INVESTIGATING THE USE OF MEDICINES IN MANAGEMENT OF CHILDREN AND YOUNG PEOPLE WITH EPILEPSY USING DATA FROM PRIMARY CARE IN THE UK

Mostafa A Sayed Ali, MSc

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Abstract

Background: Epilepsy is a serious chronic neurological disorder that has a higher incidence in children and young people (CYP) than in adults. Epilepsy negatively impacts physical and psychosocial quality of life of CYP. Good outcomes of epilepsy are associated with optimal choice of drug treatment and adequate adherence to the prescribed medicines. Research on the patterns of medication use and adherence to prescribed medicines in CYP remains limited. The long-term clinical outcomes and costs of treating epilepsy have not been extensively studied in CYP in the UK.

Aim of the study: This thesis aimed to investigate the pattern of antiepileptic drug (AED) prescribing and the dynamic of medication adherence in CYP with epilepsy. The long-term clinical outcomes and direct costs of treating epilepsy in CYP were estimated at population level.

Methods: This study is an observational cohort study of CYP, age 0-17 years, identified from The Health Improvement Network (THIN) primary care database from the UK between January 1988 and December 2004. Four different analyses were carried out on this cohort. First, a cross-sectional design repeated annually was employed to estimate the incidence and prevalence of epilepsy and the pattern of AED prescribing in this population. Secondly, the long-term adherence to prescribed AEDs was calculated using the medication possession ratio (MPR) method. Applying panel data analysis and the Generalised Estimating Equation (GEE) multivariate regression, factors that may have been associated with adherence to the prescribed AEDs were examined. Thirdly, seizure outcomes in terms of seizure frequency and remission of seizures and potential associated factors were assessed using the method of multiple failure survival analysis. Finally, the direct costs of treating epilepsy in CYP in primary care were estimated and stratified by the number of years after the first recording of epilepsy in THIN data.

Results: Of total 528,760 CYP born on or after 1st January 1988 and registered in general practices contributed to THIN until 31st December 2004, 2020 CYP were identified who had a diagnosis of epilepsy, from under 1 up to 16.3 years of age (mean=5.6; SD=4.1). The annual incidence of epilepsy in CYP stratified by calendar years ranged from 44.4 (95% CI=31.9-61.8) to 61.2 (95% CI=50.6 -74.1) per 100,000 person-years. Incidence of epilepsy was significantly higher in children with greater socioeconomic deprivation than those with lower deprivation. Around 60% of CYP with epilepsy were prescribed monotherapy each year. Old AEDs such as carbamazepine and sodium valproate were the most frequently prescribed drugs and often prescribed as monotherapy to control epilepsy throughout 1990-2003. Prescribing of lamotrigine, a new AED, increased from 0.07 per person-years in 1992 to 2 per person-years in 2003. The calculated annual adherence to AEDs showed that around 50% of CYP adhered to at least 80% of the prescribed medications each year. Demographic characteristics of CYP were of little significance to affect adherence levels.

The incidence of seizures was 0.73 (95% CI=0.71-0.75) per person-years. Incidence of seizures was higher in younger children up to 2 years and decreased with increasing age. A proportion of 94% (95% CI=93%, 96%) of CYP achieved 1 year remission of seizures, 80% (95% CI= 78%, 83%) achieved 2 years and 47% (95% CI=43%, 50%) achieved 5 years remission of seizures.

The mean total direct cost associated with treating epilepsy in CYP, according to information in the general practice records that also indicated specialist and hospital care, was estimated at £ 1,153 (SD=1,808) per child in the first year following epilepsy diagnosis and at £459 (SD=1,633) per child for subsequent years. The costs of hospital care and AEDs represented the highest contribution to the total direct costs of epilepsy. The annual direct cost was significantly higher in younger children up to 2 years old. No significant difference in the annual costs was observed between CYP who adhered to at least 80% of medications and those who adhered to less than 80%.

Conclusions: The incidence of epilepsy was highest in young children and CYP of higher socioeconomic deprivation. Old AEDs were most often prescribed as first-line drugs and as monotherapy to control epilepsy. Of newer AEDs, there was an increasing trend of prescribing lamotrigine and topiramate as add-on therapy. Long-term adherence to prescribed AEDs was suboptimal in one-half of CYP and positively associated with higher seizure frequency. Inpatient hospital care and drugs were the major contributors to the direct costs of treating epilepsy in CYP. Non-adherence to prescribed medicines was associated with higher hospital care costs but not with total direct costs as the medicines themselves made large contribution to the direct costs

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List of abbreviations

ADHS	Attention deficit hyperactivity syndrome
A&E	Accident and emergency department
AE	Active epilepsy
AED	Antiepileptic drugs
AHD	Additional health data
ANOVA	Analysis of variance
BNF	British National Formulary
CI	Confidence interval
CT	Computerised tomography
CYP	Children and young people
DH	Department of Health
EEG	Electroencephalography
GBD	Global burden of disease
GEE	General estimating equation model
GLM	Generalised linear model
GP	General practitioner
GPRD	The General Practice Research Database
HIV	Human immunodeficiency virus
HRQOL	Health-related quality of life
HRU	Health resource utilisation
ICD	International system for classification of diseases
ILAE	International League Against Epilepsy
IQR	Interquartile range
LTE	Life-time epilepsy
MPR	Medication possession ratio
MRI	Magnetic resonance imaging
NHS	National health services
NICE	National Institute for Health and Clinical Excellence
OLS	Ordinary Least Square regression
ONS	Office for National Statistics
PCT	Primary Care Trust
PSSRU	Personal Social Services Research Unit
QOL	Quality of life
RCT	Randomised controlled trial
SD	Standard deviation
THIN	The Health Improvement Database
UK	United Kingdom
WHO	World Health Organization

Chapter one: Background and rationale for the thesis

1.1 Introduction

Throughout the thesis, the term `CYP` is used to refer to children and young people less than 18 years old. The National Institute for Health and Clinical Excellence (NICE) guideline for diagnosis and management of epilepsy in children and adults defines children as ranging from 28 days to 11 years and young people from 12 years to less than 18 years [1] .

Epilepsy is a prevalent neurological disease affecting children in the UK and worldwide. Anticonvulsant drugs, commonly known as antiepileptic drugs (AEDs), are the first choice treatment strategy for managing epilepsy in CYP. However, until recently, there has not been conclusive evidence in regard to the first-line drug to use when starting monotherapy or specific guidelines in place for combining AEDs if monotherapy fails to control seizures. The first guideline for the diagnosis and management of epilepsy in children and adults was produced by NICE in 2004 [1]. There is little information about the use of AEDs in CYP in primary care in the UK and adherence to the prescribed AEDs. No study has focused on estimating the costs associated with treating epilepsy in this age group in the UK.

This thesis has investigated the trend of incidence and prevalence of epilepsy in CYP and the pattern of AED prescribing using data from primary care practices in the UK. The long-term adherence to the prescribed AEDs and the long-term recorded seizure outcomes were calculated. The direct costs of treating epilepsy in CYP were estimated at a population level. All these analyses are addressed in detail in different sections of the thesis and are presented as follows:

Chapter 1 provides an introductory background about epilepsy regarding its definition, aetiology, classification, and the burden in the UK and globally. Chapter 1 presents a review of the literature, which describes what is currently known about the use of AEDs in primary care and CYP adherence rates to prescribed

AEDs. The review also provides an overview of the common methods of measuring medication adherence and the factors associated with non-adherence. Chapter 1 also describes of the nature of The Health Improvement Network (THIN) database, the data source for all analyses in this thesis, and the strengths and limitations of using THIN in conducting medical research. This is followed by a justification of the thesis and objectives of the thesis.

Chapter 2 describes the methodology of extracting a sample of CYP younger than 18 years who were diagnosed with epilepsy and registered in general practices contributing to THIN and describes their basic demographic characteristics and co-existing morbidities. Chapter 2 also presents the first analysis on the study group that was the calculation of incidence and prevalence of epilepsy stratified by the CYP's age, sex and calendar year of diagnosis.

Chapter 3 investigates the AEDs used by CYP in primary care, as well as the proportions of CYP who were prescribed monotherapy and polytherapy. The chapter also explores trends in prescribing old and new AEDs and trends in the use of AEDs in regard to CYP age over calendar time between 1990 and 2004. Chapter 3 presents a calculation of CYP's long-term adherence to the prescribed AEDs and a regression analysis of factors that may have been associated with adherence.

Chapter 4 presents a quantification of the recorded clinical outcomes of epilepsy in THIN in terms of seizure frequency and remission of seizures and examines factors that may have been associated with the incidence of seizures.

Chapter 5 presents an estimate of the health resource utilisation (HRU) by CYP in primary care and the associated direct costs for treating epilepsy in this age group and assesses whether there were any variations in costs by CYP's age, sex, socioeconomic status and adherence to AEDs.

1.2 Definition of epilepsy

Epilepsy is a serious neurological disease characterised by spontaneous recurrence of unprovoked seizures. According to the International League Against Epilepsy (ILAE) definition, `Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition' [2]. Seizures are the main symptom of epilepsy and are defined as time-limited paroxysmal episodes that result from a transient disturbance in the electrical activity of the brain with a sudden overload of neuronal discharges. This disturbance produces temporary changes in a person's movement, behaviour or consciousness that can occur at inconvenient, embarrassing, or hazardous times [3]. The ILAE defines an `epileptic seizure' as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain [2]. Seizures are usually short, lasting less than 5 minutes, and are sometimes anticipated by a prodromal phase (vague pre-attack symptoms such as depression, irritability, giddiness, and myoclonic jerking) and are followed by a long postictal phase (post-attack symptoms, such as unconsciousness and/or headache, vomiting and pain in the muscles) [3].

The diagnosis of epilepsy requires the occurrence of at least one epileptic seizure. Although epilepsy is characterised by recurrent seizures, not all seizure attacks refer to epilepsy and misdiagnosis of epilepsy is common [4, 5].

1.3 Causes of epilepsy

Epilepsy is caused by any condition that alters the structure or disturbs the function of cerebral neurons [3]. There are three broad categories for the causes of epilepsy: 1. symptomatic epilepsy, which has a definite cause that may be congenital (such as heterotopias and cortical dysplasia), infectious (such as meningitis, encephalitis, and abscess), head trauma, tumour and vascular (such as vascular malformation, stroke and subarachnoid haemorrhage) [6].

2. Idiopathic epilepsy has no apparent cause, but could be due to a genetic tendency. Most population-based studies have reported that the aetiology of epilepsy was unknown in 60-70% of participants [7]. 3. Cryptogenic epilepsy is similar to idiopathic epilepsy in that no apparent cause can be defined. However, there is strong evidence that this type of epilepsy may be the result of a condition that causes brain damage. There are some factors that may trigger seizures in children with epilepsy, including sleep deprivation [8], flashing lights (photosensitive epilepsy) and emotional stress [9].

In addition, there are other conditions that provoke seizure attacks but may not develop into epilepsy. These conditions include metabolic abnormalities (such as hypoglycaemia, hyperglycaemia, hyponatraemia and hypocalcaemia), prescribed medications that lower individual level of resistance to seizures (e.g., theophylline and tricyclic antidepressants), systemic infection and high fever in children [10].

1.4 Classification of epilepsy and epilepsy syndromes

Epilepsy is a heterogeneous set of neurological disorders. The current familiar international classification of epilepsy and epilepsy syndromes was introduced by the 1989 ILAE classification of epilepsy syndromes (Appendix 1)[11]. Epilepsy syndrome refers to a complex set of clinical signs and symptoms that are characteristic of an identifiable disorder or disease [12].

The 1989 ILAE classification scheme depends on two main factors: seizure type (localised or generalised) and the cause (e.g., idiopathic, symptomatic, or cryptogenic). Sub-classification of epilepsy syndromes is based on anatomic localisation (e.g., frontal, rolandic, occipital, or temporal lobe epilepsies). The disorder may also be classified according to predisposing factors. A clear glossary of standard terminology for epilepsy, epileptic syndromes and epileptic seizures was developed by the ILAE in 1980 and revised in 2001[13].

Since seizure type is the main domain of classifying epilepsy syndromes, the ILAE previously introduced the 1981 classification of seizure types (Appendix 2) [14]. The

classification scheme depends on the part or parts of the brain the seizure activity starts in. Figure 1-1 illustrates the classification of seizure types. Simply, seizures are either focal (partial) or generalised.

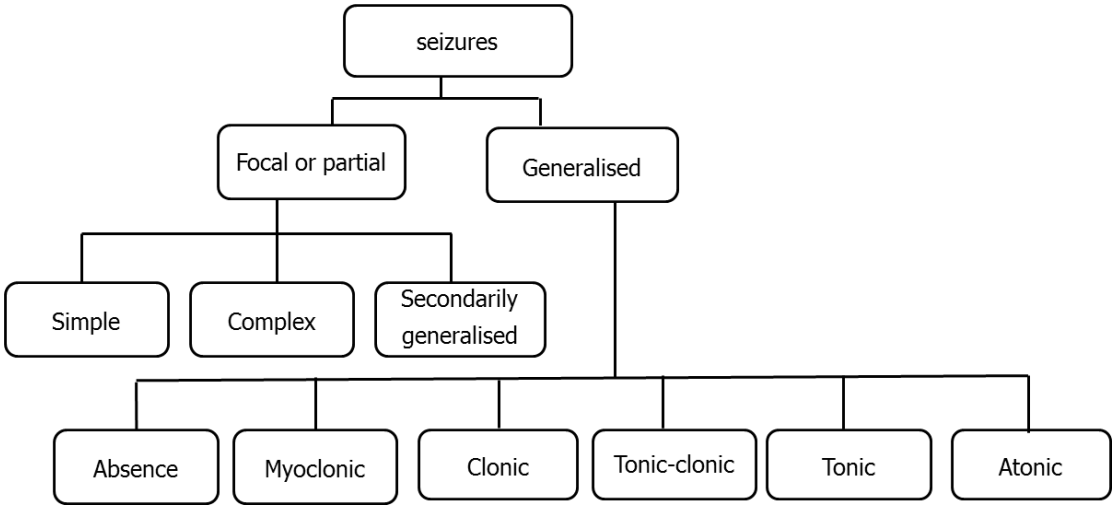


Figure 1-1: Classification of seizure types

1) Focal seizures (localised) involve seizures that arise in specific loci in the brain cortex. Focal seizures are divided into simple focal and complex focal.

a) In a simple focal seizure the patients are fully conscious and aware of their surroundings, despite seizure activity

b) In a complex focal seizure the consciousness is impaired and the patients may not remember the seizure afterwards, or they have unclear memory of it.

2) Generalised seizures involve a large volume of the brain and are usually bilateral and associated with early impairment of consciousness during the seizure attack.

Sometimes, the epileptic seizures start as a focal seizure and then spread to both sides of the brain. This type is known as secondarily generalised seizures.

Although the 1981 and 1989 classifications have received many criticisms of being dated and unsatisfactory for epidemiological research, they remain in use [15]. In 1997, the ILAE established a Task Force of experts in order to evaluate the current

system of classification and terminology. Although the Task Force has proposed some modifications [6], they have argued that it is difficult to replace the current international classification system with an updated version that would be widely accepted and universally employed. The Task Force has postponed the replacement of the current system until a better method of classification is developed [15].

1.5 Epilepsies typical of children

Children and young people can manifest specific epilepsy types that differ in prognosis from adult epilepsy [16]. There is a set of epilepsy syndromes that have the age of onset only in children and do not occur in adults; however, some of these syndromes can persist into adulthood [17]. This section summarises the most common epilepsy types occurring in CYP.

1.5.1 Epilepsy in neonates

Neonates, are also called newborns, include young infants from the date of birth to the 28th day of life [1]. The incidence of epilepsy is greatest in neonates and during the first year of life. The highest incidence occurs in neonates of younger gestational age or lower birth weight (4.4-5.75/1000 population) [18]. The most common types of neonatal epilepsy are benign neonatal convulsions and early myoclonic encephalopathy.

1.5.2 Epilepsy in infancy and childhood

Different types of epilepsy are manifested in childhood that could be classified according to age of incidence, intensity, and characteristic seizures type. In a recent report (2010), the ILAE proposed a classification of clinically defined epilepsy syndromes according to the age at onset, which is presented in Table 1-1[12]. A summary description of each syndrome is shown in Appendix 3

Table 1-1: Classification of childhood epilepsy syndromes according to age of onset

Age of onset	Epilepsy syndromes
Neonates	Benign familial neonatal epilepsy Early myoclonic encephalopathy Ohtahara syndrome
Infancy	Epilepsy of infancy with migrating focal seizures West syndrome Myoclonic epilepsy in infancy Benign infantile epilepsy Benign familial infantile epilepsy Dravet syndrome (Severe myoclonic epilepsy in infancy) Myoclonic encephalopathy in non-progressive disorders
Childhood	Febrile seizures plus (FS+) (can start in infancy) Panayiotopoulos syndrome Epilepsy with myoclonic atonic (previously astatic) seizures Benign epilepsy with centrotemporal spikes Autosomal-dominant nocturnal frontal lobe epilepsy Late onset childhood occipital epilepsy (Gastaut type) Epilepsy with myoclonic absences Lennox-Gastaut syndrome (onset at 1-7 years) Epileptic encephalopathy with continuous spike-and-wave during sleep Landau-Kleffner syndrome Childhood absence epilepsy
Adolescence	Juvenile absence epilepsy Juvenile myoclonic epilepsy Epilepsy with generalised tonic–clonic seizures alone Progressive myoclonus epilepsies Autosomal dominant epilepsy with auditory features

Adopted from Berg et al. (2010) [12]

1.6 The burden of epilepsy

The burden of disease can be evaluated from different aspects including incidence and prevalence of disease in the general population, mortality rates and morbidity associated with disease and the financial costs of disease to individuals and their societies. In 1993, the World Health Organization (WHO) developed the Disability Adjusted Life Years (DALYs) measure to quantify the global burden of diseases [19]. This measure combines the burden due to death (years of life lost due to premature mortality) and morbidity (years of life lost due to time lived in a health state less than ideal health) into one index. This section briefly discusses the relevant aspects of measuring the burden of epilepsy in CYP.

1.6.1 Age-specific incidence of epilepsy in children

The incidence of epilepsy has been reported to be higher in CYP than in adults with at least 50% of cases beginning in childhood or adolescence [20]. The peak incidence is in the neonatal and infancy periods. Despite differences in the sources of data, the definition of epilepsy and age ranges of participants, the incidences rates in childhood can be categorised into common ranges. For example, the incidence of childhood epilepsy in Europe and North America decreases from around 150/100,000 population during the first year of life to 60/100,000 population at age 5-9 years and 45-50 /100,000 population in older children [18]. The incidence in South America, Africa and Asia shows higher rates (median= 68.7/100,000) [18, 21].

Previous incidence studies of childhood epilepsy in the UK have reported similar incidence rates to that in Europe. A population-based study used a national primary care database, the General Practice Research Database (GPRD), and estimated incidence of 63/100,000 population at age ranges between 5-9 years and 54/100,000 population at age ranges between 10-14 years in 1995 [22]. However, a more recent study by Heaney et al. (2002) estimated an incidence of 190/100,000 person-years at age 0-4 years and 75/100,000 person-years at age 5-14 [23].

1.6.2 Age-specific prevalence of epilepsy

Epilepsy is one of the most prevalent neurological conditions affecting populations of all ages worldwide. Globally, the WHO reported that there are over 50 million suffer from epilepsy in the world in 2004 with an estimated 2.4 million new cases of epilepsy occurring each year [20]. Around 85% of people with epilepsy live in developing countries. However, a recent study by Ngugi et al. (2010) estimated a higher figure of the global prevalence of life-time epilepsy (LTE) and active epilepsy (AE; a patient with at least one epileptic seizure in the previous 5 years regardless of AED treatment). In developed countries, the prevalence of LTE and AE were estimated at 6.8 million and 5.7 million, respectively [24]. In developing countries, these were 45 million LTE and 17 million AE in rural areas and 17 million LTE and 10 million AE in urban areas.

Studies on children and adolescents in Europe have reported prevalence rate ranges from 4.5 to 5/1000 population [25]. The prevalence rate of epilepsy rises with increasing age of children. It has been estimated to be 3.5/1000 population at ages of 0-5 years; 4.5/1000 population at ages of 5-10 years; and 5/1000 population at ages of 11-16 years [18].

In the UK, there are no direct estimates of the prevalence of epilepsy [26]. Wallace et al. (1998) used the GPRD database and estimated prevalence rates of 3.2/1000 population at age 5-9, 4.1/1000 population at age 10-14 and 5.2/1000 population at age 15-19 years in 1995 [22]. In England and Wales, the Office for National Statistics (ONS), reported that the prevalence of epilepsy in CYP under 16 years old was 4.4/1000 for males and 4.1/1000 for females in 1998 [27]. Large population databases suggest the prevalence of epilepsy to be between 0.4% and 0.5% for CYP [22]. Based on a population of 11.6 million CYP under 16 years in the UK in 2010 [28], this would suggest there are between 46,400 and 58,000 CYP with epilepsy in the UK.

1.6.3 Mortality and morbidity associated with epilepsy

Population-based studies have reported that CYP with epilepsy have standardised mortality ratio (SMR) of 7-13, which is higher than the reported SMR of 2-3 for all age groups with epilepsy [29, 30]. A recent population-based study by Acker et al. (2011) used the GPRD in the UK and reported an SMR of 22.4 (95% CI=18.9, 26.2) in 6190 CYP diagnosed with epilepsy [31]. In newly diagnosed epilepsy, death is mainly attributed to the severe underlying disease (for example, vascular disease, and brain tumour). In chronic epilepsy, however, higher mortality is commonly caused by seizure-related death, idiosyncratic drug reactions and rarely due to sudden unexpected death in epilepsy (SUDEP) [30, 32]. SUDEP accounted for 6% of the deaths in the UK paediatric study [31].

The World Bank in collaboration with the WHO and the Harvard School of Public Health evaluated the Global Burden of Diseases (GBD) via assessing mortality and disability from diseases [19]. The WHO 2001 report assessed the GBD for 2000 and estimated that mental and neurologic conditions accounted for 12.5% of the DALYs of all diseases and injuries [33]. They estimated that epilepsy represents 0.5% of the total burden of diseases in the world [33].

A wide range of morbidities and disorders are associated with epilepsy in CYP, including cognitive and learning difficulties, behavioural, social and psychological impairments that may persist into adult life. These disorders are reinforced by the adverse effects of antiepileptic treatments, and the negative social attitude toward epilepsy [34, 35]. Common relevant morbidities associated with epilepsy in CYP are briefly discussed in the next sections.

1.6.3.1 Cognitive impacts of epilepsy

Epilepsy has been demonstrated to impair the cognitive functions and mental development of children [34, 36]. Attention, intelligence scores (IQ), visual-motor skills and language skills are important indicators for the cognitive outcomes of epilepsy. These domains can be evaluated though standard scale-measures and

tests [37]. Cognitive functions were commonly addressed by interviewing children with epilepsy and their caregivers where children were administered standard tests to measure their mental skills. Examples of studies that have addressed the impact of epilepsy on cognitive function are discussed in this section.

Schoenfeld et al. (1999) examined a cohort of 57 CYP, aged 7-16 years, with chronic complex partial seizures and 27 healthy siblings, control group, of the same age in the USA [38]. All children and control were administered a set of neuropsychological tests of intelligence, receptive and expressive language, academic achievement, visual-motor skills, verbal and non-verbal memory and problem solving. Their findings showed significantly poor performance of CYP with epilepsy than the sibling control in all domains of cognitive function; verbal memory ($p<0.005$), non-verbal memory ($p<0.01$) language and academic achievement ($p<0.01$) and motor skill and mental efficiency ($p<0.05$). Similar findings were reported by Cormack et al. (2007) who interviewed 79 CYP, younger than 18 years, with temporal lobe epilepsy in London- UK [39]. The authors reported subnormal intellectual function (IQ <79) in 57% of participants Age at onset of epilepsy was the only significant predictor of cognitive impairment where the highest cognitive dysfunction occurred in those who had onset of epilepsy in the first years of life ($p<0.001$).

In another study by Berg et al. (2008), 613 children with newly diagnosed epilepsy, aged 1 month to 16 years, were prospectively enrolled in an observational study in the USA [40]. Children and their families were interviewed at the start of the study and at about 8–9 years after enrolment. At 8-9 years after the start of the study, children were administered age-appropriate neuropsychological tests such as Wechsler Intelligence Scale for Children, WISC-III. The level of cognitive function of children was described as normal for 451 (IQ, ≥80), borderline for 31 (IQ, 70-79), mildly retarded for 21 (IQ, 60–69), moderately or severely retarded for 45 (IQ, <60), and neurologically impaired-not testable for 36 (5.6%) children. Subnormal cognitive functions were suggested for 26.4% of the participants.

