconds
- Sudden onset and termination i.e. “pause”
- Behavioral arrest - stop purposeful activity
- Resumption of prior activity with no confusion, headache or sleepiness
- Staring/blank episodes - eyes open (straight ahead > upward)
- loss/partial loss of awareness
- Eyelid blinking (slow or flutter)
- Myoclonia mild in eyebrows, chin, head, perioral, or limbs
- Autonomic component and simple automatisms only if seizures prolonged
- Family history of absence seizures
- No falls
- No warning
- Precipitants: sleep deprivation, alcohol, menstruation, stress

Myoclonic seizures

- Age of onset (major < 20 years, minor < 40 yrs)
- Brief, twitches or jerks without warning or post-ictal confusion
- May occur singly, in brief runs or clusters
- Body distribution suggestive of epilepsy syndrome
- Progressive epilepsy syndromes involve atypical regions (diaphragm, phonation, walking), greater severity, and without waking prominence

Atypical absence seizures

- Other seizure types more prominent
- Abnormal neurological, cognitive or intellectual development
- Prolonged (>45 seconds) absence seizures
- Post-ictal confusion, headache, drowsiness

Generalized tonic seizure

- May have guttural cry or grunt
- Sudden, brief, sustained symmetrical muscle rigidity, without clonic movements, fixing the limbs, most often as flexor or extensor posturing and with loss of consciousness e.g. “bear hug seizure”
- May occur during sleep (as well as awake) state
- Fall if upright, stiff, injury common
- Confusion, headache, drowsiness post-ictally

Atonic seizures

- Sudden, brief loss of posture affecting truncal musculature
- Without clonic movements
- Brief loss of consciousness (usually seconds)
- May cause abrupt falling i.e. drop attacks, head nods or limb drops
- Confusion, headache, drowsiness post-ictally

Primary or secondarily generalized tonic-clonic seizure

- Tonic seizure component: sudden, brief, sustained symmetrical muscle rigidity, fixing the limbs, most often as flexor or extensor posturing and with loss of consciousness
- Clonic seizure component: symmetric, bilateral, synchronous, semi-rhythmic jerking of the upper and lower extremities, usually increases in amplitude and decreases in frequency as the seizure progresses
- Cyanosis may be present
- Ends after a few intermittent sporadic jerks
- Convulsive activity duration < 10 minutes
- Tongue biting may occur
- Postictal confusion and muscular aching

Features more suggestive of partial seizures

Major

- Seizures with onset after 40 years age
- Seizures from deep sleep (not drowsy or arousal states)
- Warning or aura independent of convulsive seizures or seizures with impaired awareness
- Focal or asymmetric motor or sensory phenomena, prior to convulsive or seizures with impaired awareness.
 - tonic or dystonic posturing
 - clonic jerking
 - head or eye deviation
 - Parasthesias, numbness
 - Post-ictal paresis
 - Prolonged post-ictal aphasia
- Complex automatisms e.g. gestural, vocalization, walking, stepping, rocking or bicycling movements
- Focal neurological abnormalities on examination or radiological investigations

Minor

- Preceding warning or aura at onset of seizures that progress
- Simple automatisms e.g. lip smacking, lip licking, chewing, swallowing, grimacing, fiddling movements (fingers, hands, etc)

Febrile Convulsions

- Onset < 6 years
- Only occur with fever
- Attacks typically have convulsive features

Idiopathic Generalized Epilepsy (IGE)

Major

- Onset before 30 years of age and usually before 20.
- Seizures never out of deep sleep but may occur with drowsy/arousal states (except tonic seizures in MAE)
- Non-convulsive generalized seizures i.e. absence, myoclonus, atstatic, atonic
- No clear warning with convulsive seizures (may have vague premonitory symptoms).
- Normal neurological and intellectual development.

Minor

- Onset before 40 years age
- Family history of IGE, absence or myoclonus

Childhood absence epilepsy (CAE)

Major

- Typical, frequent (multiple more than daily) absence seizures.
- Age of onset 3-8 years.

- Family history of typical absence seizures.
- Normal neurological development (may have cognitive/learning problems).

Minor

- Family history of IGE seizure types
- Onset before 12 years
- Infrequent generalised tonic-clonic seizures and myoclonus

Juvenile Absence epilepsy (JAE)

Major

- Typical absence seizures
- Age of onset 9-20 years
- Infrequent (daily or greater) absence seizures
- Family history of absence seizures

Minor

- Family history of IGE
- GTCS more frequently than absence seizures
- Myoclonic jerks infrequent, mild and random distribution (afternoon > awakening)
- Myoclonic seizures and GTCS onset years after absence seizures onset

Juvenile Myoclonic Epilepsy (JME)

Major

- Age of onset 12-20 yrs
- Earliest onset, most frequent, or independently occurring non-convulsive seizure type myoclonic
 - predominantly in the limbs especially arms (not prominent in eyebrows, eyelids, chin, head, perioral, phonation, diaphragmatic, walking)
 - usually within an hour after awakening
 - manifest as: clumsiness, shakiness, tremulousness, twitching, or jerks (dropping, knocking or spilling things)
- Tonic-clonic seizures on awakening with onset months after myoclonus
- Family history of myoclonus
- Normal neurological development

Minor

- Seizure precipitants; sleep deprivation, alcohol, menstruation, stress.
- May have absence seizures

IGE not otherwise specified

- Primary generalised seizures only
- Age of onset less than 40 years
- Family history of IGE, absence seizures or myoclonic seizures

Epilepsy with myoclonic atstatic seizures (MAE)

Major

- Age of onset 1-6 years

- Predominant seizure type myoclonic astatic seizures (symmetrical myoclonic jerks followed by loss of muscle tone)
- Atonic seizures (without warning, minimal confusion)
 - sudden falls
 - head nods
 - limb drops
 - injury common
- Frequent status epilepticus (absence or myoclonic)
- No tonic seizures prior to adolescence

Minor

- Other generalised seizure types (absence, GTCS)
- FS or FS after age 6 years
- Family history of FS
- May or may not be normal developmentally

Epilepsy with myoclonic absences

Major

- Age of onset 1-12 years
- Myoclonia associated with absences
- Myoclonia: rhythmic myoclonic jerks on shoulders, arms and legs with concomitant tonic contraction, which may be unilateral or asymmetrical
- Absences: more than daily, duration < 90 second
- Perioral myoclonias frequent
- Eyelid twitching absent/not prominent

Minor

- Family history of myoclonic absences
- GTCS
- Atonic seizures
- Absence status epilepticus rare

Benign myoclonic epilepsy in infancy (unlikely to be observed in sample)

Major

- Age of onset 4 months to 4 years
- remission within one year of onset
- Myoclonic jerks on awakening or first hours of sleep

Minor

- Seizure precipitants; photic, auditory startle, tactile