Because of the heterogeneity of epilepsy in aetiology, age of onset, seizure manifestation and sensitivity to pharmacological treatment, cognitive outcomes in CYP vary by diagnostic epilepsy subtypes [34]. Difficult-to-treat epilepsy syndromes, such as West syndrome, Dravet syndrome and the Lennox-Gastaut syndrome, have the poorest cognitive prognosis. The case may be worsened by the fact that treating CYP with AEDs, particularly phenobarbital and topiramate, is usually associated with cognitive side effects [41, 42]. However, some studies have shown that the effect of AED treatment on cognition is dose-related or due to polypharmcy [37, 43].

The above discussion indicates that the cognitive and educational impairments associated with epilepsy syndromes in CYP are of major importance and necessitate an appropriate choice of AED treatment and dose adjustment for better prognosis.

1.6.3.2 Psychosocial impacts of epilepsy

Psychosocial problems and psychiatric comorbidities are common in CYP with epilepsy [35, 44-46]. These problems include learning difficulties, poor social maturation and functioning, unemployment and mental health problems.

Educational and employment status were often assessed in randomised controlled trials (RCTs) by interviewing adults with childhood-onset epilepsy and/or prospectively observing CYP with epilepsy. For example, a population-based cohort of childhood-onset epilepsy, 245 CYP with epilepsy younger than 16 years, were prospectively observed for a mean follow-up of 35 years [47]. In 1992, the 100 surviving patients of the cohort and an additional 100 randomly selected employee controls without epilepsy of the same birth were interviewed. The authors found learning disabilities, lower education levels [Odds Ratio (OR) 2.4; 95% CI, 1.4-4.1], and lower employability [OR, 3.7; 95% CI, 1.9-7.3)] among patients with epilepsy compared to control cases. Questions about self-assessed health, life satisfaction, and life management were also included in the interviews [47]. The authors found significantly lower levels of life satisfaction [OR, 6.7; 95% CI, 1.9-

24.1] and poor perception of general health [OR, 5.1; 95% CI, 1.2-21.3] among people with epilepsy compared to controls from the general population.

In a review article by Pavlou and Gkampeta (2011), the authors concluded that learning disabilities and low academic performance are more frequent among children with epilepsy to the extent that some epilepsy syndromes may cause permanent learning disabilities [48].

Aspects of interpersonal relationships and social behaviour associated with childhood epilepsy were explored by Kokkonen et al. (1997) in Finland. The authors interviewed 81patients with childhood-onset epilepsy and 211 healthy controls and investigated independence from original family (e.g. living with parents, spouse, or outside home), and social development and functioning inside and outside homes. The authors found significantly poorer social maturation in 30% of patients versus 17% of controls ($p< 0.05$), dependent life styles in 49% of patients versus 21% of controls ($p< 0.05$), and persistent social adjustment and competence problems in patients with epilepsy.

This illustrates that the behavioural and social progress of children with epilepsy are influenced greatly by the disease and that epilepsy is a burden at both individual and societal levels.

1.6.3.3 Impact of epilepsy on quality of life

Research on the impact of epilepsy on health-related quality of life (HRQOL) of children and their families has grown in the last two decades [49]. Epilepsy has been demonstrated to influence a variety of life functions, such as physical function, social function and mental health, particularly in children with recurrent seizures or uncontrolled epilepsy [50, 51]. Emotional (e.g., irritability, anger, and persistent sadness) and behavioural problems (e.g., social isolation and reckless behaviour) are more common in children with epilepsy than children of the general population [52]. Population-based studies have revealed that CYP with epilepsy have higher risks of depression and anxiety symptoms [53, 54] and an associated higher risk of

suicide attempts in adolescents [55]. A nationwide epidemiological survey (British Child and Adolescent Mental Health Survey) in 1999 examined the rates of psychiatric disorders in children aged 5-15 years throughout England, Wales and Scotland [56]. The survey was conducted by interviewing a main carer and teacher for 10, 316 children including 67 children with epilepsy, 47 with diabetes and 10,202 controls. Rates of psychiatric disorder were 37% in children with epilepsy versus 9% in control children.

A variety of generic instruments [e.g., the Child Health Questionnaire and the Paediatric Quality of Life Inventory (PedsQL)] [57] were designed to address different aspects of HRQOL in paediatric populations irrespective of their medical conditions [58]. These generic instruments were found insufficient to detect specific problems related to epilepsy [50]. Therefore, a number of specific HRQOL scales have been designed for children and adolescents with epilepsy [59]. Examples of these specific instruments include the Epilepsy and Learning Disabilities Quality of Life Scale (ELDQOL), the HRQOL in Children with Epilepsy measure, Adolescent Sigma Scale, Hague Restrictions in Childhood Epilepsy Scale, Quality of Life for Adolescents with Epilepsy (QOLIE-AD-48) and the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE)[58, 59].

A study by Ronen et al. (2003) provided an example for the development and content description of epilepsy-related quality of life (QOL) measuring instruments. The authors developed the HRQOL in Children with Epilepsy questionnaire, which can be administered to children of 8 years or older, and a parent-scale for proxy response [60]. The authors examined 381 children with epilepsy, aged 6-15 years, and their parents [61, 62]. Using the refined version of the questionnaire, the authors concluded that impairments in HRQOL in children with epilepsy were associated with severity of seizures and the number of prescribed AEDs [30].

Many other studies implemented a variety of generic and specific HRQOL measures and have emphasised the negative impacts of epilepsy on HRQOL of CYP with epilepsy [51, 63, 64].

It is clear from the published literature that epilepsy has serious negative effects on the QOL of CYP.

1.6.4 Cost of illness as a measure of the burden of epilepsy

Cost of illness analysis comprises another measure of disease burden in terms of resources consumed. An estimate of the total cost of epilepsy in Europe based on epidemiological data from published population-based prevalence studies and reported data on the cost of epilepsy has shown that epilepsy represents a socioeconomic burden at individual, family, health services and societal levels [65]. The estimated total cost of epilepsy in 25 European countries converted to Euros for 2004 was €15.5 billion of which the indirect cost was €8.6 billion, i.e., represents 55% of the total cost [65]. This indicates that the higher proportion of epilepsy burden is imposed on the society in the form of unemployment and decreased productivity of patients with epilepsy. A review of the cost-of-illness studies in childhood epilepsy reported that the annual cost per child, generated at 2002 rate, ranged from €869 to €11,980 per year [66].

In the UK, no study has focused on the cost of treating epilepsy in CYP. Only aggregated data of adults and children with epilepsy were reported by Cockerell et al. (1994) who conducted a survey study on 1628 patients (including 14% under 20) identified from general practices [67]. Extrapolating to the whole UK population, the authors estimated total costs of £1930 million per year of which the indirect costs were £1345 million in the form of unemployment and premature mortality.

Recently, Beghi et al. (2005) reviewed published studies on the cost of epilepsy in childhood and concluded that the knowledge of the economic impact of epilepsy in children is limited due to the scarcity, inconsistency and poor comparability of the published articles [68].

Data from the UK and Europe on the cost of epilepsy indicate that epilepsy represents an economic burden to individuals and health care services.

1.7 Management of epilepsy

The principal goals of managing epilepsy are to achieve a seizure-free state (remission of seizures) or at least lower the rate of seizure recurrence [1]. The main strategies of managing epilepsy include antiepileptic medications, neurosurgery and vagus nerve stimulation. The first choice treatment strategy and the standard approach to manage epilepsy is the use of AEDs, which is the focus of this study. There is strong evidence that 70-80% of CYP respond well and enter long-term remission of seizures after starting AED therapy [69-71]. This means that 20-30% of children have refractory epilepsy syndromes (difficult-to-treat) and may seek other treatment options, such as the surgical approach [72].

The surgical approach to the treatment of refractory epilepsy includes epilepsy surgery (neurosurgery) and vagal nerve stimulation [73]. Epilepsy surgery involves surgical removal of the small part of the brain where seizures start (e.g., temporal lobe) or separating the part of the brain that is causing seizures from the rest of the brain. Epilepsy surgery is usually considered when a child's seizures fail to respond to two or three AEDs in appropriate combination. [73]. Studies have reported conflicting conclusions about the short and long-term effects of surgery on seizure control as well as the cognitive and psychosocial outcomes after epilepsy surgery [74].

Vagus nerve stimulation has been demonstrated as a relatively safe and effective adjunctive therapy for refractory seizures in CYP. Vagus nerve stimulation therapy is an operation in which a small generator is implanted under the skin below the collar bone with two electrical wires wrapped around the vagus nerve at the side of the neck [75]. The generator sends electrical impulses, at intervals, to the vagus nerve and then to the brain. This helps to lower the seizure frequency and severity of seizures. The procedure has been shown to decrease seizure frequency to 50% of its baseline [76, 77]

Pharmacological treatment with AEDs is usually convenient, non-invasive and always applied as the first choice. For effective treatment, the 2004 NICE

guideline recommended that AED treatment usually has to be individualised according to the seizure type, epilepsy syndrome, concurrent medication and coexisting morbidity, and counselling of the individual and their family and/or carers about the treatment plan [1]. The appropriateness of AEDs also depends on absence of contraindications to the drug, potential interactions with other drugs, potential adverse effects and the licensed indication of the drug [1].

AEDs are classified into two main classes [3]. Conventional or old AEDs were approved before 1990 and include clobazam, clonazepam, carbamazepine, phenobarbital, phenytoin, ethosuximide primidone and sodium valproate [78]. All members of this class have troublesome side effects, such as sedation and idiosyncratic hepatitis and blood dyscrasias (Appendix 4).

The second class comprises new AEDs which were approved after 1990 and include felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin and zonisamide. The initial licence of this class was to act as adjunctive (add-on) treatment to old AEDs in refractory seizures although they can be prescribed as a monotherapy [79]. New AEDs have been proven as effective as the older drugs and better tolerated by patients [70].

1.7.1 Trends in treatment of epilepsy: monotherapy versus polytherapy

Monotherapy is considered to be the gold standard for treatment of epilepsy with the exceptions of some epilepsy syndromes where polytherapy is advised [80, 81]. Monotherapy is encouraged to avoid the acute and chronic toxicity associated with unnecessary polytherapy [82]. Moreover, the fact that old AEDs exhibit a wide range of pharmacokinetic and pharmacodynamic variability has led to common awareness that effective management can be achieved only with careful individualisation of dosage through monitoring serum drug concentrations [82]. In the late 1970s and early1980s, a series of studies demonstrated that with implementing serum drug monitoring, seizure control of both newly diagnosed patients and chronic patients was often improved with single-drug therapy [83-86]. Since the introduction of sodium valproate in 1973, numerous clinical trials have

demonstrated that monotherapy with sodium valproate is the most effective first-line choice for treatment of childhood generalised-onset seizures, such as juvenile myoclonic epilepsy [87-89] and absence seizure [90-92]. Based on the results of clinical trials, approximately 60-70% of children with epilepsy can be effectively controlled by a single AED [93, 94].

Although monotherapy has been proven effective, arguments have developed around the use of low dose polytherapy in the other 20-30% patients who respond poorly to monotherapy [80]. A multicentre study by Mattson et al. (1985) showed higher effectiveness of combined phenytoin and carbamazepine over single barbiturate treatment in patients with partial and secondarily generalised tonic-clonic seizures [95]. The introduction of new AEDs in 1990s which act with diverse mechanisms [96], as an effective add-on therapy has promoted the value of safe and effective combination therapy (rational polytherapy) in refractory epilepsies in adults and children [82]. However, other multicentre clinical trials showed that polytherapy was not advantageous and there was no significant difference between groups of patients treated with monotherapy compared to polytherapy [81, 97]. Another issue was that little evidence was available to support clinicians in determining how to use combination of AEDs when monotherapy fails [98].

The concept of monotherapy is well-established and remains widely favoured over polytherapy by neurologists for the treatment of CYP with newly diagnosed epilepsy [99-101]. However, the choice of an initial effective AED monotherapy for CYP with newly diagnosed epilepsy remains uncertain and clinicians most often select the initial AED treatment based on the CYP's seizure/epilepsy type [102]. There is a consensus in clinical practice that carbamazepine monotherapy is considered the first-line choice for treatment of partial-onset seizures [92, 103]. In childhood generalised epilepsy, sodium valproate monotherapy is considered the drug of first choice [78, 104]

In 2006, the ILAE including adult and paediatric epileptologists, clinical pharmacologists, clinical trialists and statisticians worked on producing a therapy guideline. The aim was to provide evidence-based guidance about which AEDs

possess long-term effectiveness as an initial monotherapy for patients with newly diagnosed or untreated epilepsy [102]. They evaluated all available evidence from a structured literature review of all related articles up to 2005. Because of the lack of comprehensive data on AED adverse effects, they failed to develop an evidence-based guideline to identify the optimal initial AED monotherapy. They concluded that the ultimate choice of an AED for any individual patient with newly diagnosed epilepsy should consider many variables. These variables include the strength of the efficacy and effectiveness evidence for each AED, the AED safety and tolerability profile, pharmacokinetic properties, formulations and expense [102].

The choice of second-line monotherapy when the first monotherapy fails to control seizures remains uncertain. In 2006, a panel of epilepsy neurologists and clinical pharmacologists (SPECTRA; Study by a Panel of Experts: Considerations for Therapy Replacement in Antiepileptics) was assembled in the US to develop a consensus concerning conversions between AED monotherapies [99]. Although the panel concluded that conversion from one AED to another monotherapy is complex, it developed a consensus on the principles for fully titrating an adjunctive AED before tapering the baseline drug. When patients are switched from one AED to another, a period of transitional polytherapy should be followed. This process may be complicated by drug interactions and complex AED pharmacokinetics.

In the UK health system, similar work was conducted by NICE. The aim was to support UK health care providers in improving the quality of care and to provide clinicians with an evidence-based reference for the treatment of patients with epilepsy. The first NICE guideline for the diagnosis and management of epilepsies in adults and children in primary and secondary care was developed in October 2004 [1]. The guidance provided some recommendations for better management of CYP with epilepsy. NICE principal recommendations specified that AED therapy for CYP should be initialised by specialists of managing epilepsy. The treatment plan should be individualised according to the seizure type, epilepsy syndrome, concurrent medication and coexisting morbidity [1]. Moreover, children should be treated with a single AED whenever possible. If the initial treatment fails after the

maximum tolerated dose has been achieved, then substituting the first drug using another drug (monotherapy) is recommended [1]. The NICE guideline suggested that new AEDs can be prescribed as adjunctive therapy with old AEDs in case of refractory partial seizures in children and in case old AEDs are poorly tolerated or contraindicated [1]. If the drug combination is believed to be successful, some individuals may be favoured to remain on the combination. The NICE recommendations on the choice of initial monotherapy are described in Appendix 5 and Appendix 6.

In 2007, the NHS R&D-Health Technology Assessment Programme sponsored a large pragmatic, randomised, unblinded, parallel group clinical trial which was conducted in hospital-based outpatient clinics in the UK by Marson et al. [105, 106] The study was also supported by the pharmaceutical companies with AEDs included in the study. The SANAD (Standard and New Antiepileptic Drugs) trial comprised two arms; one arm compared the effectiveness of new AEDs to carbamazepine and the other compared new AEDs with sodium valproate. The effectiveness of valproate monotherapy in generalised epilepsy was confirmed. Valproate was proven superior in efficacy to both lamotrigine and topiramate, maintaining its place as the drug of choice in treatment of generalised epilepsy. Lamotrigine was found to be a more active and cost-effective alternative to carbamazepine in partial-onset epilepsy.

There is no strong evidence of superior efficacy of new AEDs in children although they are considered better tolerated by children as compared with old AEDs [70, 107-109]. Therefore, the old AEDs remain the first-line clinical choice for management of newly diagnosed epilepsy in CYP [110].

1.8 Prescribing of AEDs for CYP in primary care

1.8.1 The organisation of primary care in the UK

The National Health Service (NHS) is the publicly funded healthcare system that was established to provide comprehensive and free health services for all residents of the UK [111]. Since 1948, the NHS has been funded and controlled by the UK government through the Department of Health (DH). The NHS provides health care for people through two main sections: primary care and secondary care. Primary care refers to all health services offered at the first point of contact for most people within the health system. Health services in primary care are delivered by a wide range of independent contractors, including GPs, dentists, pharmacists and optometrists [111].

The primary care services are operated by Primary Care Trusts (PCTs). PCTs are local organisations that commission community services and secondary care and spend around 80% of the total NHS budget [112]. The health care services in the UK are centred on general practices; referrals to specialists and secondary care are arranged by GPs [113]. Patients in the UK can only be registered with a single GP at a time. Access to care is cost-free for individuals in the UK [113-116]. In chronic diseases like epilepsy, the majority of medicines used by children are prescribed in primary care [113]. Most UK general practices maintain electronic records of all prescriptions which have been available for an increasing percentage of practices since 1988 [131]. Therefore, the healthcare system in the UK allows for the development of many powerful clinical databases, such as THIN database which is the source of data for this thesis. The nature and advantage of using THIN to conduct health research is discussed later in section 1.10.

1.8.2 Prescribing pattern of AEDs in CYP diagnosed with epilepsy

Until recently, no separate data were available about the prescribing rates of AEDs in CYP diagnosed with epilepsy in the UK. Prescribing data for CYP were usually aggregated in adult data. For example, a previous study was conducted in the Northern and Yorkshire regions in the UK between 1992 and 1995 [117]. The study used the records of all registered patients from the Prescription Analysis and Cost (PACT) database across 16 health authority areas to examine the primary care prescribing rates and trends of AEDs. Children were included as part of the ~6.8 million study population; however, no separate prescribing data were presented for children. Another study was conducted by the Office for National Statistics using the GPRD database between 1994 and 1998 in England and Wales, UK [27]. The study examined the prevalence of epilepsy and prescribing of AEDs and included prescribing data from children as part of 1.4 million study population.

Recently, Ackers et al. (2007) used the UK GPRD database to examine the trend of prescribing AEDs in CYP under 18 years old between 1993 and 2005[118]. The prescribing data of a total of 7721 CYP revealed that 75% of subjects had a diagnosis of epilepsy and 70% of subjects were prescribed one drug. Old AEDs were most frequently prescribed to CYP; however, their prescribing significantly decreased by 17% by 2005 ($p< 0.001$). The authors reported a significant 5-fold increase in prescribing of new AEDs between 1993 and 2005 ($p< 0.001$). The rapid uptake of the new AEDs in the UK, particularly lamotrigine, topiramate and levetiracetam, drove the authors to recommend further research on the safety of these drugs due to the patchy evidence available at the time.

A similar prescribing pattern of AEDs for CYP was reported by van de Vrie-Hoekstra et al. (2008) from the Netherlands [119]. The authors used a pharmacy dispensing data of 1527 CYP, aged 0–19 years, between1997 and 2007. Sodium valproate was the most frequently prescribed drug followed by carbamazepine and lamotrigine. Prescribing of lamotrigine increased during the study period.

1.9 Adherence to AEDs in children and young people

AEDs represent the first-line treatment strategy for managing childhood epilepsy. Assuming the drug is appropriately prescribed, adherence to AED regimens is essential to achieve seizure control and improve prognosis of epilepsy and CYP's quality of life. Poor adherence to medication can be the major cause of therapy failure and seizure recurrence [120, 121].

1.9.1 Definition of adherence to medicines

Three related terms are often used in the literature to describe the process of medication taking behaviour; these are compliance, adherence, and concordance.

Compliance

The term `compliance' generally refers to `the extent to which the patient's behaviour matches the prescriber's recommendations' [122]. Although the term compliance is commonly used in the medical and pharmaceutical literature, it has been criticised of carrying negative implications in terms of the clinician-patient relationship. It signifies a relationship in which the role of the clinician is to decide the appropriate treatment and provide the relevant instructions, while the role of the patient is to obey the prescriber's orders [122].

Adherence

`Adherence' is a synonymous term and is often used interchangeably with compliance; however, it is used by some to imply a more active and collaborative involvement of the patient in the implementation of a medication regimen [123]. Adherence is usually defined as `the extent to which a patient's behaviour (in terms of taking medications, following diets, or executing lifestyle changes) matches agreed prescriber's recommendations' [124]. It has been adopted by many, particularly within the psychological and sociological literatures, as an alternative to compliance, in a way to emphasise that the patient is free to decide whether to follow the prescriber's recommendations and that the patient should not be blamed

if they fail to do so. Adherence is suggested to carry some reasoned agreement from the patient toward the treatment regimens [125].To some, the concept of adherence seeks to empower patients by providing them with information which enables them to decide how they react toward the health care regimen [126].

Concordance

Concordance is a relatively new term that has attracted increasing interest in relation to medication-taking, particularly within the UK [127]. It is a complex concept relating to the patient/professional relationship and interaction. Concordance is defined as a patient-centred process in which the health care professional and the patient reach an agreement regarding the medicines that takes into account the beliefs and preferences of the patient [122].

The Medicines Partnership Initiative developed in 2002 by the NHS Department of Health (DH) explains concordance as a process of successful prescribing and medicine taking based on partnership where patients are informed about their conditions, the treatment options available and the risks and benefits of different options relative to their conditions [128]. On the professionals' side, they should be prepared for partnership, acquire the necessary skills to convince patients and invest time with patients to obtain an informed agreement.

1.9.2 Choice of terminology for the thesis

Compliance and adherence describe the same aspect which is patient medication behaviour based on a scientific agenda (i.e., what the patients actually do with the prescribed medications in relation to the given medical recommendations and factors that influence patient's behaviour) [122]. Compliance does not address the normative agenda (i.e., what is `right' and `good' in relation to medicine-taking and prescribing) whereas adherence tries to define the normative aspects by implying that the patient is free to decide whether to adhere or not [122].

The term adherence will be used throughout this thesis as compliance may imply a purely clinician's perspective. The adherence term is also preferred by many,

including WHO, over the term compliance in recent research and policy publications. Although concordance attempts to address the normative agenda [129], every patient-clinician interaction cannot be assumed to reflect the principles of concordance whereby shared decisions were considered in prescribing of medicines [130]. This is especially important because the study time (defined later in Chapter 2) of this thesis pre-dates the implementation of the concordance concept in the health care system. Moreover, concordance suggests that the relationship between patient and prescriber is to be measured and not the medication-taking behaviour [127]. This thesis was designed to investigate the use of medicine in terms of levels of adherence to prescribed medication.

1.9.3 Measurement of adherence

Widely varying approaches have been applied to identify and measure adherence to medicines in CYP and therefore, variant adherence rates have been reported. This may be attributed to the lack of a `gold standard' to measure adherence. Advantages and disadvantages associated with each of these methods are shown in Table 1-2 [131, 132].

Table 1-2: Advantages and disadvantages of common adherence measures

Adherence measure	Advantages	Disadvantages
Direct methods		
Drug assays	Can adjust drug dosage Objective, highly sensitive to verify if medicines have been administered. Commonly used in monitoring epilepsy medicines	Pharmacokinetics may affect absorption and excretion rates. Short-term, invasive, and expensive Patients know they are monitored and may change medicines use and produce false-positive results
Indirect methods		
Electronic monitoring devices	Provide accurate data on frequency and time of dosing. Continuous and long-term measure.	Cannot prove that medicines were ingested Mechanical failures are possible
Pill counts	Easily performed Inexpensive	Cannot prove that medicines were ingested Sometimes overestimates adherence (e.g., patient may discard pills before clinic visit)
Rates of medication refill	Easy to collect information in managed care settings Non-intrusive	Difficult to collect information if prescription source is unknown. Not proof of medication consumption
Patient report	Clinically feasible- low cost More accurate when patients report low adherence rates	Tendency to overestimate adherence Subject to reporting bias-`faking good'

1.9.4 Drug assays

This method involves measuring drug levels in blood and sometimes in urine at intervals as long as several months and is commonly used with epilepsy [133-135]. Suboptimal therapeutic levels may be indicative of non-adherence. This method is direct, quantitative, often useful for therapeutic drug monitoring and dosage adjustments, and does not depend on self or provider estimates of adherence. However, standardised assays may not be available for all drugs. Also, assays can be expensive and invasive, particularly for children [131]. In addition, sub-therapeutic drug levels may result from factors other than patient adherence, such as improper dosing, non-steady state concentrations, pharmacokinetic variations due to the type of drug formulations (e.g. enteric coating), physiological factors such as gastric pH, interactions with other medications or the patient's age [136].

1.9.5 Electronic monitoring

Microelectronic monitors or event recorder are employed to monitor the daily medication-taking process. These devices are microprocessors fixed in the caps of the standard medication bottles that record bottle openings where each time represents a dose removal from bottle [137]. These devices record information on the date and time of dose withdrawal over as long as several months and allow downloading the recorded data into a computer for analysis. Electronic monitors are considered accurate and can provide a continuous and long-term measure of medication adherence and the time of dose withdrawal which is not achieved with other indirect methods [138]. Monitors can also determine a range of adherence problems, including under dosing (the most common dosing error); overdosing; delayed dosing (dosing which exceeds recommended dosing intervals, which can lead to sub-therapeutic supply); drug holidays (avoiding taking medicines for several successive days without prescriber approval); and `white-coat adherence' (improved adherence by excessive use of medications or taking medications consistently a short time before clinic visits) [131, 139].

The major disadvantage of electronic monitors is that medication consumption is not guaranteed and may, therefore, overestimate actual adherence [137]. Monitors could also misrepresent medicine taking behaviour if patients take out several doses at once to carry away during a holiday or to load pill reminder boxes [131].

1.9.6 Pill count

Pill counts or measuring the volume of remaining medicines (for liquid medications) in a patient's bottle have been widely used in adherence research. It is easy to do and can be routinely done during clinic appointments or by phone [132]. The major disadvantage is that the amount of medicines removed does not necessarily indicate consumption and so that pill counts may overestimate adherence [140]. Also, pill counts do not give specific information about the timing of daily doses, as measurements are reported over weeks or months and not on a daily basis [131].

1.9.7 Patient self-reports

Patients' self-report of medication adherence is the most widely used measure in the research setting for patients with epilepsy. Self-report measures of adherence are commonly achieved by structured interviews, diaries or questionnaires. Researchers have used several general self-report measures for CYP with epilepsy [134, 135, 141], although few of these measures have been validated for epilepsy [141]. When the child is too young to fill in the questionnaire, parents or caregivers are usually interviewed or asked to fill in questionnaires that assess whether their children follow the treatment recommendations, react negatively to treatments and if there are problems with treatments (e.g. medication adverse effects) [132]. The utility questionnaire as a measure for adherence is however, limited. Patients/caregivers tend to report higher levels of adherence relative to more objective measures due to the feeling that reporting non-adherence may disappoint their clinicians [122]. Adherence measures by self-reports also vary greatly because

of the way they are developed, whether they have been validated, and to whom they are posted.

Studies aimed at evaluating the consistency of self-report methods of medication adherence (interview, diary or questionnaire) with non self-report methods (drug assay, pill count or electronic monitors) revealed that questionnaires and diaries exhibited moderate to high concordance with non self-report methods [142]. Interviews appeared less likely to provide a consistent estimate of adherence with other measures. This could occur because diaries and questionnaires afford a greater perception of anonymity compared with interviews [142].

1.9.8 Frequency of medication refill (measuring adherence using databases)

Worldwide, administrative databases containing anonymous prescription records have been extensively utilised to provide information on patients' adherence to medicines [143]. These databases also offer users the ability to follow up a patient's prescription history. Administrative databases can be derived from health care claims databases (i.e., medical and laboratory claims) and pharmacy claims databases [144].

The use of the databases in investigating drug use and adherence can provide a valuable source to conduct large population-based studies in a convenient, non-invasive, objective, and generally inexpensive way.

The use of the databases in assessing patients' adherence is, however, limited by the inability to determine if the patient actually ingested the dispensed medication [143]. Therefore, measuring adherence using databases assumes the consumption of prescribed medicines by patients. Hence, it is a proxy indicator of the level of adherence. The assumption is made that as long as a patient was prescribed the medication, it is likely that the patient will consume part or all of the medication. Patients' records in claim databases in the USA/Canada are linked to the pharmacy dispensing data, so the prescription filling rate is also available and is a better proxy measure of adherence. This is not the case with databases from primary care

in the UK where pharmacy dispensing records are not linked to GP records and the measurement of adherence depends on the pattern of issued prescriptions.

Medication adherence measured using claim databases has been validated using other adherence measures such as patient reports, pill counts, questionnaires, and interviews [145-147].

The majority of research on estimating patients' adherence using databases was conducted using pharmacy claims data. The first distinctive methodology for estimating medication adherence using databases was provided by Sclar et al. (1991) through the introduction of the medication possession ratio (MPR) [148]. Since this time, MPR has become a widely adopted and validated method to measure adherence using databases [143, 149]. The MPR is often defined as `the sum of the days' supply of medication divided by the number of days between the first fill and the expiration date of the last refill' [150].

The MPR as a ratio is usually a value between 0 and 1, where 0 means no medication supply or adherence and 1 means highest adherence to prescribed medicines. MPR >1 would occur in cases of overuse, early collection `early refill' or oversupply of prescriptions.

To the researcher's knowledge, no published study has examined adherence to prescribed AEDs using THIN database or any primary care databases from the UK. However, databases from the UK were used to measure adherence for other disorders. For example, Brankin et al. (2006) examined three UK general practice-sourced databases; the GPRD (recently re-named as CPRD), the MEDIPLUS and the (DIN-LINK) in order to estimate adherence to bisphosphonates among postmenopausal women in the UK [151]. The authors concluded that overall levels of adherence observed using the UK databases are in line with findings from other countries. The study revealed the value of using the prescribing information recorded in general practice data to examine prescribing patterns and medicine taking behaviours.

1.9.9 Adherence rates among children with epilepsy

The prevalence of non-adherence to AED regimens in the literature varies according to the method of adherence measurement, patient sample size, duration of study and the criteria or cut-off score for classifying patients as adherent or non-adherent.

It is a convention in the adherence literature that patients are considered to be adherent if they take 80% or more of their prescribed medications [152-154] The cut-off score of `80% adherence' has its origin in early studies on adherence to antihypertensive medications, which found that participants who took 80% or more of their medications had better blood pressure control than those who took less than 80% [155]. The cut-off score of 80% adherence has not been clinically validated for epilepsy but it has been applied in studies of other neurological conditions [156].

Medication adherence is a complex issue in CYP. It involves not only the patient, but also parents and other caregivers who are often responsible for giving the medication.

Systematic searches of three electronic databases were performed, including the MEDLINE (1946-2008), EMBASE (1980-2008) and PsycINFO (1806-2008), all via OVID, in December 2008, to search for articles relating to adherence to AEDs in CYP. Search terms comprised three main categories: 1) terms describing medication taking behaviour (e.g. adherence, compliance, drug adherence and patient compliance); 2) terms describing the age range of the participants (e.g. child$, paediatric, young people$, boy$ and girl$); and 3) terms relating to epilepsy (e.g. epilepsy, epilep$, seizure$ and antiepilep$).The search was restricted to the English language. Details of the systematic search are described in Appendix 7.

Studies were included in this review if 1) age range of participants was less than 18 years. 2) medication adherence rates were reported and 3) study design and methods for calculation of adherence were described (e.g., self-report, drug assay, pill count and prescription refill). Studies that described factors affecting children's

adherence and categorised participants into highly and poorly adherent without reporting adherence estimates were excluded from this review. Papers of interventions that did not include adherence rates were excluded. A total of 88 abstracts were identified including the key words of the search. A review of the titles and abstracts using the inclusion criteria identified eight reports as having relevant data on adherence in CYP (Table 1-3). According to these studies, adherence to AED regimens ranges from 44% to 88% depending on the method of measurement [134, 137, 157]. Studies which used children or parents' reports as a measure of medication adherence have reported higher adherence rates in comparison to other adherence measures. This may indicate that self-reports tend to show overestimation of medication adherence. In addition, few of these self-reported measures were validated for use in epilepsy. A study by Modi et al. (2008) used an electronic monitoring device and reported a high overall medication adherence of 79% [137]. However, this study was done over only one month and was aimed primarily at assessing adherence for the first month of therapy for children newly diagnosed with epilepsy. It is more likely that parents and children adhere to their treatment regimens initially.

An update of the search was carried out on March 2012 which added one relevant study by Modi et al. (2011) [158].

Table 1-3: Paediatric studies on adherence rates to prescribed medications for epilepsy

Study	Study design/setting	Sample size n(M:F)	Age range (Years)	Method of measurement	Main findings and limitations
Lisk 1985[159] UK	The study population were children attending an out-patient clinic at Birmingham Children's Hospital (May-July 1981)	16 (7:9)	0.8-14	Pill counts and a single blood drug analysis of AEDs	The authors counted pills left in a container of drug quantity for 1-month. 10 out of 16 children (62%) were good adherent (consumed 85% of drug). Blood drug level may mislead actual adherence as some children who adhered in pill count showed low therapeutic levels in blood analysis. Small sample size limited to one clinic and short duration of follow-up
Hazzard 1990[134], USA	Observational study at Paediatric Neurology Clinic for 1 year	35 (19:14)	9-16	Blood drug analysis at 3 time points on 1-month intervals versus parent-report (questionnaire)	Based on the blood data relevant to therapeutic levels, 12% of the children were adherent on 1 of 3 visits, 29% were adherent on 2 of 3 visits, 44% were adherent on 3 of 3 visits, and 15% had consistent sub-therapeutic levels but were seizure-free (full adherence was 44%). Adherence reported by parent report was not correlated with blood data Small sample size limited to one clinic and short duration of follow-up

Whitehouse 1997[160], UK	Cross-sectional survey study for one day at one outpatient paediatric clinic. The study was to assess accuracy of data in medical records and its effect on adherence	25 (14:9)	1-16	Parent-report via questionnaire	About 52% of children properly adhered to medication regimen. The remaining 48% of children did not take AEDs as prescribed mainly due to taking different AEDs than prescribed or different planned doses. Small sample size limited to one outpatient setting and short duration of study. Non-validated measure of adherence.
Kyngas 2000[141], Finland	Cross-sectional survey study. Study population were adolescents with epilepsy who were registered with the Finnish Social Insurance Institution	232 (118:114)	13-17	Self-report via patient questionnaire	Overall adherence was 66%. Only 22% of adolescents reported full (100%) adherence to their regimens, 44% chose the category of satisfactory adherence and the remaining 34% reported poor adherence. Self-report subject to false-positive bias
Mitchell 2000[135], USA	Observational longitudinal study of children for at least 6 months as long as 2.5 years. Children were newly diagnosed children with epilepsy at a Paediatric Neurology Clinics	119 (51:68)	4-13	Parent-report adherence using questionnaire, serum drug levels, and adherence to scheduled appointments	The principal aim was to model some psychosocial, behavioural, and medical factors that can predict adherence. Outcome measures were self-report of adherence, blood level adherence and visit adherence. Mean adherence by parent report =88% and by drug assay=86% The study was conducted at one clinic so it cannot be generalised to all populations.
Otero 2000[161], UK	Prospective study of children and their mothers attending a central hospital in London. Assessed in	21 (13: 8)	Mean age=12 (SD=2.9)	Sum score of adherence to scheduled appointments and medication using case-note review	Good adherence was reported with 12 children (57%) Higher levels of expressed emotions were observed for children with poorly controlled seizures and poor medical adherence as

	two points estimates; initial started in 1993 and then 3 to 4 years later. Main aim was to investigate whether there was an association between maternal expressed emotion and children's psychiatric symptoms and adherence				compared with children with well-controlled seizures and good medical adherence Not clear how medication adherence was measured. No data reported on the follow-up adherence rate. Very small sample size
Asadi-Pooya 2005[157], Iran	Cross-sectional study on children who attended a university clinic (Jan-Jun 2004)	181 (101:80)	Mean age=7 (SD 4.6)	Self or parent-report via interviews	Satisfactory adherence was reported by 72% No data was reported on questions asked to score adherence and what is Satisfactory adherence. Cross-sectional study in one epilepsy clinic with the possibility of false-positive bias Non-validated measure of adherence.
Modi 2008[137], USA	Cross-sectional measure of adherence at one-point estimate on children attending a new-onset epilepsy clinic	35 (13:12)	2-12	Electronic monitor	Adherence rate of 79% was reported and only 8 children (23%) were completely adherent (100%). The aim was to measure adherence shortly after the clinic visit (the duration of study was one month). Small sample size
Modi 2011[158], USA	Prospective longitudinal observational study of daily medication adherence up to 6 months after initial prescribing	124 (79:45)	2-12	Electronic monitor Adherence rates were set as 0, 50% or 100% based on specific regimens	About 42% of children showed near-perfect (100%) adherence and 58% demonstrated different levels of non-adherence (mild-moderate- severe) based on group modelling of children with similar adherence behaviour.

1.9.10 Impacts of non-adherence

Non-adherence with pharmacotherapy is considered one of the greatest challenges facing medical care and can have adverse effects on patients' quality of life, mortality rates and economic outcomes [162].

Limited data are known about the consequences of non-adherence in CYP with epilepsy [158]. However, the data from adult studies could be extrapolated to CYP because epilepsy in CYP manifests the same symptoms and has a similar drug treatment strategy to that of adults. In cross-sectional studies on adults with epilepsy, the potential consequences of medication non-adherence are considered to be serious and include loss of seizure control and therapy failure [120, 121, 162]. In a national survey of 661 adults with epilepsy by Cramer et al. (2002) in the USA, 45% stated that they had a seizure when missing a dose. There was a higher risk of having seizures among patients taking AED treatment four times daily ($p=0.04$) and among those taking a greater number of pills per day ($p=0.02$) [120]. Poor adherence was associated with frequent emergency visits and hospitalisations and reduced quality of life [162]. In a local university hospital in the UK, 265 (6.5%) of 4093 adult admissions in 2001 were considered to be medicine-related and 30% of these were due to non-adherence to medicines for chronic illness [163]. In a survey of 408 adults with epilepsy in the USA, 29% of patients were grouped as non-adherent (based on self-report of missing a dose or stopping an AED within the last month) [162]. Of the non-adherent group, 54% (versus 37% adherent) had lower scores in mental health and 29% (versus 12% adherent) had significant absence from school or work due to frequent seizures or termination from employment ($p<0.001$).

Cross-sectional design can be effective in displaying the short-term consequences of non-adherence to AEDs such as experiencing seizures. Cross-sectional surveys, however, may be of limited power to identify the long-term consequences of non-adherence to AEDs, such as mortality and HRQOL due to the short time frame of observation and data collection. Therefore, longitudinal population-based studies may be of higher value in describing the long-term consequences.

Poor adherence has been reported to be a significant risk factor for higher mortality and sudden unexpected death from epilepsy [164-167]. A population-based study conducted in the US using Medicaid claims data of 33,658 adult patients with epilepsy was aimed at investigating the relation between non-adherence to AED and mortality rates [168]. The authors concluded that non-adherence to AEDs is associated with a 3-fold increase in mortality risk among epilepsy patients, compared with those who are adherent (hazard ratio = 3.32).

Non-adherence to medications increases the consumption of healthcare resources and may impair the ability of health care systems to achieve health goals for populations [169]. Consequently, the negative outcomes of non-adherence increase direct health care costs related to epilepsy [156, 170]. A recent population-based study conducted in the US by Faught et al. (2009) using a retrospective database of 33,568 adult patients with epilepsy estimated the potential association between AED non-adherence (defined as dispensing of less than 80% of medications) and health care costs [170]. The authors estimated that non-adherence to AED treatment was associated with higher additional cost for inpatient ($4,320 per quarter) and emergency admission ($303 per quarter). In another population-based study by Davis et al. (2008) estimated the costs of non-adherence to AED therapy in 10,892 adults with epilepsy in the USA [156]. Non-adherence to AEDs (defined as dispensing of less than 80% of medications) was associated with an 11% increased likelihood of hospital admissions ($p < 0.001$) and $1,799 additional inpatient costs ($p = 0.001$) per patient per year. Non-adherence was also associated with a 48% increased likelihood of emergency room admissions.

1.9.11 Forms of non-adherence to medication

Non-adherence to prescribed medications can take different forms, including dose omissions [120], failure to fill the prescription [156], incorrect dosage, improper dosing intervals [171], premature discontinuation of the drug [172], drug holidays and `white-coat adherence' [173]. Studies on paediatric epilepsy have suggested that non-adherence to paediatric medication regimens may be unintentional due to forgetfulness [174], misunderstood directions, busy parents, complex medication schedules, and difficulties in access to care [135]. In some

circumstances, non-adherence was intentional as a result of stigma at school [174], lack of caregiver support [175], lack of trust of physicians [134] parents' fears of addiction, sedation and cognitive problems from AEDs [135].

This thesis investigated available factors in THIN as possible causes of non-adherence to AED treatment, which are presented in Chapter 3. In fact, causes of non-adherence to medications are numerous and multidimensional. The next section will discuss these causes in more detail.

1.9.12 Risk factors for non-adherence to medications

Research has uncovered numerous factors as possible causes of non-adherence. Generally, non-adherence to medication regimens in CYP with epilepsy is multidimensional with no single factor predicting adherence alone [176]. The common barriers to optimum adherence are simply illustrated in Figure 1-2 [152]:

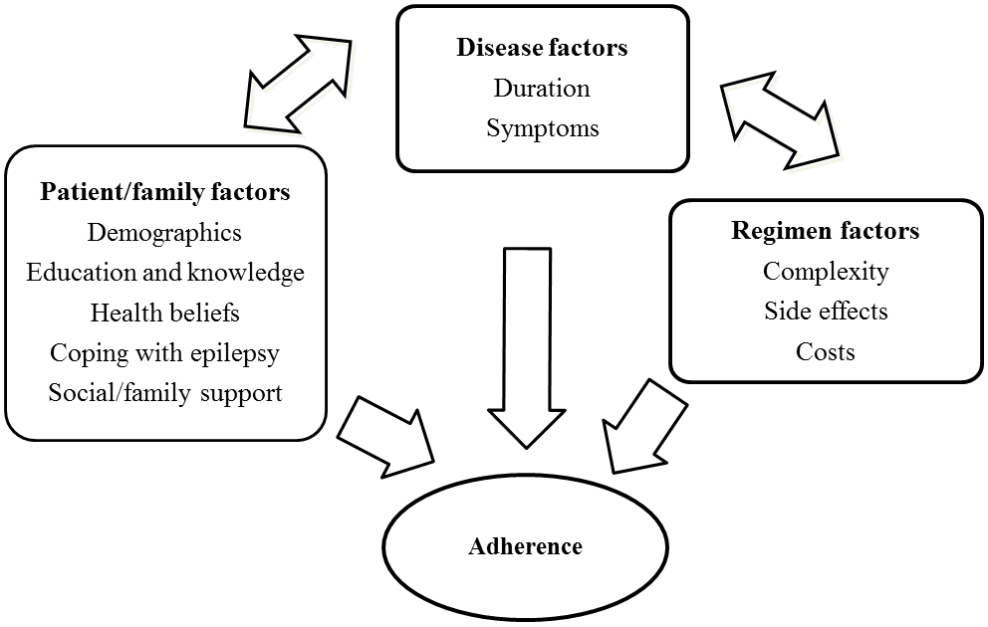


Figure 1-2: Common factors that may contribute to non-adherence in CYP

1.9.12.1 Patients/family factors

Patients' demographics

Studies in CYP with epilepsy have found no significant difference or correlation between sex and adherence [134, 174, 177].

Adherence to medical regimens has been observed to decrease as a child grows older with adolescents being more likely to be non-adherent than younger children [174, 178]. Kyngas (2000) found that only 22% of 232 adolescents with epilepsy in Finland, aged 13-17 years, were ranked as showing full adherence to their medication regimens [141]. The reasons why adolescents are less likely to adhere are complex. Increased feelings of embarrassment and stigma among peers associated with taking AEDs was a possible cause [178]. Forgetting to take the medication may simply be the cause when adolescents take over the responsibility for their own medicines and parents are less involved in ensuring adherence. Anderson et al. (2000) reported that 18 out of 19 adolescents with epilepsy forgot to take medication at least once during their treatment courses [174].

At preschool and primary school age, parents and other caregivers supervise and are responsible for the child's medication regimen. As the children begin to perceive of the effect of disease on their daily lives, they are either adherent or poorly adherent according to their awareness of how illness impacts their daily lives [179]. Adolescents may also refuse to follow medical instructions as a means of expressing their independence and autonomy from their family [180-184] or due to a perceived sense of immortality [185].

Family size can affect the level of adherence in CYP. Asadi-Pooya (2005) reported that the number of people in a family could negatively affect adolescent adherence to AEDs in Iran [157]. Kyngas (2000), however, reported no significant association between the family size and composition and adherence to AEDs in Finland [141]. The effect of family size might depend on cultural differences between countries.

The effect of socioeconomic status on a child's medication taking behaviour has been studied extensively. While poor adherence in adults with epilepsy was

associated with low socioeconomic status and financial distress [186], parents' income was not related to adherence to epilepsy medication in 211 CYP in the USA, aged 1-15 years, in a study by Shope (1988) [177]. Similar findings were also reported by Mitchell et al. (2000) who examined the effect of sociocultural factors and family environment on adherence to treatment in 119 children (4-13 years) with epilepsy in the USA[135]. They concluded that children who belonged to lower income families with high levels of stressful life events were more likely to adhere to treatment. The authors suggested that families reporting high levels of stress used medical recommendations and contact with physicians as a helpful coping mechanism [135].

Parents' education and culture are presumed to contribute to adherence regimens as they mediate understanding and following of medical instructions [135]. However, families reporting less parental education showed higher levels of adherence to AED regimens [135]. Shope (1988) also found that parents' education was not related to children's adherence to AEDs [177].

Knowledge about the disease

Amongst the factors that can contribute to medication adherence is self or parent knowledge and received education about the disease [135]. Shope (1988) revealed that parents' knowledge only of their child's prescribed regimen in epilepsy was significantly associated with adherence ($p<0.01$) [177]. However, there was no difference in children's adherence associated with parents' knowledge of the cause of seizures and seizure care.

A study by Galletti et al. (1998) of 41 CYP with epilepsy in Italy, aged 6-18 year, reported that CYP were less involved with clinicians in communication about diagnosis, treatment plan and life-style counselling [187]. Often children appeared to have little information or were completely unaware of their condition and the reason for taking medication [187, 188]. The lack of enough information can also contribute to poor adherence and, therefore, to a less desirable prognosis [161]. In a survey study by Aytch et al. (2001), parents of 31 young children with epilepsy, aged 1-5 years, expressed their need for sufficient and easy-to-understand information about diagnosis, treatment, how

to cope with seizures and how to act when a child has an emergency situation [189].

Beliefs about illness/treatment

Factors such as necessity of medicines and health beliefs (alternative treatment practices) may influence parents' ability and tendency to follow prescribed medication [135].

No evidence was found in CYP with epilepsy. In a survey conducted in 2002 of 661 adult patients with epilepsy in the USA, some patients who had not experienced seizures for some time began to gradually reduce their adherence to prescribed medication [120]. They believed that taking medication was unnecessary, particularly if they had omitted doses previously with no seizure occurring. Patients may not perceive non-adherence as the main attributing factor in seizures occurring. When adult patients were asked if anything increased the likelihood of a seizure, 41% mentioned stress/emotion, 19% fatigue, and only 13% stated missed medication [190]. This could be relevant in children if their parents' belief about epilepsy medication coincide with what is mentioned above.

Some cross-sectional studies have found that some people particularly in Africa, believe that epilepsy is an infectious disease and other people believe that traditional treatment is the best choice [191, 192]. Therefore, amongst the aims of the ILAE/IBE (the International Bureau for Epilepsy)/WHO Global Campaign Against Epilepsy Demonstration Projects is to show that with educational activities and improved awareness about epilepsy, the social attitude towards epileptic patients and their families can be reduced [191, 193].

Patient/physician partnership

Young people with epilepsy who perceived that their physicians were easy to communicate were more likely to adhere to medication [178]. Hazzard et al. (1990) found that parents' satisfaction with their children's medical care

influenced adherence to AEDs, while unclear communication with clinicians impaired satisfaction with medical care and adherence [134]. Failure to appropriately communicate with or trust the physicians was suggested as a reason for intentional non-adherence to epilepsy medication [135]. Kyngas (2000) found that support from physicians positively correlated with adherence of adolescents with epilepsy [141]. Around 60% of 232 adolescents, aged 13-17 years, reported that physicians were concerned only with epilepsy as a disease and gave them orders and made decisions concerning their care without negotiating a treatment plan.

CYP have demonstrated that their health concerns are not always taken seriously by their clinicians; they felt excluded from the discussion with parents and clinicians tended to decide about their illness without seeking their perspective [194]. Recent research has suggested that children over 5 years should be involved in their healthcare choices [194]. At this age, children gain more knowledge, skills, and responsibility for their own conditions and are able to take care of their medicines in partnership with healthcare professionals [188]. Therefore, doctor-patient communication and counselling children and parents was suggested highly important to prevent bad prognosis of epilepsy and to motivate adherence to medication [187].

Coping with epilepsy

Coping refers to `a dynamic process of cognitive and behavioural efforts to manage demands when a person is faced with a stressor' [195]. Successful adherence, particularly in epilepsy, requires psychosocial adjustments on the part of the children and parents (e.g., improved self-efficacy and lower fear of seizures and complications) in order to cope with epilepsy and the medication regimen (e.g., its scheduling, side effects, and costs)[196].

Negative attitudes towards epilepsy, low motivation and disturbance in emotional well-being were associated with poor medication adherence in 232 adolescents with epilepsy in Finland [197]. Whereas, adolescents who had a strong sense of normality and felt that epilepsy was not affecting their social

well-being showed an 8.4-fold higher tendency to adhere to medication regimens ($p<0.01$) [197].

Young people may feel that taking an AED is stigmatising and distinguishes them from their peers [198]. Although, many studies have reported the feeling of stigma among CYP with epilepsy and their families [198-200], the effect of feeling stigma on adherence to AEDs in CYP has not been well-documented. In a survey study of 696 young people and adults with epilepsy in the UK, young people (defined as 16-20 years) who had difficulty in social coping due to the stigma associated with epilepsy have reported lower adherence [178].

Parents' well-being also can influence their ability to adhere to their child's prescribed therapy. Parents of children with epilepsy who were highly anxious and worried about their child's health have placed more restrictions on their child's behaviour, which has negatively affected the children's adherence to antiepileptic regimens [134, 161].

Social and family support

Generally, social support from friends and family members has been associated with higher medication adherence, while poor family support has been linked to poor adherence [135, 141]

Assistance and support from friends and family can contribute to children's adherence by encouraging optimism and self-esteem, reducing depression, and giving practical assistance [201]. Practical support from family is important for adherence (for instance, from the first diagnosis of epilepsy, family are advised to help by monitoring seizures and medication dosages, maintaining medical appointments and are involved in the initial explanation of the dosing regimen) [202].

Support from parents and friends was associated with a statistically significant increase ($p<0.001$) in adherence to medication regimens in 50% of 232 adolescents with epilepsy in Finland [141, 197]. In a survey of 47 school CYP with epilepsy in the USA, about half felt embarrassed by their seizure disorder, one-

third had difficulty in making friends and felt excluded by their peers and less than 20% felt that they were mocked because of their epilepsy. Children with epilepsy described the attitude of their classmates as having a more negative effect than experiencing seizures [174].

In a study of 21 CYP in London, UK, mean age=12 (SD=2.9), good medication adherence in 12 out of 21 children was found to be associated with less critical comments and hostility from mothers (p=0.049). Children and mothers in the good adherence group had less depressive and stress-related symptoms [161].

1.9.12.2 Disease factors

Duration of treatment

Studies in children and young people have demonstrated that adherence to medical regimens is inversely related to, and tends to deteriorate with longer duration of a disease condition [203]. The length of time a an adolescent has been taking medications has a negative impact on their adherence level to AEDs [141]. Adolescents who had epilepsy for 1-3 years demonstrated a significantly higher adherence ($p< 0.001$) than those who had the disease more than 3 years [141].

Seizure type and frequency

It can be assumed that patients with more frequent and severe symptoms are more likely to adhere to their regimen. Shope (1988) examined predictors to adherence by assessing serum levels of AEDs in two paediatric populations with epilepsy (n=90, n=211) [177]. The author concluded that adherence was higher in the group that experienced a higher frequency of seizures ($p<0.025$).

However, Hazzard et al. (1990) found that children with more parent-reported seizures during the previous year were associated with lower adherence to medications [134]. However, this study was conducted over a short period (3 months) and it is possible that lower adherence may have produced increased disease activity.

No evidence was found from paediatric studies in epilepsy on the association between seizure type and adherence. Specht et al. (2003) assessed AED levels of 52 adult patients in Germany and found that out of the non-adherent group those with generalised tonic clonic (GTC) seizures were less likely to adhere compared to other seizure types [204]. However, the authors suggested that this finding should be interpreted carefully as patients having GTC seizures were more likely to see a clinician soon after having a seizure compared to patients with other types of seizures.

1.9.12.3 Regimen factors

Complexity

The general findings throughout the research literature indicate that the simpler the schedule, the greater probability of medication adherence. For example, adherence with oral medicines was better with twice daily regimen versus four times a day [205]. Asadi-poya (2005) found that adolescents with epilepsy who were on once daily regimen showed a higher adherence than those on 2-3 times daily regimens [157]. Cramer et al. (2002) calculated that the odds of missing a dose increased by 27% each additional time an AED was expected to be taken daily [120]. Logistic regression models indicated that the likelihood of a seizure following a missed dose of medication was positively associated with the number of medication pills taken daily [120].

The possibility of taking AEDs once a day was a significant preference for children with epilepsy, aged 5-14 years, who chose once daily monotherapy with sustained-release formulation of sodium valproate over conventional twice daily valproate [206]. Adult patients with epilepsy also preferred to be switched from immediate-release to the sustained-release formulation of sodium valproate. Patients stated that they could easily fit this into their everyday routine which would minimize the chance of forgetting to take doses [207].

Forms and palatability

It has been observed that parents prefer oral liquid to solid forms but adherence was measured in only few studies [205]. No evidence was found for children with epilepsy. However, poor adherence to prescribed medications has been associated with the bad taste of some drugs (such as HIV, immunosuppressive and asthma medications) as reported by many children and their caregivers [208-211]

Side effects

Adverse effects from medications were associated with lower adherence. Studies of CYP have suggested that these groups are less aware or worried about possible long term harmful effects of medicines compared with adults, but CYP are concerned about side effects, and dislike feeling dependent on medicines [135].

Most AEDs have some neurological side-effects which impair an individual's psychosocial functioning particularly in children and adolescents [178]. In a survey of 47 school children and adolescents, half of the children were dissatisfied with taking AEDs and all reported that sleepiness was the major adverse effect of AEDs [174]. Children and adolescents have reported that side effects are a cause of non-adherence to AEDs [134, 157, 178].

Cost

Treatment costs may represent a burden to some families particularly in chronic illnesses. A recent review of current published research has focused on the relation between out-of-pocket medication costs and adherence [212]. The review also examined how patients cope with medication costs in chronic illnesses. The authors have concluded that based on cross-sectional and longitudinal data, higher out-of-pocket medication costs and lower patient incomes are each associated with the underuse of prescribed drugs with considerable evidence of cost-related poor adherence. This issue may be

unimportant for children and many young people with epilepsy in the UK as children up to 16 years are entitled to free prescriptions and standardised access to diagnostic facilities and epilepsy services.

1.10 The data source for the thesis

All analyses throughout the thesis have been conducted using THIN database. The structure, advantages and limitations of using THIN are discussed below.

1.10.1 Introduction to THIN data

The Health Improvement Network (THIN) is a longitudinal computerised primary care database that contains electronic medical records from general practices around the UK. THIN database contains data from 514 general practices with a total of more than 10 million patients which, in 2010, covered 5.8% of the UK population. Of these, about 3.6 million patients are actively registered with practices and can be prospectively followed [213]. The remaining patients have either left the practice or died but their historical data are still stored. THIN comprises over 57 million person-years of data.

The data included in THIN is the information that GPs and general practice surgeries record on their patients using the Vision general practice computer system (In Practice Systems, London, UK) as part of everyday clinical care [214, 215]. Patient records (stripped of identifying details) are extracted on a regular basis and electronically downloaded via a secure internet connection by EPIC, UK, the company responsible for incorporating the raw data into the final THIN database. In fact, many of general practices contributing to THIN are previously and/or currently contributing data to the GPRD; one of the UK largest and validated database for pharmacoepidemiological research. Other THIN practices have never contributed data to GPRD [214].

The data collection in THIN started prospectively from general practices in September 2002; however, for many practices, electronic records have been available since 1987 and these records were assimilated into THIN [215].

THIN provides anonymous data on demographic information, lifestyle characteristics, medical diagnoses (including those resulting from referrals to specialists), prescriptions issued by GPs, laboratory results, measurements taken during medical practice and free text comments [215, 216].

A number of different versions of THIN, from different stages of the project's development, are available. Major versions are named according to the number of practices contributing at the time of data incorporation. For example, THIN-255 contains data from 255 general practices. Within each major version, there may be a number of sub-versions resulting from periodic updates to the collected data. For example, THIN-255 (November 2004) provides data from 255 practices, where the last date of data collection was 30 November 2004.

1.10.2 Strengths of using THIN in health research

Size and representation

The main advantage of using the THIN database in health research is that it contains an anonymous and nearly comprehensive history of patients in the NHS system. Patient histories include clinical, morbidity diagnosis, treatment, disease monitoring, outcomes and health care utilisation data collected throughout the daily routine work of the GPs [217]. Thus THIN is a large population-based database that was derived from a representative subset of the UK population. THIN provides longitudinal data which make it attractive for studying trends of prescribing, long-term medication use and clinical outcomes, particularly for chronic diseases such as epilepsy [217]. THIN can reflect the real-life situation of communication with patients through GP's recorded notes and can also provide information that is generalisable to the general populations.

Convenience and applicability

Using THIN database is relatively less expensive and less time-consuming for conducting research than other study designs, such as RCTs, which are often carried out for shorter durations than would be desirable. Since its establishment in 2002, general practices contributing to THIN are increasing which has provided prospectively recorded and computerised data [217]. This makes THIN of potential use for conducting observational primary research for chronic conditions such as epilepsy. In terms of medicine use and adherence, THIN is not intrusive, since patients and GPs are not contacted for data collection purposes. Therefore, frequency of drug use and other study outcomes are not affected by research activities.

Validity and reliability

The validity of THIN data has been examined for clinical diagnosis of major diseases. Studies have demonstrated that the THIN database has a high level of completeness and reliability in recording of hepatitis C [215], gastrointestinal ulcer [216], death [218], lymphoma [219], and skin cancer [220]. All previous studies have suggested the usefulness of THIN database in conducting medical and pharmaco-epidemiological research. Another study was able to reproduce well-established associations between diseases and drugs utilising a case-control design [214] . THIN has showed a high level of completeness in recording rates of prescribing of smoking cessation medication compared to the reported rates of dispensing of prescriptions from the NHS Prescription Services data [221].

A recent study by Meropol and Metlay (2012), concluded that THIN has good quality in recording hospitalisation codes of acute pneumonia hospital admissions [222]. Recording admission dates was of accurate timing for short stay, however, not for longer stay.

1.10.3 Limitations of using THIN

The use of THIN has many advantages, but there are also limitations and weaknesses for clinical and medication research. These limitations include incomplete recording of certain information that may be desirable for research purposes, such as diagnostic subtypes of epilepsy, frequency of occurring seizures and some dosage instructions. This is because the data collection is based on what the GP considers to be important for the long-term care of individual patients [223, 224].

Drugs prescribed by hospital doctors or other specialists during inpatient stays are not recorded in THIN database. However, drugs prescribed on discharge, to be continued, are included on the discharge summary, since the GP will be responsible for subsequent prescribing of these drugs.

Measurement of adherence to AEDs relies on the pattern of issued prescriptions by GP. There is no link between CYP's records in THIN and dispensing data, so measuring adherence assumes that CYP dispensed their prescriptions and consumed their medications.

Although THIN provides longitudinal data, the length of follow-up of many individual patients is short as patients are free to move and change general practice as they like.

1.11 Rationale for the thesis

Epilepsy is a widespread and heterogeneous set of chronic neurological disorders that requires continuous treatment for good clinical and psychosocial outcomes [27, 135]. Epilepsy has been demonstrated to carry social stigma and to have adverse educational, psychosocial and vocational consequences in CYP [35, 40, 44, 225].

Appropriate evidence-based prescribing accompanied by patient adherence to medical advice and AEDs is a key factor for achieving better clinical outcomes and improvement of individuals' quality of life. Limited data are available about the pattern of AED prescribing in CYP in primary care. Research into measuring medication adherence in CYP remains sparse with many studies using non-validated and non-objective measures. Moreover, the majority of research that has examined the problem of non-adherence to AEDs in paediatric epilepsy has been carried out using cross-sectional designs and small populations. This may influence the statistical power and generalisability of the results and therefore, may not necessarily give a precise picture of the general population's drug-taking behaviour. Since adherence to medication is described as a dynamic process [169], the change of adherence levels over time cannot be reflected in cross-sectional surveys. This may depict the strength of a longitudinal study in characterising the long-term changes in adherence.

Only three studies have been conducted on the adherence of CYP with epilepsy in the UK, which are out of date and non-generalisable [159-161]. The aims of two studies were to examine the accuracy of data in medical records of CYP [160] or to measure the association between mother's expressed emotions and the well-being of the child and possible effects on medication adherence [161]. No study has addressed the long-term adherence and its dynamics.

Very little is known about the consequences of non-adherence in CYP with epilepsy in terms of seizure control and prognosis of the disease. Research on adults with epilepsy has demonstrated that poor adherence lead to poor prognosis and increased mortality rates. The optimal or minimal level of

adherence in paediatric epilepsy that is necessary to achieve good clinical outcomes remains uncertain [137].

In addition, very limited data are known about the costs associated with treating epilepsy in children in the UK. Aggregated data of small cohorts of CYP with adult data were only reported in predated studies in the UK prior to 1999. A population-based study will provide a more robust estimate of the cost of illness and, therefore, will aid in assessing the burden of epilepsy in children in the UK.

In chronic diseases like epilepsy, GPs are responsible for prescribing the majority of AEDs for CYP and, therefore, play a key role in management of disease in the UK. THIN database will most likely provide access to large representative samples of CYP with epilepsy in the UK. Using the prescribing information recorded in THIN, the pattern of AED use can be illustrated and adherence rates of CYP diagnosed with epilepsy can be measured.

This thesis represents a population-based study of paediatric epilepsy in order to quantitatively assess medication use in CYP, examine the longitudinal dynamic adherence rates to medicines over time and reveal possible clinical outcomes associated with it. Furthermore, the thesis will provide an estimate of the direct costs associated with treating epilepsy in CYP in the UK primary care.

1.12 Aims and objectives of the thesis

1.12.1 Aims

The aim of this research study is to examine the prevalence of epilepsy in CYP in UK primary care and to quantify adherence to AEDs using THIN data. The long- term clinical outcomes and the direct costs associated with treating childhood epilepsy will be estimated at the population level.

1.12.2 Objectives and thesis outline

The objectives of the study are to:

Chapter 2

1. Determine the incidence and prevalence of epilepsy in a population of children under 18 years old who were registered at THIN participating general practices between 1988 and 2004.

Chapter 3

2. Examine the prescribing pattern of various AEDs that have been prescribed for each child initially and over time.
3. Measure the adherence of the CYP to AEDs, initially and over time, and determine how this varies by key clinical and sociodemographic variables (e.g., age, sex, socioeconomic status, type of epilepsy and the number of AEDs).

Chapter 4

4. Investigate the association between adherence and clinical outcomes, such as seizure counts (frequency) and duration and proportion of patients that are seizure-free (remission period).

Chapter 5

5. Quantify primary health-care resource utilisation by CYP over time, from the point of diagnosis and estimate the direct costs of treating epilepsy in primary care.

Ethical approval

Ethical approval for the research project was granted from the THIN internal Scientific Review Committee (SRC).

Chapter 2 Estimating the incidence and prevalence of epilepsy in children and young people in the UK

2.1 Introduction and rationale for this analysis

Over the last four decades, findings from published literature have reported that the incidence of epilepsy varies substantially with age with its highest peak in childhood [21]. Estimates in Europe have reported incidence of epilepsy in CYP to be 50-70 per 100 000 population and is slightly higher in males [21, 25]. A number of studies have examined the incidence and prevalence of epilepsy in the UK (Table 2-1 and Table 2-2) [22, 23, 27, 226-231]. Some of these studies have provided period estimates of the incidence and prevalence because of the cross-sectional design [22, 228, 230]. Other studies were conducted in specific locations in the UK [23, 229, 231]. Some studies included children as a part of a wider age-range study cohort [228-230]. Other studies were designed to examine incidence of specific seizure pattern (such as prevalence of acute repetitive seizures) [230].

Table 2-1: Previous incidence studies of epilepsy in CYP in the UK

Reference	Study period	Study population	Age group (years)	incidence/ 100,000 population
Verity 1992[227] UK	Survivors of 1970 British birth cohort followed up 10 years	14,676	0-10	43
Cockerel 1995[228] England	Notes and letters of GPs in 1993	6000	0-20	61
Wallace 1998[22] UK	GPRD 1995	134,389 124,521 121,450	5-9 10-14 15-19	63 54 101
Heaney 2002[23] London and South east England	1995-1997	Person-years were reported	0-4 5-14	190* 75* Crude 51.5
Reading 2006[231] Norfolk, England	2001-2003	77952	0-14	66
Martinez 2009[230] UK	GPRD 2005	160,118 169,261 365,968	0-4 5-9 10-19	57* 41* 36*

* Incidence calculated per 100,000 person-years

Table 2-2: Previous prevalence of epilepsy in CYP in the UK

Reference	Study period	Study population	Age group (years)	Prevalence/ 1000
Ross 1980 [226] UK	Follow up cohort born in 1958	15,496	11	4.1
Verity 1992[227] England	Survivors of 1970 British birth cohort followed up 10 years	14,676	0-10	2.8
Cockerel 1995[228] UK	Notes and letters of GPs 1993	6000	0-20	4.3
Wallace 1998[22] UK	GPRD 1995	134,389 124,521 121,450	5-9 10-14 15-19	3.2 4.1 5.2
Purcell 2000[27] (ONS) England and Wales	GPRD 1994-1998		1994 0-4 5-15 1998 0-4 5-15	 2 4.2 1.9 4.4
Wright 2000[229] Bradford, England	83 G Practices 1996-1998	360 000	All ages (Including adults)	4.5
Martinez 2009[230] UK	GPRD 2005	160,118 169,261 365,968	0-4 5-9 10-19	1.3 2.8 4.1

Not only incidence is higher in children than in adults, but a population-based study conducted by the Office for National Statistics using the GPRD database has reported 7% increase in age-standardised prevalence of epilepsy between 1994 and 1998 for all ages [27]. Furthermore, there appear to be variations in incidence and prevalence within the population linked to socioeconomic status. Some studies have examined association between incidence of epilepsy and socioeconomic status in the UK. A study conducted by Heaney et al. (2002) identified 119 patients with epilepsy (including 65 CYP aged 0-14 years) from 20 general practices in London and south east England [23]. The authors reported that the incidence of epilepsy varied by socioeconomic status with a possible twofold increase in the odds of epilepsy in CYP living in highly deprived areas than those living in least deprived (p=0.001). However, in a more recent study,

Reading et al. (2006) identified 182 CYP, aged 1 month-14 years, who had a confirmed diagnosis of epilepsy in the Norfolk university hospital, UK. The authors found no association between incidence of epilepsy and area of deprivation (p=0.98) [231]. A limitation of both studies was that they were conducted in specific geographic areas in the UK and on relatively small populations of children.

The current state of evidence in the UK suggests that the prevalence of epilepsy is increasing in the population, with the highest incidence in childhood, and a possible association with socioeconomic status, However, this evidence is sparse or out-of-date, so a population-based study is needed to investigate trends of incidence and prevalence over time, to allow more appropriate planning for current and future health care resource allocation. This chapter aimed to use THIN database to estimate the incidence and prevalence of epilepsy in CYP in the UK between 1990 and 2004.

2.2 Objectives of the analysis

The objectives of this chapter were to:

1. Identify a study cohort of CYP with epilepsy using THIN.
2. Estimate the incidence rate and prevalence of epilepsy in CYP in the UK between 1990 and 2004.
3. Perform a descriptive analysis of the basic characteristics of the study cohort by age, sex, level of socioeconomic deprivation and co-existing morbidities.

2.3 Methods

2.3.1 Data source and study population

The estimation of the incidence and prevalence of epilepsy was conducted using The Health Improvement Network (THIN) primary care database (Chapter 1).

This study used a preformed THIN dataset (THIN-255) that contained anonymised patients' records from 255 general practices across England, Northern Ireland, Scotland, and Wales. The study population were CYP younger than 18 years old who were born on or after January 1st, 1988 and contributed to THIN up to November 30, 2004 [232].

The incorporated data in THIN are supplied in the form of four separate standard files and two linked files. The standard files are patient, medical, therapy and additional health data (AHD) files. Each file contains a unique practice identification code and a unique (per practice) patient identification code, which together form a unique identifier for individuals within the database. The linked files are postcode variable indicators (PVI) and dosage records. The main information recorded in the four basic files is shown in Table 2-3.

Table 2-3: Structure of The Health Improvement Network database

THIN data File	Available information
Patient	Patient's demographic information and registration details (e.g. registration date, transfer-out date, month and year of birth for children up to 15 years and then only year of birth for patients older than 15/date of death, sex, and a unique (per practice) household identifier for members of the same family or patients reside at the same address)
Medical	Records of medical symptoms, disease diagnoses, hospital admissions, medical procedures and investigations
Therapy	Details of prescriptions such as date of prescription, name of drug, drug formulation, quantity prescribed, dosage frequency, and duration of prescription
Additional Health Data (AHD)	Additional information such as lifestyle and preventative health care (e.g. smoking and alcohol habit, weight, height, blood pressure, vision, hearing, physical/mental child development, immunisations, biological test results, diagnostic radiography, drugs serum levels)

Diagnoses of diseases and other medical disorders are recorded using the READ codes scheme. The Read codes exist in a hierarchical structure of comprehensive clinical terminology system relating to observations (signs and symptoms), diagnosis, investigations and surgical procedures. The first version of the Read code scheme (4-Byte READ) was developed in the early 1980s by Dr James Read, a Loughborough (UK) general medical practitioner [233]. The technical properties of 4-Byte READ scheme were extended to 5-Bytes new code structure prior to January 1991. The Read Thesaurus (Version 3 of the Read Codes) is a progressive version of medical terminology that aims to support clinicians from the primary, secondary and tertiary settings in recording all processes of care and manage data in electronic patient records. It was developed during the Terms Projects (1992-95).

In 1988, the National Health Service (NHS) recommended the Read Codes scheme as the standard for general practices[233]. The Read codes scheme is structured into chapter headings contained in a comprehensive dictionary.

The clinical terms in the Read scheme allows cross-mapping to other coding systems such as the UK mandated classifications of the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS-4) and the International Statistical Classification of Diseases ICD 9 and ICD 10.

Prescriptions are recorded using the Multilex coding system developed by First Databank, UK.

Data from the four basic files were used to identify the study cohort for this analysis and other subsequent analyses throughout the thesis.

2.3.2 Identification of children and young people diagnosed with epilepsy

The inclusion criteria for extraction of a relevant cohort involved CYP younger than 18 years at their registration date at general practices contributing to THIN. Neonates who were less than 28 days were included because children's precise date of birth (day, month, year) is not available in THIN records as part of ensuring anonymity. The month and year of birth are recorded until the child's 15th birthday, after which only the year of birth is recorded [234].

The CYP were required to have at least one diagnostic code of epilepsy or epilepsy subtype (Appendix 8) and at least one prescription of an antiepileptic drug (AED) shown in Appendix 9. This criterion comprised the study definition of epilepsy and it has been commonly applied to identify children and adults with epilepsy using databases [22, 156, 230]. The researcher consulted a clinical associate professor (William Whitehouse) in the Division of Paediatric Neurology-Queen's Medical Centre Hospital – Nottingham, to assist in refining the diagnostic codes list of epilepsy clinical terms to avoid misdiagnosis of epilepsy. Infants and young children who had only diagnoses of febrile convulsions were not included in this study.

2.3.3 Data management for the extraction of CYP diagnosed with epilepsy

Extraction of CYP with an epilepsy diagnosis from THIN was carried out using multiple data files; medical, therapy and AHD file. The CYP's records from each file were subsequently linked and compiled into one dataset, which then comprised the study cohort. Figure 2-1 illustrates a schematic diagram of building up the study cohort.

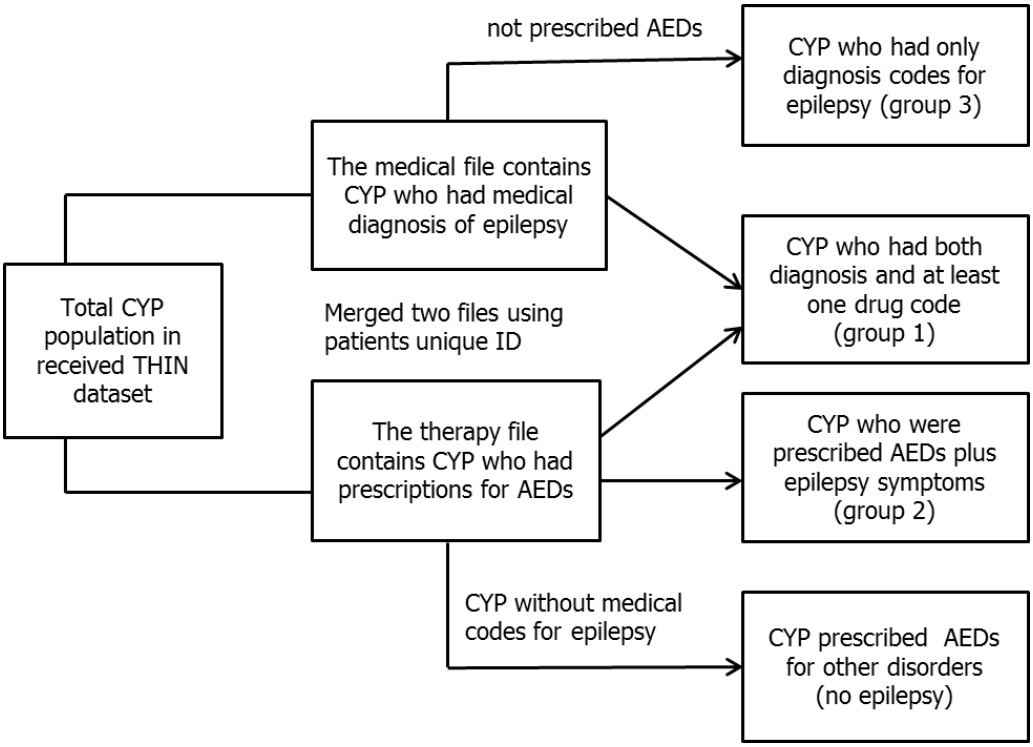


Figure 2-1: Summary of building the study cohort of children and young people with epilepsy

To extract CYP who had an epilepsy diagnosis from the medical file, the master Read code dictionary (Version October, 2008) was used to create a diagnostic Read code list. This diagnostic Read code list comprised all possible clinical terms of epilepsy and epilepsy syndromes (Appendix 8). The Read codes dictionary was in Microsoft ACCESS format. A Read code list was generated by running a simple search query using the keywords of epilepsy and epilepsy syndromes. The keywords included `epilepsy', `epileptic' and

`seizures'. The keywords of epilepsy syndromes were identified according to the ILAE's classification of epilepsy and epilepsy syndrome shown in Appendix 10.

To avoid misdiagnosis of epilepsy, the final Read codes list in Stata format was refined according to ICD 10 (Appendix 10) by excluding codes that did not relate to a diagnosis of epilepsy. For example, CYP who only had Read codes that referred to symptoms such as `seizures', `fits' and `convulsions' without a clear code for epilepsy were not included in the extraction of CYP with epilepsy because not all seizures are epilepsy. However, these symptom codes (Appendix 11) were used later in Chapter 4 and 5 for calculation of incidence of seizure events for the defined study population.

The AHD file of THIN database was also searched for any codes related to epilepsy. Some AHD codes used for epilepsy monitoring and follow-up and others for epilepsy medication review were extracted. These AHD codes were added to the diagnostic code list to define study cohort with epilepsy diagnosis (Appendix 8).

The medical file of THIN data was screened using the refined Stata format list and then all CYP who had a diagnosis of epilepsy were identified and extracted.

2.3.4 Extraction of CYP with epilepsy from therapy files using drug codes

As mentioned in section 2.3.1, THIN database uses the Multilex coding system to code the name of prescribed drugs. This Multilex coding system corresponds with the codes assigned to drugs in the British National Formulary (BNF).

A list of 20 approved AEDs until 2004 was generated to extract CYP who were prescribed AEDs to control epilepsy and status epilepticus from the therapy file (Table 2-4). Status epilepticus is an emergency condition which defined as a repeated generalised tonic-clonic seizures lasting over a 30-minute period without recovery of consciousness between seizures [235]. The drug codes of status epilepticus were not used in extracting the CYP with epilepsy but

instead they acted as seizure marker and were used together with seizure codes to calculate incidence of seizure events for the defined population in Chapters 4 and 5.

THIN Multilex drug codes were searched for drugs listed in Table 2-4. The BNF codes and the Multilex codes for the identified AEDs are shown in (Appendix 9). This drug codes list shows that each drug type can have multiple Multilex codes by different dosage packages, dosage forms and dosage strength. This Multilex drug codes was copied into Stata format and subsequently the therapy file within THIN database was screened using this list to extract CYP who were prescribed any AEDs.

Table 2-4: List of approved antiepileptic drugs in the UK up to 2004

Control of epilepsy (year of UK licence) [a]	Control of status epilepticus
Carbamazepine (1965)	Diazepam (1963)
Clobazam (1979)	Midazolam (1975)
Clonazepam (1979)	Paraldehyde (1882)
Ethosuximide (1955)	
Gabapentin (1993)	
Lamotrigine (1991)	
Levetiracetam (2000)	
Oxcarbazepine (2000)	
Phenobarbital (1912)	
Phenytoin (1938)	
Primidone (1952)	
Sodium valproate (1973)	
Tiagabine (1998)	
Topiramate (1995)	
Valproic acid (1993)	
Vigabatrin (1989)	

a: Source: Epilepsy Action, http://www.epilepsy.org.uk/info/treatment/uk-anti-epileptic-drugs-list

Thereafter using the unique child ID, all the extracted records from the medical and AHD files containing diagnosis of epilepsy were linked to the extracted

records from the therapy file containing drug codes. By this linking, all CYP who had both epilepsy diagnosis and at least one prescription of AED treatment where identified in one dataset as the main study cohort (group 1 in Figure 2-1). Other groups of CYP who had only a diagnosis of epilepsy or prescriptions of AEDs without diagnosis were defined separately.

2.3.5 Classification of the children and by epilepsy subtypes

Because of the heterogeneous nature of epilepsy, CYP diagnosed with a particular epilepsy subtype had multiple Read codes of clinical terms for this subtype which may be clinically attributed to a different set of symptoms, condition severity and/or age at onset.

To simplify the classification of the study cohort by epilepsy subtypes, the clinical terms that referred to the same epilepsy subtype were combined in one diagnostic term (Appendix 12) based on the glossary of descriptive terminology of the ILAE [13]. Thereafter, CYP were assigned a final epilepsy subtype. When a child had more than one diagnostic epilepsy subtype, the latest diagnosis was considered. For instance, focal epilepsy was recorded by multiple Read code clinical terms such as `partial epilepsy without impairment of consciousness', `idiopathic epilepsy with local onset', `temporal lobe epilepsy', and `unilateral epilepsy'. All these clinical terms were combined in one epilepsy subtype which is `focal epilepsy'.

2.3.6 Extraction of Read codes of other conditions treated with AEDs

Many CYP were issued prescriptions for AEDs without finding any diagnostic codes for epilepsy in their records. Some of these CYP may have had epilepsy and others may have been treated from other mental and behavioural disorders due to the fact that AEDs have proven effective as mood stabilizers [236] and in the management of certain kinds of dysfunctional anxiety [237] and other diseases [238-242].

A list of the Read codes of disorders treated with AEDs rather than epilepsy was created. This list included childhood migraine, neuropathic pain and some mental and behavioural disorders such as bipolar and conduct disorders,

anxiety and other psychoses (Table 2-5). The Read code dictionary was used to search for these conditions.

According to the WHO ICD-10, mental and behavioural disorders include [243]:

Organic, including symptomatic, mental disorders
Mental and behavioural disorders due to psychoactive substance use
Schizophrenia, schizotypal and delusional disorders
Mood [affective] disorders
Neurotic, stress-related and somatoform disorders
Behavioural syndromes associated with physiological disturbances and physical factors
Disorders of adult personality and behaviour
Mental retardation
Disorders of psychological development
Behavioural and emotional disorders with onset in childhood and adolescence
Unspecified mental disorder

The list of Read codes (Appendix 13) was generated by running search queries using the keywords of each disease or disorder as shown in Table 2-5. Searching the medical files by keywords of specific diseases or disorders produced some Read codes of other mixed behavioural disorders or disorders of adult patients. These Read codes were removed in accordance to ICD-10, 2007 guidance[243]. For instances;

- The Read codes of single manic and depressive episodes were excluded from the codes of bipolar affective disorders.
- Coding of certain sexual attitudes and hyperkinetic disorders overlapped with conduct disorders.
- Coding of certain adjustment disorders was distinguished from coding of depression.
- Coding of certain organic mental disorders was separated from neurotic disorders.
- Coding of behavioural disorders of childhood onset and adolescent was distinguished from neurotic disorders.
- Coding of nonorganic sleep disorders was distinguished from that of

neurotic anxiety disorders.

- Disorders of adult personality and behaviour were distinguished from behavioural and emotional disorders of childhood and adolescent onset.

The refined Read code list of 655 codes was used to extract CYP without epilepsy who were treated from any of the above-mentioned conditions (Appendix 13).

Table 2-5: Conditions treated with AEDs, Read codes and ICD-10 codes

Condition	Key words	Read codes chapter headings	ICD-10 codes
Mental and behavioural disorders			
Anxiety and stress	Anxiety, stress	E200.00, Eu41.00	F40, F41, F43
Bipolar affective disorder	Bipolar disorder	E114.00, E115.00, E116.00, Eu31000, Eu34.00, Eu3y.00	F31
Conduct disorder	Conduct disorder	E2C..00, Eu90100	F91
Nonorganic sleep disorder	Insomnia, sleepwalking, Sleep terrors, nightmares	E274.00, Eu51.00	F51
Psychotic disorders	Psychosis, delusion, hallucinations, paranoia, paranoid	Eu22.00, Eu23.00, Eu24.00	F22, F23
Migraine	Migraine	F26..00	G43
Neuropathic pain	Peripheral neuropathy, neuralgia, Neuropathic	F300.00, F36..00 N242.00	G60-G64

2.3.7 Extraction of Read codes of co-morbidity

This study is concerned with co-morbidity and prescribing of multiple drugs as part of descriptive analysis of study cohort. Therefore, a list of common chronic co-morbidities was developed to investigate whether CYP with epilepsy was treated from other co-morbidities (Appendix 14). This list included asthma, cardiovascular diseases, chronic renal diseases, cystic fibrosis, diabetes, human immunodeficiency virus infection (HIV), and juvenile rheumatoid arthritis.

Some studies have revealed an increased risk of co-existing psychiatric and behavioural disorders among CYP with epilepsy [244, 245]. It has been shown that CYP with epilepsy have higher incidence of psychiatric disturbances relative to CYP with other neurological disorders and CYP of general population [54, 244, 245]. Therefore, mental behavioural disorders which could be associated with epilepsy included Attention Deficit Hyperactivity Syndrome (ADHS) [246], anxiety, stress, depression [247], conduct disorder, lethargy, cognitive disorders [248], mental retardation and other psychoses [249, 250] were added to the co-morbidity code list.

The master Read code dictionary (Version October, 2008) was used to search diagnostic Read codes of these co-morbidities using Microsoft ACCESS. A list was generated by running search queries in using the keywords of each disease. The searches in ACCESS were also carried out using the Read codes chapter headings of each co-morbid disease as another query (Table 2-6).

The two lists generated from the ACCESS queries were compiled and refined according to ICD-10-2007 codes and copied into Stata format. Overlapping codes of differential diagnostic disorders which did not belong to the co-morbidity of interest were distinguished and removed as previously discussed in section 2.3.6. There were other examples of code refining shown below:

- Coding of acute and transient psychotic disorders such as oneirophrenia, brief schizophreniform and schizotypal disorders overlapped with schizophrenia.
- Coding of specific personality disorders such as paranoid and schizoid personality disorders was separated from coding of paranoia and schizophrenia.
- Coding of transient global amnesia of transient cerebral ischaemic attacks was separated from cognitive disorders
- Coding of certain chronic obstructive pulmonary diseases was separated from coding of asthma
- Coding of diabetes mellitus in pregnancy, childbirth and the puerperium was separated from diabetes mellitus.

The final Stata format returned a total of 1476 Read codes which were used to extract the co-morbidities from the CYP's medical file of THIN database. The obtained extracted co-morbidities data was then screened against the epileptic cohort to identify CYP with epilepsy who had other concurrent co-morbid diseases during the study period.

Table 2-6: Co-morbidity extraction, key words, Read codes and corresponding ICD-10 codes

Condition	Key words	Read codes chapter headings	ICD-10 codes 2007
1.General common co-morbidities			
Asthma	Asthma	H33..00, 663..00	J45
Cardiovascular diseases	Cardiovascular, angina, myocardial infarction, heart failure, Rheumatic fever	G....00, G1...00 G3...00,G54..00, G58..00,G5y..00	I00, I01, I05, I06, I07, I08, I09, I20, I21, I22, I23, I24, I25, I34, I35, I37
Diabetes	Diabetes mellitus Insulin-dependent	C10..00,F420.00, F372.00,66A..00	E10, E11, E12, E13, E14, H36, G63.2 N08.3
Cystic fibrosis	Cystic fibrosis	C370.00	E84
Human immunodeficiency virus (HIV)	AIDS, HIV Human immunodeficiency	A788.00, AyuC.00	B20-B24
Rheumatoid arthritis	Juvenile arthritis, Rheumatoid arthritis	N04..00, N043.00, N045.00	M05, M06, M07, M08, M09
Renal disorders	Renal impairment, Renal failure	K04..00,K05..00, K06..00,K07..00, K08..00,K0B..00, K10..00	N10, N11, N12, N17, N18, N19
2.Other co-morbidities 2.1.Mental and behavioural disorders			
Attention deficit hyperactivity disorder	Hyperkinetic disorder, Attention deficit hyperactivity disorder	E2E..00, ZS9..00	F90
Behavioural disorders of childhood and adolescent onset	Stammering Stuttering Tics Nail-biting Thumb-sucking	E292000, E270.00, Eu9.00	F93-F98
Depression	Depression	E112.00,Eu32.00	F32, F33
Mental retardation	Mental retardation	E3...00, Eu7..00	F70-F79

Schizophrenia	Schizophrenia Catatonia	E10..00	F20, F21
2.2.Developmental disorders including cognitive disorder	Cognitive disorder, Learning difficulties, memory impairment	28E..00, Eu8..00, Z7C..00	F80-F89 R41

2.3.8 Quantifying the characteristics of the study cohort

Group 1 (Figure 2-1) represented the main study cohort that met the inclusion criteria of having epilepsy diagnosis and at least one AED prescription. The basic characteristics of the CYP of this group including CYP's demographics such as age, sex and socioeconomic status were described and tabulated. Group 2 of CYP with a prescription for AEDs and a medical code for seizures did not have a clear code for epilepsy diagnosis, so they may have had non-epileptic seizures. Group 3 of CYP with only a diagnosis of epilepsy and no treatment may have had a history of epilepsy but seizures are in remission for ≥5 years [251] The characteristics of two groups were presented separately as discussed later in section 2.3.13.

The age of CYP (group 1) was calculated at the date of first recording of epilepsy in THIN. This date was defined as the date of first recording of epilepsy diagnosis or the date of first prescription of AEDs, whichever occurred earlier. The number of CYP was stratified according to the assigned diagnostic codes of epilepsy subtypes.

THIN database provides anonymous postcode linked area-based socioeconomic status measure. The socioeconomic status of CYP was measured using the Townsend deprivation quintile (index). The Townsend index measures multiple deprivation by area and the overall score is calculated by summing the Z-scores of four variables derived from 2001 census:

- The percentage of unemployment in active people over 16 years
- The percentage of households without access to a car
- The percentage of households of non-home ownership
- The percentage overcrowding of households

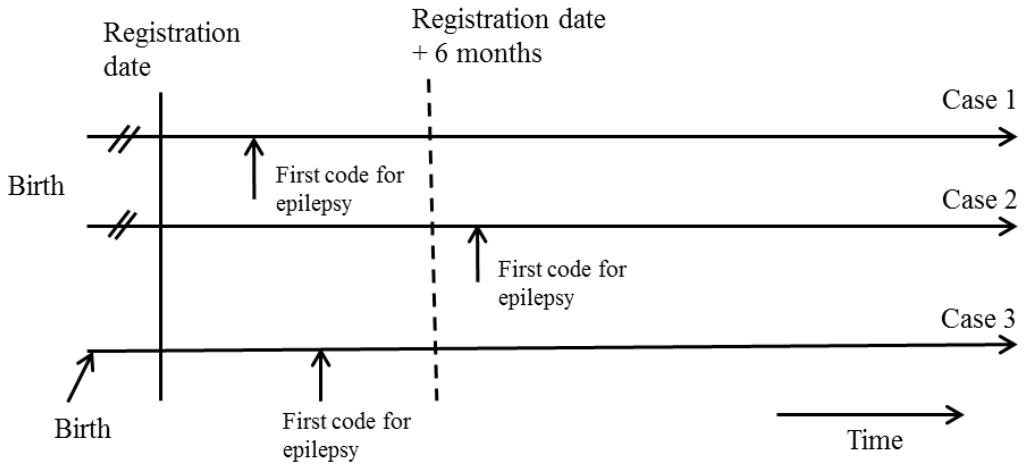
Therefore, the Townsend score is an indicator of individual's socioeconomic status where the higher the score, the greater the deprivation. The scores are then grouped into 5 deprivation quintiles from 1 (least deprived) to 5 (most deprived).

Information on co-existing morbidities was included.

2.3.9 Estimating the overall and age-specific incidence rates of epilepsy

The estimation of the incidence of epilepsy was performed on CYP of group 1 (Figure 2-1) between 1st Jan 1990 and 30 Nov 2004. Data before 1990 were excluded because of the small number of practices contributing to THIN database at this time.

A child was considered an incident case if the date of first recording of epilepsy diagnosis or drug code for AEDs occurred at least 6 months after the registration date with the general practice in order not to miscount a prevalent case as an incident case (Figure 2-2). However, in order not to underestimate incidence in the first year of birth, CYP who had their registration date within the first 6 months from birth and had a diagnosis or treatment for epilepsy within this first 6 months of life were included as incident cases. The assumption was that those CYP had their first ever diagnosis of epilepsy at that time.



Case 1: First code for epilepsy diagnosis or treatment within 6 months of date of registration= prevalent case
Case 2: First code for epilepsy diagnosis or treatment after 6 months of date of registration= incident case
Case 3: First code for epilepsy diagnosis or treatment within 6 months of date of registration but in the first 6 months after birth= incident case

Figure 2-2: Definition of incident and prevalent cases of epilepsy

The overall incidence rate (person-time incidence) of epilepsy for the whole study period was calculated by dividing the total number of newly diagnosed cases with epilepsy (as defined above) as the numerator by the total person-years of registered data contributed by CYP younger than 18 years at risk as the denominator. The person-years of registered data were calculated from the registration date in THIN to the practice finish date. The finish date was the date of death, the date where the child transferred out of the general practice, or the last date of data collection, whichever occurred first. The person-years and 95% confidence interval (CI) were generated using the method of survival analysis.

The overall incidence rate was stratified by age of CYP at diagnosis. Age was calculated at the incident date and grouped into four groups (0-4 years, 5-9 years, 10-14 and ≥ 15 years). The person-years contributed by each age group of the study population were calculated. Incidence was calculated as the total number of new cases of each age group per 100,000 person-years of the study population at risk of same age group. Mantel-Haenszel test was used to assess

whether incidence was different across age groups. The rate ratio (RR; ratio of two incidence rates) by age and significance tests were calculated using a Mantel-Haenszel type method.

The crude incidence rate was also stratified by different deprivation levels as measured by Townsend index to examine whether incidence rate varied with socioeconomic status. The Chi-squared test for trend was used to test the association between incidence and different deprivation levels.

2.3.10 Estimation of incidence rates by sex and calendar years

The annual incidence rate was defined as the number of newly diagnosed cases of epilepsy each calendar year divided by person-years of registered data contributed by the CYP younger than 18 years in each calendar year. The annual incidence rate was estimated then stratified by sex between 1990 and 2004 to examine the trend of the incidence rate over time. The 95% confidence intervals of incidence rates were calculated each calendar year using the survival analysis. The Mantel-Haenszel method was used to assess whether the rate ratio (ratio of two incidence rates) was significantly different between males and females each calendar year.

2.3.11 Estimating overall prevalence of epilepsy using the mid-year population numbers

All CYP who had diagnoses of epilepsy were considered prevalent cases from their date of first diagnosis onward. The overall prevalence was estimated by dividing the number of all epilepsy cases by the mid-year population number of CYP of THIN. The mid-year population number was all study population younger than 18 years who had registration in THIN on the July 1st, each year. The difference in overall prevalence between males and females was tested using the Chi-squared test. The 95% confidence interval of overall prevalence in sex was calculated.

2.3.12 Estimation of age and sex-specific prevalence of epilepsy by calendar years

Repeated cross-sectional prevalence measurements were performed annually to assess any changes in prevalence during the study period. This was done by dividing the total number of epilepsy cases each calendar year between 1990 and 2004 by the mid-year population numbers of study population in THIN each year.

The annual estimates of prevalence were calculated for males and females and across different age groups each calendar year. Age of all populations was calculated on July 1st, each year and grouped in three groups (0-4 years, 5-9 years and ≥ 10 years) because there was few numbers of children older than 15 years.

2.3.13 Quantifying the characteristics of other study groups

To compare with the study group, the basic characteristics of other groups; CYP with seizure symptoms and AEDs codes (group 2; Figure 2-1) and those with only epilepsy diagnostic codes (group 3; Figure 2-1) were described by sex, age distribution at first recording of symptoms or epilepsy codes and socioeconomic status. Other explored characters included number of prescribed medicines and number of epilepsy diagnosis codes per individual.

2.4 Results

2.4.1 Study population

The total number of CYP registered in the source population of the received THIN dataset 1988-2004 was 528760, of whom 270144 (51%) were males. The age of population at their registration dates ranged from one day to 16.4 years (mean=2.2 years; SD=3.4)

By screening the medical file of the source population, 2908 CYP were identified to have had diagnosis codes for epilepsy or epilepsy subtypes (Figure 2-3). The therapy file contained 4028 CYP who have had prescriptions records for one or more AEDs.

By linking the records of the two files, Figure 2-3 shows that group 1 (the study group who met the inclusion criteria) consisted of 2023 CYP who had at least one diagnosis code for epilepsy and at least one prescription for an AED. The diagram also shows that 2005 CYP had records for at least one prescription of an AED without a diagnosis for epilepsy. Of those, 376 CYP were prescribed AEDs for other conditions (such as bipolar disorder, conduct disorder, anxiety, migraine and neuropathic pain) and 405 CYP (group 2) had codes for epilepsy symptoms such as convulsions and fits.

Figure 2-3 also illustrates that 885 CYP (group 3) had only epilepsy diagnoses without having records of prescriptions for any medication.

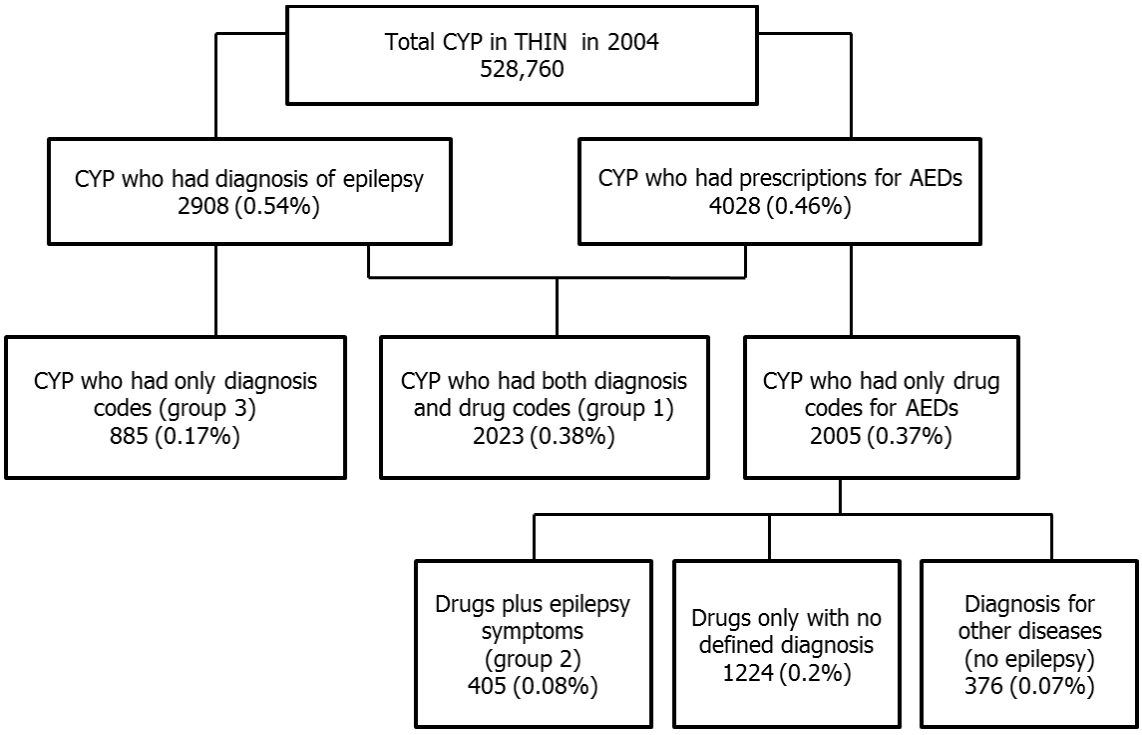


Figure 2-3: Summary of extracting CYP with epilepsy from THIN database

2.4.2 Characteristics of CYP diagnosed with epilepsy

Of the extracted 2023 CYP with epilepsy (group 1), three CYP were excluded because they were transferred out of general practices on the same date of their registration. Therefore, a total of 2020 CYP represented the study cohort, of which 1115 (55.2%) were males (Table 2-7). The age at the date of first recording of epilepsy (incident date) ranged from 0.02-16.28 years (mean=5.58 year; SD=4.03). About one-half of CYP (50.2%) were below the age of 5 years. A large number of CYP (27%) had only one diagnosis code for epilepsy or epilepsy subtypes during the total follow-up time.

The socioeconomic status data showed that 40.5% were in a deprivation quintile higher than 3 (see Table 2-7). More than one-third of CYP (35.8%) had other co-morbidities of whom, 387 (19.2%) had co-morbidities before the incidence of epilepsy. Asthma represented the most common co-morbid disease (23.2%) and

mental and behavioural disorders comprised the second common category (18.3%) of co-morbidities.

Table 2-7: Characteristics of the CYP with epilepsy (N=2020)

Characters	No of CYP (%) N=2020
Age at first record of epilepsy (year)	
0-4	1013 (50.2)
5-9	666 (32.9)
10-14	317 (15.7)
≥15	24 (1.2)
Sex	
Males	1115 (55.2)
Females	905 (44.8)
Townsend deprivation quintile	
1 (least deprivation)	364 (17.9)
2	291 (14.5)
3	402 (19.9)
4	447 (22.1)
5 (most deprivation)	372 (18.4)
Missing	144 (7.1)
Number of diagnostic codes of epilepsy	
1	552 (27.3)
2	378 (18.7)
3	301(14.9)
4	218 (10.8)
>4	571(28.3)
Co-morbidities and other disorders	724 (35.8)
Asthma	468 (23.2)
Conduct disorders	142 (7.0)
Nonorganic sleep disorder	56 (2.8)
Behavioural disorders of childhood & adolescent	55 (2.8)
Anxiety and stress	51 (2.5)
ADHS	44 (2.2)
Cognitive disorders	38 (1.9)
Diabetes	19 (0.9)
Mental retardation	17 (0.8)
Cardiovascular disease	15 (0.7)
Renal diseases	15 (0.7)
Psychoses	13 (0.6)
Depression	8 (0.4)
Cystic fibrosis	4 (0.2)
Juvenile rheumatoid arthritis	4 (0.2)
Bipolar disorders	1 (0.1)
HIV	1 (0.1)

2.4.3 Results of compilation of medical terms of epilepsy and epilepsy subtypes

The classification of CYP with epilepsy according to epilepsy subtype is shown in Table 2-8. The table also shows the assigned epilepsy subtype according to ILAE classification of epilepsy and epilepsy syndrome and ICD-10, 2007.

The coding of epilepsy subtypes showed that the majority of CYP (69.3%) were not assigned a Read code for specific epilepsy subtype or syndromes and instead they only had a general code for epilepsy. The two most common epilepsy subtypes were the generalised absence epilepsy (9.8%) and the generalised tonic-clonic epilepsy (6.2%).

Table 2-8: Classification of epileptic cohort by epilepsy subtypes

Read code diagnostic term	Number of CYP with the diagnosis (%) n=2020
Epilepsy (unspecified)	1399 (69.3)
Focal epilepsy	
Simple focal epilepsy	83 (4.1)
Benign rolandic epilepsy	27 (1.3)
Complex focal epilepsy	25 (1.2)
Generalised epilepsy	
Absence seizures	198 (9.8)
Tonic-clonic seizures	125 (6.2)
Myoclonic seizures	25 (1.2)
Tonic seizures	21 (1.0)
Clonic seizures	13 (0.6)
Atonic seizures	7 (0.4)
West Syndrome	63 (3.1)
Juvenile absences epilepsy	25 (1.2)
Lennox- Gastaut syndrome	7 (0.4)
Juvenile myoclonic epilepsy	2 (0.1)

2.4.4 Overall incidence of epilepsy in children and young people

Of the total 2020 extracted CYP with epilepsy, 1457 incident cases were identified giving an overall incidence rate of 51.5/100000 person-years of study population (Table 2-9). Of the incident cases, 823 (54.9%) were males. The male group had significantly higher (Chi-squared; $p<0.001$) overall incidence (56.8/100000 person-years) than females (45.8/100000 person-years).

A higher overall incidence rate was found in the younger children, decreasing from (54.4/100000 person-years) below the age of 5 years to (44.4/100000 person-years) over the age of 15 years. However, the decrease in incidence rates was not significant across age categories (Mantel-Haenszel test, RR= 0.99 [95% CI; 0.97-1.00], $p= 0.05$). Of the age group 0-4 years, incidence of epilepsy was higher during the first year of life (82.9/100000 person-years).

The incidence rates were found to be higher in CYP who lived in relatively higher deprived areas as compared to those who lived in the less deprived areas. The incidence of epilepsy was higher in CYP who were in deprivation quintiles 4 and 5. The association between incidence and deprivation was significant (Mantel-Haenszel test, RR= 1.12 [95% CI; 1.08-1.16], $p<0.01$).

Table 2-9 shows the cross-sectional calculated overall incidence rates each calendar year between 1990 and 2004. The overall incidence ranged from 41.9 to 61.2/100,000 person-years over the years of study periods. The incidence rate ratio was not significantly different per each unit increase of calendar year of diagnosis (Mantel-Haenszel test, RR=0.99 [95% CI; 0.98-1.01], $p= 0.41$).

Table 2-9: Incidence rate of childhood epilepsy per 100,000 person-years, 1990-2004

Total	Epileptic cases	Person-years of THIN population	Crude incidence/100,000 person-years [95% CI]
Total	1457	2,828,680	51.5 [48.9 -54.2]
Sex			
Male	823	1,447,090	56.8 [53.1 -60.9]
Female	634	1,381,590	45.8 [42.4 -49.6]
Age			
0-4	719	1,320,860	54.4 [50.6 -58.6]
5-9	489	988,340	49.5 [45.3 -54.1]
10-14	233	483,410	48.2 [42.4 -54.8]
>15	16	36,080	44.4 [27.2 -72.4]
Townsend index			
1 (least deprived)	272	652,022	41.7 [37.1 -46.9]
2	209	514,453	40.6 [35.5 -46.5]
3	321	522,709	60.4 [55.1 -68.5]
4	327	502,386	65.1 [58.4 -72.5]
5 (most deprived)	235	408,526	57.5 [50.6 -65.4]
Missing	93	228,581	40.6 [33.2 -49.9]
Calendar year			
1990	20	38,810	51.5 [33.3 -79.9]
1991	32	58,390	54.8 [38.8 -77.5]
1992	35	78,830	44.4 [31.9 -61.8]
1993	45	100,160	44.9 [33.5 -60.2]
1994	67	124,500	53.8 [42.4 -68.4]
1995	74	148,280	49.9 [39.7 – 62.7]
1996	105	171,490	61.2 [50.6 -74.1]
1997	90	195,170	46.1 [37.5 -56.7]
1998	115	218,800	52.6 [43.8 -63.2]
1999	141	241,160	58.5 [49.6 -68.9]
2000	138	262,520	52.6 [44.5 -62.1]
2001	173	284,520	60.8 [52.4 -70.6]
2002	153	306,430	49.9 [42.6 -58.5]
2003	152	320,260	47.5 [40.5 -55.6]
2004	117	279,330	41.9 [34.9 -50.2]

2.4.5 Sex-specific incidence rate over time

Sex-specific incidence rates stratified by the calendar years of epilepsy diagnosis are shown in Table 2-10. Incidence rates were significantly different between males and females with unit increase in calendar year of diagnosis (Mantel-Haenszel test; RR=0.81 [95% CI; 0.73- 0.90], p<0.001). The incidence was higher in males than in females. The incidence ranged from 42.7 to 71.4 per 100000 person-years in males along the years of the study period. The incidence ranged from 34.4 to 63.5 per 100000 person-years in females along the years of the study period.

Table 2-10: Incidence of childhood epilepsy by sex and year of diagnosis

Calendar year	Male incidence/100,000 person-years [95% CI]	Female incidence/100,000 person-years [95% CI]
1990	44.9 [23.4- 86.4]	58.5 [32.4 -105.6]
1991	46.6 [27.6 -78.7]	63.5 [39.9 -100.7]
1992	54.2 [35.7 -82.4]	33.9 [19.7 -58.5]
1993	42.7 [28.1 -64.8]	47.3 [31.4 -71.2]
1994	54.7 [39.3 -76.2]	52.8 [37.3 -74.7]
1995	56.5 [41.9 -76.3]	42.9 [30.2 -60.9]
1996	70.6 [55.1 -90.6]	51.4 [38.1 -69.2]
1997	51.1 [38.8 -67.2]	40.9 [29.9 -55.9]
1998	52.7 [40.8 -68.1]	52.4 [40.3 -68.1]
1999	63.2 [50.7 -78.9]	53.5 [41.8 -68.4]
2000	52.1 [41.2 -65.9]	53.0 [41.8 -67.3]
2001	71.4 [58.9 -86.6]	49.6 [39.2 -62.8]
2002	61.9 [50.8 -75.6]	37.4 [28.8 -48.5]
2003	53.2 [43.1 -65.7]	41.5 [32.5 -52.9]
2004	49.0 [38.8 -62.0]	34.4 [25.8 -45.8]

2.4.6 Overall prevalence of childhood epilepsy

A total of 2020 prevalent cases gave an overall prevalence of 3.83/1000 study population (Table 2-11). Of the identified cases, 1115 (55.2%) were males and had a significantly higher overall prevalence (Chi-squared; $p<0.001$) compared to females. Males were found to be 18% more likely to have epilepsy than females (odds ratio=1.18 [95% CI; 1.08-1.29].

Table 2-11: Prevalence of childhood epilepsy, 1990-2004

	Epileptic cases	THIN mid-year population	Crude prevalence/1000 population (95% CI)
Total	2020	526,560	3.83 (3.67-4.01)
Sex			
Male	1115	268984	4.14 (3.90-4.39)
Female	905	257576	3.51 (3.02-3.74)

2.4.7 Age-specific prevalence of epilepsy over time

A cross-sectional annual prevalence of epilepsy was calculated and stratified by age of CYP starting in the year 1990. The annual overall prevalence of epilepsy in all ages was found to increase from 0.89 per 1000 in 1990 to 4.48 per 1000 population in 2004 (Table 2-12). The age-specific annual prevalence values stratified by calendar years were found to increase with age. The prevalence estimates in the age group 0-4 years grew less than twofold between 1990 and 2004 where small changes occurred (6%) between 1995 and 2004. However, 80% rise in prevalence within the age group 5-9 years was observed (from 2.26 (95% CI; 1.44-3.09) in 1993 to 4.06 (95% CI; 3.67-4.45) per 1000 population in 2004). There was also 47% rise in prevalence within the age group ≥10 years (from 4.44 (95% CI; 3.40-5.50) in 1998 to 6.50 (95% CI; 6.12-6.95) per 1000 population in 2004).

Table 2-12: Age-specific prevalence of childhood epilepsy, 1990-2004

Calendar years	0-4 years			5-9 years			≥10 years			All ages
	Epileptic cases	Mid-year Population	Prevalence /1000	Epileptic cases	Mid-year Population	Prevalence /1000	Epileptic cases	Mid-year Population	Prevalence /1000	Prevalence/1000 (95% CI)
1990	33	36892	0.89	0	0	0	0	0	0	0.89 (0.59-1.21)
1991	70	56636	1.24	0	0	0	0	0	0	1.24 (0.95-1.53)
1992	112	77162	1.45	0	0	0	0	0	0	1.45 (1.19-1.73)
1993	134	85050	1.58	29	12838	2.26	0	0	0	1.67 (1.42-1.93)
1994	160	92939	1.72	81	30007	2.70	0	0	0	1.96 (1.72-2.22)
1995	168	95975	1.75	164	50514	3.25	0	0	0	2.27 (2.03-2.52)
1996	190	96569	1.96	261	73257	3.56	0	0	0	2.66 (2.42-2.91)
1997	185	97447	1.90	263	96257	2.73	0	0	0	2.83 (2.60-3.08)
1998	184	97628	1.88	417	104235	4.00	69	15549	4.44	3.08 (2.86-3.32)
1999	197	97219	2.02	473	108798	4.35	160	33892	4.72	3.46 (3.23-3.70)
2000	193	96592	2.00	474	109138	4.34	306	55562	5.51	3.72 (3.50-3.96)
2001	183	96419	1.90	485	107974	4.49	477	79152	6.02	4.04 (3.81-4.28)
2002	184	95557	1.92	470	107215	4.38	644	102779	6.26	4.25 (4.02-4.48)
2003	172	92725	1.85	439	103677	4.23	789	122556	6.44	4.39 (4.16-4.62)
2004	161	91436	1.76	410	100970	4.06	930	142337	6.51	4.48 (4.26-4.71)

2.4.8 Sex-specific prevalence of epilepsy over time

The difference in prevalence of epilepsy between males and females stratified by age and calendar years is illustrated in Figure 2-4. The graph shows that only the prevalence of age group 0-4 started from the origin of the line (1990) whereas prevalence of age group 5-9 started from 1993 and from 1998 for age group ≥10 years. This reflects the structure of the study cohort as those CYP who were born on or after January 1st 1988. Before 1993, no child in the cohort had yet reached their 5th birthday and so the graph started at 1993 for the age group 5-9 years. Before the year 1998, no child in the cohort had yet reached their 10th birthday.

The prevalence of epilepsy in increased linearly from 1990 to 2004. The prevalence in males was higher than females from 1996 onwards. The prevalence in males increased 7 fold during the study period (from 0.69 (95% CI; 0.31-1.06) in 1990 to 4.91 (95% CI; 4.58-5.24) per 1000 population in 2004). The prevalence in females increased 3.6 fold during the study period (from 1.12 (95% CI; 0.63-1.62) in 1990 to 4.04 (95% CI; 3.73-4.34) per 1000 population in 2004).

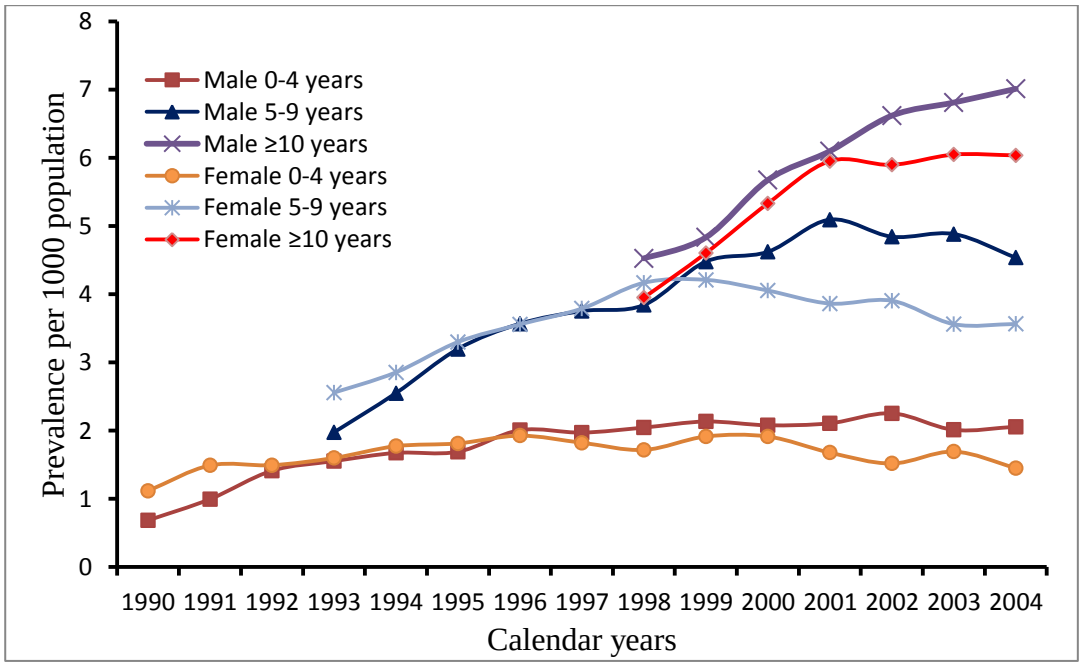


Figure 2-4: Age and sex-specific prevalence of epilepsy in CYP (per 1000 population)

2.4.9 Characteristics of CYP with seizure symptoms

The characteristics of CYP defined by AEDs and symptoms of seizures (Figure 2-3, group 2) are presented in Table 2-13. The group showed similar demographic characteristics to that of the main study group. The total number of this group was 405 where more than one-half, 214 (52.8%) were males. The mean years of follow-up from the date of first symptom was 5.4 (SD=4.3). The age at first recording of symptom ranged from one day to 16.1 years (mean= 2.9; SD =3.3). The majority (82.9%) were below the age of 5 years on the date of first recorded symptom compared to that of 50.2% in the main study group. Higher proportions (38.5%) of CYP of this group were in a deprivation quintile of more than 3 compared to only 40.5% of the main study group.

Most of CYP of this group (74.3%) were assigned medical codes for convulsions. The remaining medical codes were for symptoms of fits and status epilepticus. The majority of CYP (78.5%) received only one drug during the whole follow-up years. The most frequently prescribed drugs to CYP were old AEDs; sodium valproate (38.8%, carbamazepine (17.3%), phenobarbital (12.1%) and phenytoin (7.4%).

Table 2-13: Characteristics of CYP of group 2 (without diagnosis codes)

Characters	No of CYP (%) N=405
Age at first recoding of symptom (year)	336 (82.9)
0-4	45 (11.1)
5-9	20 (4.9)
10-14	4 (0.1)
≥15	
Gender	
Males	214 (52.8)
Females	191 (47.2)
Deprivation score	
1 (least deprivation)	88 (21.7)
2	52 (12.8)
3	79 (19.5)
4	70 (17.3)
5 (most deprivation)	86 (21.2)
Missing	30 (7.4)
Unspecified symptoms of epilepsy	
Convulsions	301 (74.3)
Fits	74 (14.8)
Convulsion and fits in new born	15 (3.7)
Status epilepticus	15 (3.2)
Number of prescribed AEDs	
1	318 (78.5)
2	61 (15.1)
3	20 (4.9)
> 3	6 (1.5)
Most frequently prescribed AEDs	
Sodium valproate	157 (38.8)
Carbamazepine	70 (17.3)
Phenobarbital	49 (12.1)
Phenytoin	30 (7.4)
Lamotrigine	18 (4.4)
Vigabatrin	10 (2.5)

2.4.10 Characteristics of CYP with a diagnosis of epilepsy, but no prescription of AEDs

The characteristics of CYP in the third group (Figure 2-3, group 3) who had only diagnosis of epilepsy are shown in Table 2-14. This group had also similar demographic characteristics to that of the main study cohort. Of the identified 885 CYP, 515 (58.2%) were males. The mean years of follow-up from the date of first recoding of epilepsy in THIN was 4.8 (SD=3.8). The age at first recoding of epilepsy codes ranged from one day to16.3 years (mean=5.1; SD=3.9). More than one-half (54.9%) were below the age of 5 years. The socioeconomic status of CYP measured using the Townsend deprivation index was also similar to the main study group. The data showed that 43.9% were in a deprivation quintile of more than 3.

The highest percentage of CYP (78.5%) had only one diagnosis code for epilepsy or epilepsy subtypes. The percentage of CYP with co-morbidity (35.5%) was similar to the main study group. Asthma was the major (26.3%) recorded comorbid disease and mental and behavioural disorders comprised the second most common comorbid disease (12%).

Table 2-14: Characteristics of CYP of group 3 (without drug treatment)

Characters	No of CYP (%) (n=885)
Age at first record of epilepsy (year)	
0-4	484 (54.9)
5-9	272 (30.7)
10-14	116 (13.1)
≥15	13 (1.5)
Gender	
Males	515 (58.2)
Females	370 (41.8)
Deprivation score	
1 (least deprivation)	149 (16.8)
2	128 (14.5)
3	159 (18)
4	202 (22.8)
5 (most deprivation)	187 (21.1)
Missing	60 (6.8)
Number of diagnostic codes for epilepsy	
1	695 (78.5)
2	117 (13.2)
3	49 (5.5)
> 3	24 (2.7)
Other co-morbidities and disorders	314 (35.5)
Asthma	233 (26.3)
Conduct disorder	45 (5.1)
Stress and anxiety	25 (2.8)
Behavioural disorders of childhood & adolescent onset	19 (2.2)
Nonorganic sleep disorder	19 (2.2)
ADHS	12 (1.4)
Cardiovascular disease	10 (1.1)
Diabetes	6 (0.7)
Psychoses	5 (0.6)
Cognitive disorders	5 (0.6)
Depression	5 (0.6)
Mental retardation	4 (0.5)
Renal diseases	2 (0.3)

Table 2-15 shows the classification of CYP by epilepsy subtypes. Similar to the main study group, the majority of CYP in this group (573, 64.8%) were not assigned a diagnostic epilepsy subtype and they only had a general code for epilepsy.

Table 2-15: Combined diagnosis terms for epilepsy and epilepsy subtypes of group 3

Epilepsy description	Number of CYP n=885	Frequency of records (%) n=1171
Epilepsy (unspecified)	578	664 (55.8)
Focal epilepsy		
Simple focal epilepsy	23	28 (2.4)
Benign rolandic epilepsy	22	34 (2.9)
Generalised epilepsy		
Absences seizures	266	298 (25.0)
Tonic-clonic seizures	54	59 (4)
West Syndrome	29	34 (2.9)
Tonic seizures	13	13 (1.1)
Clonic seizures	11	11 (0.9)
Myoclonic seizures	11	11 (0.9)
Juvenile absence epilepsy	8	8 (0.7)
Epileptic seizures - atonic	6	6 (0.6)

Note: a child can have multiple diagnostic codes so the total number of CYP is higher than the actual number of CYP.

2.5 Discussion

2.5.1 Key findings

In this study, the identified CYP with epilepsy were classified into three groups. Group 1 was the main study population upon which incidence and prevalence estimates were performed. This group1 included all CYP who had a medical diagnosis of epilepsy and at a least one code for a prescription of AEDs. The second group (group 2) included all CYP with medical codes of seizures and codes of AEDs. The third group (group3) comprised all CYP who had only medical codes for epilepsy. The CYP of the second and third groups were not included in incidence and prevalence estimates either because they did not have a clear code for epilepsy diagnosis (group 2) or they may have a history of epilepsy but in long-term remission.

The three groups, however, showed comparable demographic characteristics in terms of age range at first recoding of epilepsy, sex distribution and level of deprivation according to Townsend index. The numbers of medical codes of epilepsy or type of concurrent co-morbidity were also comparable between groups 1 and 3.

This study estimated an overall incidence rate of epilepsy of 51.5 (95% CI, 48.9 -54.2) per 100,000 person-years. The annual incidence rates ranged between 41.9 and 61.2 per 100,000 person-years. Males had a significantly higher incidence of epilepsy than females. The age-specific incidence in this study was found to be higher in children less than 5 years old and decreased with increasing of age. Moreover, the overall incidence rate was higher in children during their first year of life 82.9 (95% CI; 72.7-94.6) per 100,000 person-years. The incidence of epilepsy was significantly higher in CYP lived in more deprived areas than those lived in the least deprived areas.

The overall calculated prevalence of epilepsy was 3.83 /1000 population and males had significantly higher prevalence than females. The annual estimated prevalence increased from 0.89/1000 in 1990 to 4.48/1000 population in 2004.

2.5.2 Incidence of epilepsy compared to previous studies

The estimated overall incidence rate of epilepsy and the annual incidence rates were consistent with previous incidence rates reported in the UK and Europe [252]. It has been concluded that the overall incidence was around 50 per 100,000 person-years (range of 50-70 per 100,000) in developed countries [25, 252].

Previous cross-sectional population-based studies in the UK have reported crude incidence rates ranged from 43 to 80 per 100,000 populations [22, 23, 227, 228]. These crude incidence rates were estimated on cohorts of all ages including CYP [22, 23, 228]. Of the paediatric studies, Verity et al. (1992) estimated the incidence of epilepsy in the survivors of 1970 British birth cohort, aged 0-10 years. The authors reported a similar crude incidence of 43 per 100,000 populations [227]. The annual estimate of overall incidence in the present study were slightly lower than that of Reading et al. (2006) who examined the association between incidence of epilepsy and deprivation [231]. The authors used a cohort of 77952 CYP, aged 29 days to 14 years, presenting to the Norfolk and Norwich University Hospital, UK and reported an annual incidence of epilepsy of 66 per 100,000 populations throughout 2001-2003. However, their finding was applied to Norfolk and Norwich area and not to the whole UK.

Regarding sex-specific incidence rate of epilepsy, the study finding supported that of Reading et al. (2006) who reported a slightly higher incidence of epilepsy in male CYP than for females [231]. Macleod and Andrews reported that adult males with epilepsy had significantly higher rates hospital admissions than females in Scotland [253]. A possible cause of higher incidence in males may be the higher susceptibility for certain risk factors for epilepsy such head injury, stroke, central nervous system infection [21]. However, a similar finding was reported where only cases with idiopathic or cryptogenic epilepsy were examined [21].

The trend of higher incidence rates of epilepsy in young children its decrease with increasing of age was consistent with the epidemiology of epilepsy worldwide that is the incidence of epilepsy is high in childhood with the highest peak during the first year of life [18, 25]. Incidence of epilepsy has been described to have a bimodal distribution with 50% of cases of epilepsy start in childhood

and elderly [25, 254]. Possible aetiologies for higher incidence of epilepsy in children are congenital, developmental and genetic [7]. The age-specific incidence rate was similar to that reported by Martinez et al. (2009) using the GPRD database in the UK for the age groups 0-4 and 5-9 years [230]. However, the incidence rate for age group≥10 years was slightly higher than that reported by Martinez and colleagues. This may be because the case definition was slightly different where in this study, epilepsy was defined by one diagnosis code and at least one prescription; however, Martinez et al. defined epilepsy by one diagnosis code and at least two prescriptions.

This study suggests that there is a link between the incidence of epilepsy in CYP and deprivation areas. This finding supported that of Heaney et al. (2002) who reported a significantly higher incidence of epilepsy by twofold in the most deprived areas (P=0.001) [23]. However this finding is more generalisable to the UK population of CYP than that of Heaney et al. (2002) who used data from London and the South East of England with bulk of deprived areas in London. Macleod and Andrews (2002) reported a significantly higher association between deprivation and incidence of hospital admissions from 3,340 adults with epilepsy in Scotland [253]. The authors concluded that likelihood of hospital admissions from epilepsy was 3.3 times higher in adults who lived in most deprived areas (P<0.001).

Few studies have addressed the association between socioeconomic deprivation and incidence of epilepsy, so it is poorly explained [23, 231]. It could be related to any other factors like ethnicity. For example, epilepsy has been reported to be less prevalent among people with south Asian origin residing in the UK [229]. However, evidence from the US has suggested no significant difference in the incidence of epilepsy among different races based on a cohort enrolled in the health maintenance organizations in Houston [255]. Ethnicity has been addressed in a previous study by MacDonald et al. (2000) as whether it represents a risk factor in the incidence of neurological disorders in London-UK[256]. However, the study sample was not representative to the whole UK population and thus the authors recommended conducting a population-based study to address the effect of ethnicity.

There was no recorded data in the received THIN database version to account for ethnicity.

2.5.3 Prevalence of epilepsy compared to previous studies

The estimated overall prevalence of epilepsy in this study was consistent with previous prevalence studies in the UK and Europe. The prevalence of active epilepsy in CYP in Europe has been estimated at 4.5–5.0 per 1000 population [25]. Previous prevalence studies in the UK have reported that prevalence of epilepsy in CYP ranged from 2.8 to 5.2/1000 population [22, 226-228].

A possible explanation for the rise in the annual estimated prevalence between 1990 and 2004 can be attributed to a cohort effect where prevalence was found to increase with increasing age of the children. The study population consisted of CYP who were born on or after January 1st, 1988 and were registered at general practices over time so contributed over the years. The mean contribution of incident cases in the database was 7.5 (SD 4.7) years which reflect the general practice registration time. Therefore, as CYP remained registered in the database and became of older ages, they contributed as prevalent cases in the later calendar years.

The estimated age-specific prevalence of epilepsy showed that the prevalence of epilepsy was almost unchanged in age group 0-4 years over the study time. Whereas the prevalence in the other two age groups (5-9 and ≥10 years) increased over time between 1990 and 2004. However, the increase in prevalence of epilepsy in age group 5-9 years (from 2.26 to 4.06/1000) was within the reported estimates of the ONS for 1994 (4.2/1000) and 1998 (4.4/1000) using the GPRD database [27]. The annual age-specific prevalence of epilepsy was consistent with period estimates of prevalence using the GPRD database by Wallace et al. (1998) for 1995[22] and the ONS for 1994 and 1998. However, it was slightly higher than age-specific estimates by Martinez et al. (2009) for 2005 [230], particularly for the age group ≥10 years. The present study estimated the prevalence of epilepsy to be 6.5/1000 CYP, aged >10 years, in 2004, while Martinez and colleagues estimated a prevalence of 4.1/1000 CYP, aged 10-19 years, in 2005.

A recent review by Banerjee et al. (2009) reported that prevalence increased by age to be higher in young people than early childhood [257]. Increases in the survival rates of children with severe neurodisability and metabolic diseases which require gastrostomies may be a risk factor for epilepsy [258, 259]. In addition, the poor prognosis because of the presence of neurodeficit and frequent seizures may contribute to higher prevalence in older children [260].

2.5.4 Strength and weakness of findings

This study is a population-based longitudinal study that estimated the trend of incidence and prevalence in childhood epilepsy in the UK over 14 years. The study has been performed using electronic records of large sample of CYP from all parts of the UK that may be representative of the whole CYP population.

The findings of this study were comparable to the published literature in the area of incidence and prevalence of childhood epilepsy in the UK and worldwide. This study can contribute to previous validation studies which have demonstrated the strength of THIN database to examine the epidemiology of medical conditions on a population level such as incidence and prevalence of diseases in the UK.

There were a number of limitations to this study which included the nature of the study cohort of only children who were born in or after 1988, so it did not include all children registered in general practices contributing to THIN. However, the study cohort was representative of variable ages (infants, children and young people).

CYP with epilepsy were defined by having at least one diagnostic code for epilepsy and one prescription for an AED. However, the diagnosis was not ascertained, for example, by examining whether the diagnosis of epilepsy was accurate or whether it had been confirmed by a specialist in secondary care. This could be done by requesting paper records of a random sample of CYP with a diagnosis of epilepsy from GP and then consulting a paediatric specialist to examine these records. The reason for not doing this was that paper records of patients are available to researchers with extra cost which would have increased the cost of this study and made it unfeasible. In additions, some of

population-based studies on epilepsy using the GPRD database have not preformed case ascertainment and have relied only on the validity of database [27, 230].

The study only included diagnosed codes of epilepsy and hence cases that have not had a diagnosis code by a GP were not included. However, by not including these cases misdiagnosis of epilepsy, which is considered an important problem in the management of epilepsy [5, 261], would be avoided.

2.6 Conclusions

The analysis supports earlier findings on the epidemiology of epilepsy that is incidence of childhood epilepsy is higher in young children with the highest value in the first year of life. The study showed a social gradient in the incidence of epilepsy in CYP in the UK which suggests that socioeconomic status may represent a risk factor for the development of epilepsy. However, there was not enough data to explore the association between incidence and socioeconomic status, so the association is not understood. The prevalence of epilepsy tends to be higher with increasing age of children.

Chapter 3: Prescribing patterns and adherence to AEDs in children and young people

3.1 Rationale for the study

Antiepileptic drugs (AEDs) are the standard approach in the treatment of epilepsy. Because of the chronic nature of epilepsy, long-term (in some epilepsy syndromes, life-long) prescribing of AEDs is necessarily for better prognosis of epilepsy. Thus appropriate evidence-based prescribing and therapeutic monitoring of medicines, combined with patient adherence to these prescribed medicines remain a key factor in the control of seizures, reduction of disease progress and psychosocial sequelae and optimisation of quality of life [176, 262].

Prescribing of AEDs for newly diagnosed or untreated CYP with epilepsy in terms of choosing the initial drug, second-line drug and add-on drugs remained for so many years complex and uncertain [99, 102]. Before the release of NICE first guideline for the diagnosis and management of epilepsy in adults and children in 2004 [1], No conclusive evidence-based guidelines were available for standardised clinical prescribing of AEDs in CYP [263, 264]. Clinicians usually initialise drug treatment based on their own beliefs and experience with AEDs [265]. The first US evidence-based guideline for pharmacological management of epilepsy was also published in 2004 and focused on new AEDs [70, 266]. Both NICE and the US guidelines referred to the paucity of data from studies including only children.

There are little available data in the literature on the utilisation of AED in CYP in primary care in the UK. Chapter 1 provided a review section about the available data regarding the prescribing of AEDs in primary care. Aggregated prescribing data for children and adults with epilepsy have been reported in two studies from primary care settings [27, 117]. One population-based study by Ackers et al. (2007) focused on AED prescribing in CYP younger than 18 years old using the GPRD database [118]. The study concluded a straight rise in prescribing of new AEDs for which, the authors recommended further research

on their safety in children. However, this study examined all CYP (including those with epilepsy diagnosis) who were prescribed at least one prescription of AEDs and the case definition of epilepsy was not included.

Patient adherence remains an important issue to physicians and health care providers [176]. Moreover, factors associated with adherence in CYP are complex and multidimensional as they involve parents as well [135, 267]. Available data to understand reasons behind different adherence behaviours among CYP with epilepsy are, however, still scarce.

The majority of research that has examined adherence to AEDs in paediatric populations has been carried out using small cohorts of patients and/or specific age-ranges [134, 135, 137, 141, 157, 160, 268, 269]. This may reduce the statistical power and generalisability of the results and therefore, may not necessarily give a precise picture of the general population's drug-taking behaviour. No large paediatric cohort study has been reported in the UK to address adherence to AEDs in CYP. Therefore, this study was conducted to include a large representative sample to quantitatively assess the adherence behaviour of CYP and capture any potential factors which may precipitate non-adherence to AEDs regimens.

This chapter presents an exploration and description of actual AED prescribing in CYP with epilepsy. The different AEDs prescribed to control epilepsies in general, and by age of CYP and years from diagnosis, are presented using THIN database. The chapter then provides a method of measuring adherence behaviour to the prescribed medicines and explores factors which may be associated with adherence.

3.2 Aim and objectives of the study

The aim of this chapter was to investigate the frequency and pattern of use of AEDs in CYP with epilepsy in the UK and to assess their adherence to the prescribed medicines using THIN database.

The objectives were to:

1. Identify individual AEDs prescribed to children and young people.
2. Describe the frequency of prescribing of AEDs and proportions of monotherapy and polytherapy.
3. Explore any trends in the use of old and new AEDs with regards to CYP's age and changes over calendar time between 1990 and 2004.
4. Estimate overall adherence to AEDs and adherence over time to assess any changes in adherence levels of CYP during the study period.
5. Perform bivariate and multivariate analysis to determine potential factors that may be associated with adherence to AEDs in CYP.

3.3 Methods

3.3.1 Study cohort

The population for this analysis was the 2020 CYP diagnosed with epilepsy in THIN between 1st January 1990 and 30th November 2004. The study population were included if they had at least one diagnosis code for epilepsy and at least one prescription for an AED, as previously described in Chapter 2. To explore the use of AEDs, the CYP's therapeutic files were used. Data before 1990 were excluded because of the small number of practices that contributed to THIN database. Data from the year 2004 were also excluded because of lack of a full calendar year of data. So the study time for exploring the prescribing patterns of AEDs started on 1st January 1990 until 31st December 2003 (Figure 3-1). The total person-years of registered data contributed by the study cohort for this analysis were calculated from the date of first recording of epilepsy diagnosis or the first prescription for an AED in THIN (whichever occurred first) to the practice finish date. The finish date was the date of death, the date where the child transferred out of the general practice, or the last date of data collection, whichever occurred first.

The measurement of medication adherence was then carried out using the method of MPR on a subgroup of CYP diagnosed with epilepsy. For adherence measurement, additional inclusion criteria were that CYP had at least one year of follow-up from the date of first recording of epilepsy-related diagnosis or prescription (index date) and at least two prescriptions during their registered follow-up time. The study time for adherence calculation started at the index date and ended at the individual's finish date. This subgroup was also required to have at least one prescription with complete daily dosage instruction to calculate the length of AED supply for the prescriptions (described later in section 3.3.5). This subgroup comprised 1067 out of the initial 2020 CYP with epilepsy (Figure 3-1).

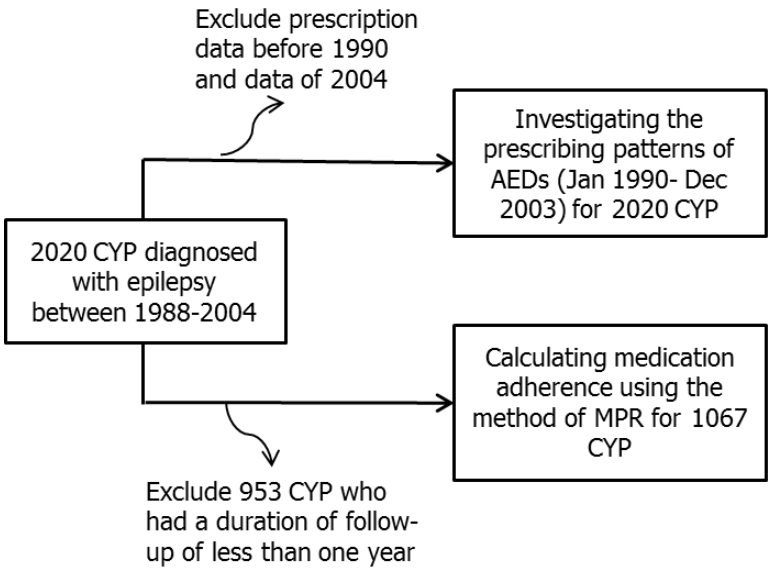


Figure 3-1: Study populations for prescribing and medication adherence analyses

3.3.2 Overall prescribing of AEDs for the study cohort

This study used the number of prescriptions for each AED as a measure of prescribing volume of AEDs. Antiepileptic drugs were classified into two groups, according to their market launch year (old: before 1990, new: after1990) [78, 79]:

a. Old AEDs included carbamazepine, clobazam, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone and sodium valproate
b. New AEDs included gabapentin, levetiracetam, lamotrigine, oxcarbazepine, tiagabine, topiramate, and vigabatrin.

All different drug preparation codes of each individual prescribed AED had the same generic name for each particular drug except for valproic acid and sodium valproate. In this study, drug preparations of sodium valproate and valproic acid were combined under “sodium valproate” as a generic name. This resulted in 15 different AED types which were prescribed to the study cohort to control epilepsy. Three other drugs; diazepam, midazolam and paraldehyde, were prescribed occasionally to the study cohort to control prolonged or life-threatening seizures such as `status epilepticus'. The analyses

in this chapter focused mainly on prescribing of AEDs for long-term, or chronic epilepsy control, rather than for acute management of seizures.

The overall number of prescriptions for all AEDs was calculated and then stratified by sex and age at first diagnosis and presented per person-years. The total number of AEDs prescribed per individual child was calculated during the study period. CYP were considered to be on monotherapy if they were prescribed only one AED type within the same 28 days in continuous or intermittent intervals each year. This definition may miscount some CYP who were prescribed one AED for fewer than 28 days and then were switched to an alternative AED because of side effects or other clinical factors. This is considered a limitation in the study definition of monotherapy. However, these CYP were considered to be few cases because more than one-half of CYP with epilepsy were only ever prescribed one AED, as described later in the results section 3.4.3. In addition, monotherapy with old AEDs was prescribed sequentially in this cohort of CYP before trying combination therapy.

The total number of CYP who were prescribed each individual drug was calculated based on whether CYP were ever prescribed a particular AED type during the study period. The total numbers of prescriptions for each individual drug were calculated per person years.

3.3.3 Frequency of prescribing of AEDs by age, sex and calendar years, over the study period

Firstly, the annual total numbers of prescriptions for all AEDs were calculated using per-calendar year cross-sectional analyses for the entire cohort. The total number of CYP treated each year was calculated and stratified by sex and age groups. Age was calculated at July 1st each year and then grouped into 4 categories each of 5-years. The trend of AED combination was explored by calculating the proportions of CYP who were prescribed one drug or multiple drugs each year. Then the proportion of CYP who received old AEDs versus new AEDs was calculated each year to assess any trend of prescribing old versus new AEDs.

Secondly, the annual total numbers of prescriptions of each individual AED were calculated per person-years to illustrate any general trend or use of AED type over the study period. The proportions of the CYP who received each individual AED were also calculated. This was done by dividing the number of CYP who were prescribed a particular drug each year by the total prevalent cases of CYP with epilepsy in that year.

3.3.4 Identification of initial therapies, second line therapies and time to second line treatment

First, second line and subsequent drugs used to manage epilepsy were explored to investigate the frequency of medication changes and/or increasing over time to control epilepsy. The addition of, or switching to second line therapies was examined using the newly diagnosed CYP with epilepsy (incident cases). The date of individuals' first prescription was set as the start date and then time to add or switch to the second line drug was calculated from this date. It was not possible to distinguish between switching and add-on therapy because the study population were prescribed 15 AEDs with possible probabilities for any two drugs to be combined in a single a course. Combined AEDs were usually recorded on the same date within THIN; however, in some cases AEDs were issued five to seven days apart which may appear to the analysis programme as switching. A child may also have been prescribed one drug, switched to a second drug and then switched back to the first drug in a short period. This caused difficultly to set up an algorism to account for all possible options of drug switching and additions. Therefore, time for either addition of or switching to second-line therapy was examined conjointly.

3.3.5 Estimation of adherence to AEDs

Adherence was calculated using the method of medication possession ratio (MPR) [143, 149]. The calculation of adherence included a sequence of steps which are described in the next sections

3.3.6 Data management for calculating the prescription length of prescribed AEDs

To calculate adherence using the method of MPR, the prescription length of AEDs (days of supply of AEDs per prescription) were calculated based on the dosage instructions. The THIN database contains some recorded dosage instructions which enable the estimation of prescribed number of units per day (daily dosage quantity) of individual AEDs. This in turn allows calculation of length of each prescription in days. The available recorded data include variables such as the total quantity prescribed or package size and some calculated daily quantity/volume of drug dosage derived by EPIC. These data were not completely recorded for the entire study cohort particularly for liquid formulations. Therefore, it was necessary to design methods to impute the missing data for the rest of the study cohort to obtain a full picture of individuals' therapeutic courses.

For the known recorded dosage instructions, the daily dosage quantities of prescribed drugs were calculated by translating the recorded prescription instructions (daily dosage regimen) of each individual AED into amount of volume of liquid dosage forms per day or number of units of solid dosage forms per day. The length of each prescription in days "Rxdays" was then estimated by dividing the total prescribed quantity or package size of each individual AED by the calculated daily dosage quantity.

$$\text{Rxdays} = \frac{\text{Total quantity prescribed or package size}}{\text{Daily dosage quantity}}$$

3.3.7 Methods for imputation of missing dosage instructions

When it was not possible to directly calculate the prescription length (Rxdays) because the dosage instructions were unrecorded or carried unspecified instructions such as `use as directed', `as directed by doctor', `as directed by the hospital', `as directed by specialist', `as directed every night', `as directed when required', `asd', `mds' and `mdu'), alternative methods were performed to estimate the daily dosage quantities of prescribed drugs.

A set of assumptions were derived to impute the missing dosage instructions. These assumptions were made in a hierarchical order based on the best available recorded data within THIN as follows:

Assumption 1: The missing or unspecified dose instruction for a specific prescription event was assumed to be the same as the previous instruction of the closest prescription date (not longer than 6 months) for the same child who was prescribed the same drug type, package size and dosage strength. The hypothetical example shown below (Figure 3-2) is for a child who was initially prescribed sodium valproate syrup (200mg/5ml) and then carbamazepine tablets 400mg. The unknown dosage instruction of the prescription (P3) was imputed from the known prescription (P2) of sodium valproate and the unknown dosage instructions of P5 and P6 were imputed from the known P4 of carbamazepine. The imputed dosage instructions were then used to calculate the missing length of prescriptions (Rxdays).

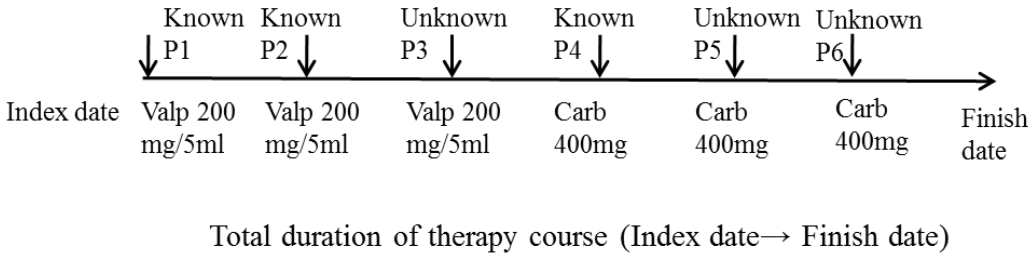


Figure 3-2: Illustrating example of the imputation of prescription length using previous known prescriptions

Assumption 2: for the still missing Rxdays, length of prescriptions was imputed using the median length of time between each two successive

prescriptions for each individual child. This time was calculated as the difference between each two successive issued prescriptions if the time difference did not exceed 90 days. The cut-off of 90-days was considered because from the known recorded data, a prescription often supplied an AED for a maximum of 90 days. A hypothetical example is shown below (Figure 3-3) for a child who had unspecified dosage instructions for the prescriptions (P2-P6) such as `take as directed'. The length of each prescription was imputed by calculating the median value of the five intervals between prescriptions. This means that Rxdays of P2, P4 and P5 were imputed to be 1 month (30 days) and Rxdays of P3 were imputed to be 2 months (60 days).

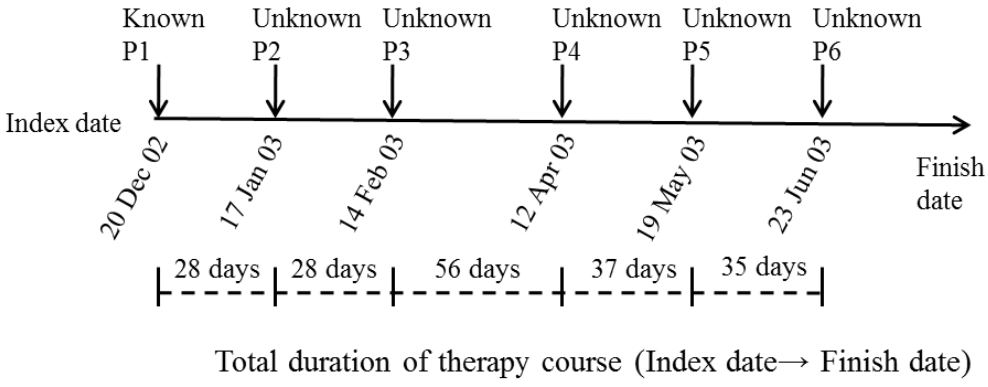


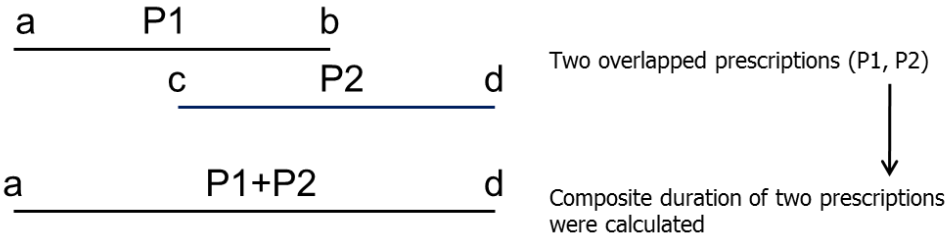
Figure 3-3: Illustrating example of the imputation of prescription length using the time between two issued prescriptions

Assumption 3: For the still missing Rxdays (e.g. in case of the time between two unknown prescriptions was more than 3 months), length of prescriptions was imputed using the median length of all other recorded prescriptions calculated individually for each child.

3.3.8 Dealing with the overlapping prescription dates

To avoid double counting of the number of days' supply of AEDs and hence overestimating adherence, the overlap between prescription episodes for the same or different drug types was eliminated by two ways. First, when two or more prescriptions were issued on the same day, the longest one was considered. Second, when a prescription (P2) started before the end date of a previous prescription P1, the overlapping days of P1 were discarded (an example is shown in Figure 3-4)

The assumption was that if P1 and P2 were for the same drug, P2 was assumed to carry a new dosage instruction. If P1 and P2 were for different drug types then leftover supplies from previous P1 were discarded to start the new drug (P2).



P1 is a prescription to supply drug X for duration of ab. P2 is an overlapped prescription to supply drug Y for a duration cd. ad is composite duration of P1 and P2.

Figure 3-4: Dealing with overlapping prescription dates

These assumptions were suggested in an earlier study by Briesacher et al. (2008) [270]. The authors assessed the drug adherence levels for 4984 adults with seizure disorders using health care claim data in the USA and the method of MPR.

3.3.9 Estimation of the Medication Possession Ratio (MPR)

The overall MPR was calculated first on the aggregated data for the whole course of therapy during the study period for the subgroup of 1067 CYP. The calculation of overall MPR was to provide an overall picture of the distribution of adherence of the CYP in the sample. The calculation of overall MPR was additive of all prescribed AEDs. This means that proportions of days supplied for the initial AED were added to those days of all consecutive AEDs to control epilepsy for individuals after accounting for different types of prescription overlapping. For example, if a child received a prescription for sodium valproate as the initial drug, then the proportions of days supplied for sodium valproate as well as those for any further AEDs were calculated. This sort of calculation was previously performed in an earlier study by Briesacher et al. (2008) [270].

The individual's duration of follow-up was calculated as the difference between the index date (date of first recording of epilepsy in THIN) and the finish date of the individual child's data.

The overall MPR was simply calculated as follow:

$$\text{MPR} = \frac{\text{Total days supplied by AEDs during the follow-up}}{\text{Duration between the index date and finish date of CYP}}$$

The distribution of MPR before and after data imputation of the length of prescriptions was assessed. As the distribution was left skewed, the Wilcoxon-Mann-Whitney test was used to examine whether there were differences between MPR distribution before and after imputation of missing data.

3.3.10 Sensitivity analysis for the calculation and description of MPR

A sensitivity analysis was performed to examine whether there were any artefacts in the method of imputation of missing dosage instructions and/or length of prescriptions.

The MPR values were calculated on the raw data of the subgroup of CYP who were included to calculate adherence; however, without executing any assumptions to impute the missing dosage instructions.

This analysis was carried out in two ways; one way was to calculate the MPR without imputation of missing data, however, adjusting for the overlapping prescriptions. The second way was to calculate MPR without imputation of missing data and without accounting for the overlapped prescriptions.

3.3.11 Factors influencing adherence to AEDs

Factors that may hinder optimal adherence to the prescribed AEDs in CYP are complex and multilayered. These factors were simply classified by Rapoff (1999) as described earlier in Chapter 1 [152]. Among these diverse factors, this study was able to investigate specific factors that were available within THIN data. The investigated factors that may have been associated with non-adherence are summarised in Table 3-1.

Table 3-1: Factors influencing adherence to AEDs

Factor/variable	Justification/ definition
Age and sex	Higher adherence levels were reported in girls. Adolescents have been demonstrated to have lower adherence than school age children or infants. Sex was set as a binary variable (0=female, 1=male). Age of children was calculated on the index date of each child and then categorised into four groups; < 2, 2-6, 7-12 and > 12 years old. This classification of age groups was used according to the BNF categorisation of age for indication and dosage of AEDs as the dosage instructions usually vary at 2, 6, and 12 years cut-off ages [271].
Socioeconomic status	Socioeconomic classes have been proved to affect the level of social support and care received by CYP from their parents or caregivers and consequently affects adherence behaviour of CYP.

	The database uses the Townsend deprivation index as a marker of socioeconomic status (as described in Chapter 2). Socioeconomic status of CYP was defined in quintiles of Townsend score where 1=least deprived and 5=most deprived.
Family size	CYP with epilepsy belonging to a large family size showed low adherence levels. A larger family size with higher number of children to the same parents was suggested to decrease the quality of care given to a child with epilepsy. This in turn may lead to a lower level of adherence. As mentioned in Chapter 2, the study was conducted on a preformed dataset of THIN database [232]. General practices assign the same `family number' to individuals who reside at the same address, which is anonymised and available for research. This means that individuals in institutions such as residential homes or in apartment buildings may have the same family number. To ensure those were excluded, the authors excluded individuals with family number of more than 20 people. The family number enabled the examination of the effect of a proxy of family size or household size on the level of adherence. Family size was classified into four groups; family size up to 5 members; 6-10 members; 11-15 members and family size >15 members.
Complexity of prescribed AED regimens	Complexity of AED regimen was investigated from two aspects; the number of AEDs taken concurrently and the frequency of doses per day. The hypothesis was that an increasing complexity of regimens by adding more prescribed drugs and/or increasing frequency of daily dosage may be associated with lower adherence [272]. The complexity of prescribed drugs for other co-morbid conditions, although was expected to affect adherence of CYP by increasing the number of medicines of daily regimen, was not investigated. It was possible to extract all

	drug codes in THIN for all co-morbid conditions in the time frame of the study period. This would have made the study more time consuming to conduct and more difficult to manage so many drugs altogether. A binary variable was set whether CYP were on one drug or combined two or more AEDs. The child was considered on combined drugs if he/she was prescribed two or more AEDs within the same 28 days in continuous or intermittent intervals. The frequency of doses was also set as a binary variable based on the median doses per day of each individual child where 0= once daily and 1= twice or more daily.
Co-morbid diseases	Concurrent co-morbidities are another factor that can add to complexity of drug regimen. Epilepsy has been shown to be associated with coexisting psychiatric and behavioural disorders [244, 245]. It has been reported that adults suffered from cognitive disorders and other mental behavioural disorders reported lower medication adherence [273, 274]. Co-morbidities were addressed as binary variables whereas a dummy variable was derived as either having asthma, mental health disorders or other co-morbid diseases. Asthma and mental health disorders were tested separately from other co-morbidities as these two diseases represented the most common two co-morbid classes in the study cohort as shown in Chapter 2.

Adherence levels were assumed different to individual AED types because of different pharmacokinetics of drugs, tolerability and available drug preparations [176]. As above-mentioned that the MPR was calculated additively for all AED, so estimation of adherence for individual AEDs may be affected by switching of medications (i.e., a child may start a particular AED, switch to a second-line AED and then switch back to the initial drug in which the period of the second drug will be calculated as a gap for the initial drug). Therefore, the variation in adherence to different AEDs was examined separately on

subgroup of CYP who received only one AED type during the total study period. A variable was generated to include the AED type that was prescribed to each individual child. To examine the difference in adherence between old and new class AEDs, a binary variable was also created whether CYP were ever prescribed old or new AEDs.

3.3.12 Bivariate analysis of factors influencing adherence to AEDs

Bivariate analysis was carried out to test the association between CYP's demographics and some regimen-related factors and the overall measured adherence to AEDs.

For bivariate analysis, adherence as a function of calculated MPR was set as a continuous outcome variable. As it had a non-normal distribution, the Wilcoxon rank sum (Mann-Whitney) test was used to test whether there was a difference in adherence distributions by sex, number of prescribed AEDs, frequency of doses per day and coexisting co-morbidities. The Kruskal-Wallis test was used to test whether each category of CYP's age at diagnosis, family size and Townsend index had the same shape of adherence distribution.

The variation in adherence distribution of different AEDs was examined using the Kruskal-Wallis test and difference in adherence distribution of old and new AEDs was examined using the Wilcoxon rank sum (Mann-Whitney) test.

3.3.13 Multivariate analysis of factors influencing adherence to AEDs on aggregated data

After performing bivariate analysis, multivariate analysis was performed to understand the relationships between the identified independent variables and which of these variables are the main independent risk factors and predictors of adherence to AEDs.

The analysis was carried out firstly on aggregated data to draw a general picture about factors that may affect adherence behaviour of CYP.

Overall adherence as a function of the calculated MPR was set as a continuous variable. The Ordinary Least Square regression model (OLS) was not appropriate because the data were skewed and not normally distributed which is a common feature of health data [275]. The log-scale residuals from a OLS model for the transformed data, ln (MPR), showed also that the random errors were significantly heteroscedastic (variance of the modelled errors was not constant). In such cases, the OLS model on log transformed data will provide biased estimates [275]. Another disadvantage of transforming data is that the regression does not provide a model for the mean function, $\mu(x)$, in the original scale, which in many cases is difficult to interpret [276].

A recommended alternative model is to choose one of the generalized linear models (GLM) [275]. The GLM model specifies the relationship between the observed outcome variable and some number of covariates. By restructuring the relationship between the linear predictor and the fit, relationships that initially seem to be nonlinear can be linearised [277].

The GLM with exponential gamma distribution was applied to analyse the relationship between overall calculated adherence and identified factors. The gamma distribution is used for data situations in which the response can take only values greater than or equal to 0. The variance function in gamma distribution is proportional to the square of the raw-scale mean function [278]. It is used primarily with data of continuous outcome variable but can also be used with count data. An overview on GLM model and gamma family is presented in Appendix 15.

3.3.14 Post estimation statistics of GLM model-family gamma

Diagnostic tests are important for deciding a model's goodness of fit, especially when the data are not normally distributed. A set of diagnostic tests can be applied after the usual estimate with the implemented GLM model to check for appropriate variance (relevant error distribution) and link functions. Three main tests were applied as GLM-diagnostics included the modified Park test to test adequacy of gamma distribution [275, 279], Pregibon link test (1980) to examine the adequacy of the (log) link function [280] and Pearson residuals statistics to measure of overall fit for GLMs.

3.3.14.1 Modified Park test

This test determines whether the gamma distribution was appropriate for the outcome variable (i.e. reflect the relationship between mean MPR and variance) in order to specify the correct power of the mean and variance for the observed raw-scale MPR values[279].

To perform this test, the tentative parameter estimates from a GLM model based on the hypothesised variance function (i.e. family gamma, link (log) regression) are computed. The linear predictors from the initial fit of the GLM regression were used to obtain raw-scale residuals by calculating the inverse link function. The second step is to regress the squared raw-scale residuals on a constant and the linear predictor from the GLM with a log link. The estimated coefficient on the linear predictor can determine which variance function (e.g. Poisson, Gamma, and Wald) is most appropriate [275].

Common data distributions based on the power function include:

- Gaussian: has a constant variance; $\upsilon=0$
- Poisson: where variance is proportional to the mean; $\upsilon=1$
- Gamma: where variance is proportional to the square of the mean; $\upsilon=2$
- Inverse Gaussian: where variance is proportional to cube of the mean; $\upsilon=3$

So if the estimated co-efficient was equal or close to 2, family gamma distribution was appropriate to model adherence data.

3.3.14.2 Pregibon's Link Test

The Pregibon's test for linearity was introduced by Daryl Pregibon in 1980[280]. The purpose of this test is to examine the adequacy of the hypothesised (log) link function used in fitting the GLM model (goodness of link). The link function specifies how the mean on the original MPR scale was related to the set of regressors (explanatory variables). Pregibon's test considers a two parameters generalization after obtaining the initial estimates for a GLM model with the hypothesised log link function. The model was refitted with the two new parameters as the only predictors. The Coefficient on square of the predicted parameters should not be significantly different from zero. If null hypothesis is rejected, then model should be kept the same.

3.3.14.3 Pearson's chi-squared residuals

Residuals are considered highly important in checking adequacy of GLM models. Pearson's residuals is a popular applied measure for overall fit of GLMs [281]. It is usually defined as the signed square roots of the contributions to the Pearson goodness-of-fit statistic, and given by:

$Ri = \varphi (Y_i - \hat{u}_i)/ V_i^{1/2}$

where $\hat{u}_i$ and V_i are respectively the fitted mean and fitted variance of function of Y_i in the regression model [281]. The purpose is to determine systematic bias in the predicted values of outcome variable on raw scale. In other words, the test reflects whether the predicted values are an accurate representation of the observed values.

3.3.14.4 Test the independence of the errors Cov (εi, εj)=0

This assumption means that error term of the independent variables are not correlated. The violation of this assumption is called "autocorrelation" and results in inefficient estimation of the coefficients.

3.3.15 Longitudinal calculation of MPR over time

Adherence behaviour is presumed to be a dynamic process with a changing and unstable pattern [267]. Measuring overall MPR (adherence) does not reflect time-based variation in the long-term CYP's adherence. Therefore, this study was concerned with investigation of CYP's long-term adherence to assess any changes over time. Repeated longitudinal biannual (6-months interval) calculation of MPR was carried out. The biannual calculation of MPR started from the date of individuals' first recoding of epilepsy diagnosis or AED prescription in THIN (index date) whichever recorded first. This was done by defining the duration of follow-up for each individual child (from the index date to the finish date). Then the individual's total duration of follow-up was divided longitudinally into a number of 6-months intervals. If the last interval of an individual child did not fulfil 6 months, the last interval ended at the child's finish date. The numbers of days supplied with AEDs in each 6-months interval for each individual child were calculated. Finally, MPRs were calculated as the proportions of days' supply with AEDs each 6 months-interval.

Figure 3-5 illustrates an example of the biannual calculation of MPR for a hypothetical child with duration of follow-up of 912 days (2.5 years)

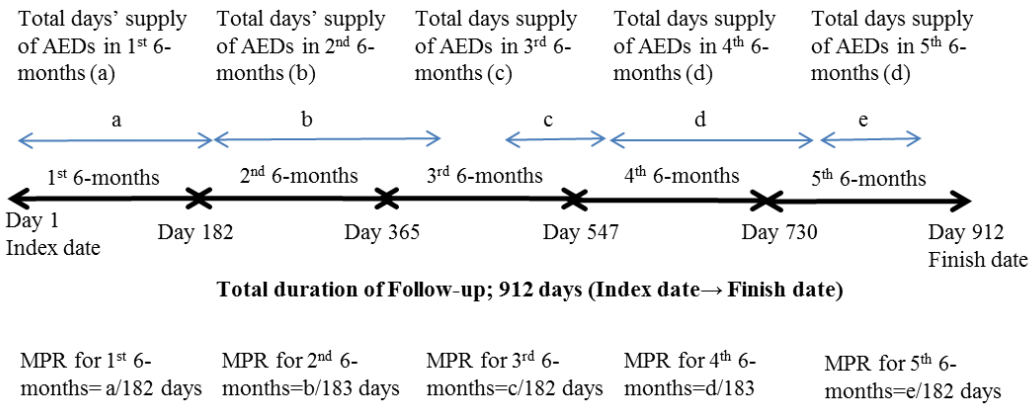


Figure 3-5: Process of biannual calculation of MPR

3.3.16 Analysis of factors affecting adherence over time (longitudinal analysis)

The long-term effects of potential factors on adherence behaviour over the years of contribution in the study period were investigated using longitudinal modelling analysis.

In longitudinal data, a group of subjects sometimes of the same age as in a `birth cohort' is often followed up at subject-specific occasions `events' which produces unbalanced or `variable occasion' data [282]. Longitudinal data are likely to have a mix of time-variant (e.g., age and income) and time-invariant variables (e.g., sex).

Multiple events on subjects cannot be assumed independent within subjects; it does mean that events are correlated with events nested in subjects so the subjects become the clusters. Therefore, it is not recommended to use ordinary regression to analyse longitudinal data because the data are clustered. It is expected that unobserved between-subjects heterogeneity leads to within-subject correlations [282].

Longitudinal data with repeated observations offers the scope to control for individual heterogeneity and the dynamics of individual behaviour. Liang and Zeger (1986) introduced the Generalized Estimating Equation (GEE) to provide more consistent and unbiased regression estimates in analysing longitudinal or repeated measures for cross-sectional designs with non-normal response variables [283]. The GEE models extend the generalised linear models to analyse correlated observations that arise from repeated measures of the same individuals over time [276]. The GEE models are consistent and can handle a variety of correlated data even if the correlation structure is misspecified [284]. The focus of GEEs is on estimating the marginal or average response over the population (`population-averaged' effects) taking into account the dependence among units nested in clusters (Appendix 16) [282]. It means that, for every one-unit increase in a covariate across the population, the GEE infers how much the average response would change [285]

One of the most important things in longitudinal analysis is set a variable referring the time period of the analysis during which the repeated observations of interest are analysed. In this study, the anniversary years of the individuals' therapeutic courses was chosen as the time variable. The outcome variable was the measured adherence to AEDs as a function of MPR. The MPR for longitudinal analysis is the per-6-months calculated MPR values over the follow-up years of individual CYP and were set in 30 waves where each wave equals 6-months interval (15 years of follow-up). It was set as a continuous variable for longitudinal analysis.

The examined factors were the same under pooled analysis which included sex, socioeconomic status, family size, complexity of AED regimen and co-morbidities. However, age of CYP was calculated at each 6-months interval as a time-varying variable and again categorised into four groups. A new variable which referred to the duration of treatment of each child was included in the longitudinal analysis.

3.3.17 Model diagnostics

As with GLM models, the GEE approach also needs diagnostic procedures for determining the goodness of fit. Among the diagnostic methods, the most common is to investigate the randomness of errors by plotting the residual values for each observation [286]. In the GEE approach, Pearson residuals are commonly used to estimate correlation parameters. However, the distribution of Pearson residuals for non-normal distributions is often markedly skewed, and may fail to have properties similar to those of normal residuals [287]. The plot of residual values against the linear predictor after the usual fitting of GEE model should show no systematic pattern (random sequence). For example, the deviance residuals are likely to fluctuate randomly above and below a horizontal line at zero [286].

However, the conventional residuals plots for model diagnosis in longitudinal data could mislead a researcher into trusting the fitted model. The scatter plots of subjects' residuals against the follow-up time are sometimes helpful [286].

In this study, the scatter plot of Pearson residuals after the fitting of GEE model on longitudinal data against the follow up time was drawn to determine the goodness of fit of the model.

3.4 Results

3.4.1 Characteristics of study cohort and overall prescribing of AEDs

During the study period, 2020 epilepsy cases contributed 9562 person-years of follow-up since the date of first recoding of epilepsy diagnosis (Table 3-2). Among the cases, 1115 (55.2%) were males and the majority (50.2%) were below the age of five years at their first date of recoding epilepsy in THIN. The patients were prescribed a total of 82,836 prescriptions of 15 AEDs for epilepsy control (shown later in Table 3-3). The CYP were also prescribed 3642 prescriptions of three drugs for controlling prolonged or life-threatening seizures. Of the total prescriptions, there were 54905 (66.3%) and 27931 (34.7%) prescriptions for old and new AEDs, respectively. A small number of CYP (80) were prescribed only one prescription during the whole duration of follow-up.

Overall, the mean number of prescriptions per person-years was 9.1 (95% CI=8.9-9.3). The younger age children, 0-4 years, had a mean of 8.8 (95% CI=8.5-9) prescriptions per person-years while older age groups; 10-14 and ≥15 years, had a mean of 10.3 and 10.5 (95% CI=9.1-11.9) prescriptions per person-years, respectively. Over the study time, one-half of CYP (n=1042; 51.6%) were prescribed only one AED type to control epilepsy with a mean of 4.5 (95% CI =4.3-4.7) prescriptions per person-years. Approximately one quarter of patients (n=489; 24.2%) were prescribed two drugs and the remainder received three (11%) or more AEDs (13.2%).

Table 3-2: Characteristics of study cohort and overall prescribing of AEDs

Character	No of CYP (%)	No of prescriptions	No of person-years	Prescriptions/ person-years (95% CI)
Total	2020	86,478	9561.95	9.1 (8.9-9.3)
Sex				
Males	1115 (55.2)	49,355	5135.00	9.6 (9.4-9.8)
Females	905 (44.8)	37,123	4426.95	8.4 (8.3-8.5)
Age (years)				
0-4	1013 (50.2)	52,368	5946.96	8.8 (8.5-9)
5-9	666 (32.9)	26,265	2853.75	9.2 (9.1-9.3)
10-14	317 (15.7)	7,675	745.04	10.3 (10.1-10.5)
≥15	24 (1.2)	170	16.20	10.5 (9.1-11.9)
Number of prescribed AEDs				
1	1042 (51.6)	18,658	4136.56	4.5 (4.3-4.7)
2	489 (24.2)	18,576	2438.91	7.6 (7.5-7.7)
3	223 (11)	14,656	1172.53	12.5 (12.1-12.9)
> 3	266 (13.2)	34,588	1813.95	19.1 (18.9-19.3)

3.4.2 Frequency of prescribing of individual AEDs over the study period

CYP were most often prescribed old AEDs such as sodium valproate and carbamazepine (65.2% and 40.8% received valproate and carbamazepine, respectively). Phenobarbital and phenytoin were less common prescribed old AEDs. Lamotrigine and topiramate were the most often prescribed drugs from the new AEDs for 24.4% and 8.5% of CYP respectively. The same order could be applied to the number of CYP who were prescribed one drug over the study period `monotherapy' (Table 3-3). Among CYP who were ever prescribed one drug, the highest number of CYP (n=606) received sodium valproate followed by carbamazepine (n=302) and lamotrigine (n=51).

Old AEDs were most often tried as first-line drugs compared to new AEDs. Out of 2020 CYP, 1667 (82.5%) received old AEDs as first line treatment.

Table 3-3: Overall prescribing of individual AEDs over the study period

Drug name	No of CYP prescribed the drug (%) n=2020*	No of prescriptions (%) n=82,836	No of CYP received drug as first line (%) n=2020	No of CYP on one drug type (%) n=1042
Sodium valproate	1318 (65.2)	29,564 (35.7)	986 (48.8)	606 (30)
Carbamazepine	824 (40.8)	20,353 (24.6)	532 (26.3)	302 (15)
Lamotrigine	493 (24.4)	16,488 (19.9)	108 (5.3)	51 (2.5)
Topiramate	171 (8.5)	3,733 (4.6)	18 (0.9)	4 (0.2)
Vigabatrin	161 (8.0)	3,540 (4.3)	61 (3.1)	18 (0.9)
Ethosuximide	109 (5.4)	1,972 (2.4)	35 (1.7)	19 (0.9)
Phenobarbital	104 (5.1)	1,083 (1.3)	76 (3.8)	28 (1.4)
Clonazepam	94 (4.7)	2,012 (2.4)	16 (0.8)	4 (0.2)
Phenytoin	84 (4.2)	1,357 (1.6)	38 (1.9)	9 (0.5)
Levetiracetam	58 (2.9)	794 (0.9)	0 (0)	0 (0)
Gabapentin	51 (2.6)	1,064 (1.3)	4 (0.2)	0 (0)
Oxcarbazepine	15 (0.7)	265 (0.3)	2 (0.1)	1 (0.1)
Clobazam	14 (0.7)	260 (0.3)	0 (0)	0 (0)
Tiagabine	9 (0.4)	37 (0.1)	0 (0)	0 (0)
Primidone	3 (0.2)	316 (0.4)	1 (0.1)	0 (0)

*Note: A child can be prescribed more than one individual AED, therefore the number of CYP does not add to the total 2020 CYP.

3.4.3 Frequency of prescribing of AEDs by age and calendar years, over the study period

The study cohort had a specific feature in that it consisted of CYP who were born in or after 1988. Data illustrated in Table 3-4 show an increase in number of CYP who were treated with AEDs each year from 31 children in 1990 to 1060 CYP in 2003. The total numbers of prescriptions of AEDs were also increased each year during the study period. The number of treated CYP ranged from 58% to 69% each year. Around one-third of CYP did not receive any medicines each year and ranged from 43% in 1990 to 31% in 2002-03. The proportions of CYP who were on one drug each year ranged from 58% to 64% of treated CYP and slightly changed over the study period. Each year, between 17% and 27% of CYP were received at least two AEDs each year to control epilepsy. Higher proportions of children were on one drug in the age category 0-4 years during the first 6 years (1990-95). From the year 1996 and as children became older and still contributed to THIN data, the higher proportions on one drug were in older age categories, 5-9 and $\geqslant$ 10 years, as shown in Table 3-4.

Table 3-4: Prescribing of AEDs by age and calendar years, over the study period

Calendar years	No of prescriptions N=82,836	No of CYP* n=2020		Sex (treated)		No of CYP on one drug by age groups (%/year)* n=1042				No of CYP on more than one drug by age groups (%/year)* n=978			
		All	Treated (%/year)	Male	Female	0-4	5-9	≥10	All ages	0-4	5-9	≥10	All ages
1990	239	54	31 (58)	17	14	22	0	0	22 (41)	9	0	0	9 (17)
1991	575	105	71 (68)	31	40	44	0	0	44 (42)	27	0	0	27 (26)
1992	880	151	89 (59)	49	40	52	0	0	52 (34)	37	0	0	37 (25)
1993	1307	220	132 (60)	69	63	65	11	0	76 (35)	43	13	0	56 (26)
1994	1789	308	190 (62)	95	95	83	32	0	115 (37)	50	25	0	75 (24)
1995	2846	419	265 (63)	136	129	90	72	0	162 (39)	64	39	0	103 (25)
1996	3940	536	369 (69)	195	174	102	126	0	228 (43)	70	71	0	141 (26)
1997	5020	652	431 (66)	224	207	89	166	0	255 (39)	71	105	0	176 (27)
1998	6273	792	527 (67)	272	255	94	212	35	341 (43)	70	106	10	186 (24)
1999	7439	945	651 (69)	357	294	105	232	80	417 (44)	70	131	33	234 (25)
2000	8870	1089	733 (67)	411	322	95	205	146	446 (41)	77	147	63	287 (26)
2001	10385	1267	865 (68)	491	374	94	220	218	532 (42)	72	155	106	333 (26)
2002	11819	1410	974 (69)	560	414	94	215	298	607 (43)	84	142	141	367 (26)
2003	12991	1534	1060 (69)	607	453	88	217	378	683 (45)	81	119	177	377 (25)

* The number of CYP does not add to total as a child can contribute to more than one calendar year

The proportions of CYP on old and new AEDs are shown in Figure 3-6. Over the study period, the proportions of CYP on old AEDs ranged from 57% to 63% with slight change over time. The proportions of CYP who were prescribed new AEDs increased from 11% in 1990 to 24% in 2003. Non-treated CYP ranged from 43% in 1990 to 31% in 2002-03. Some of non-treated CYP were incident cases and received their first prescription later and others were prevalent cases but were not prescribed any drug in a particular year.

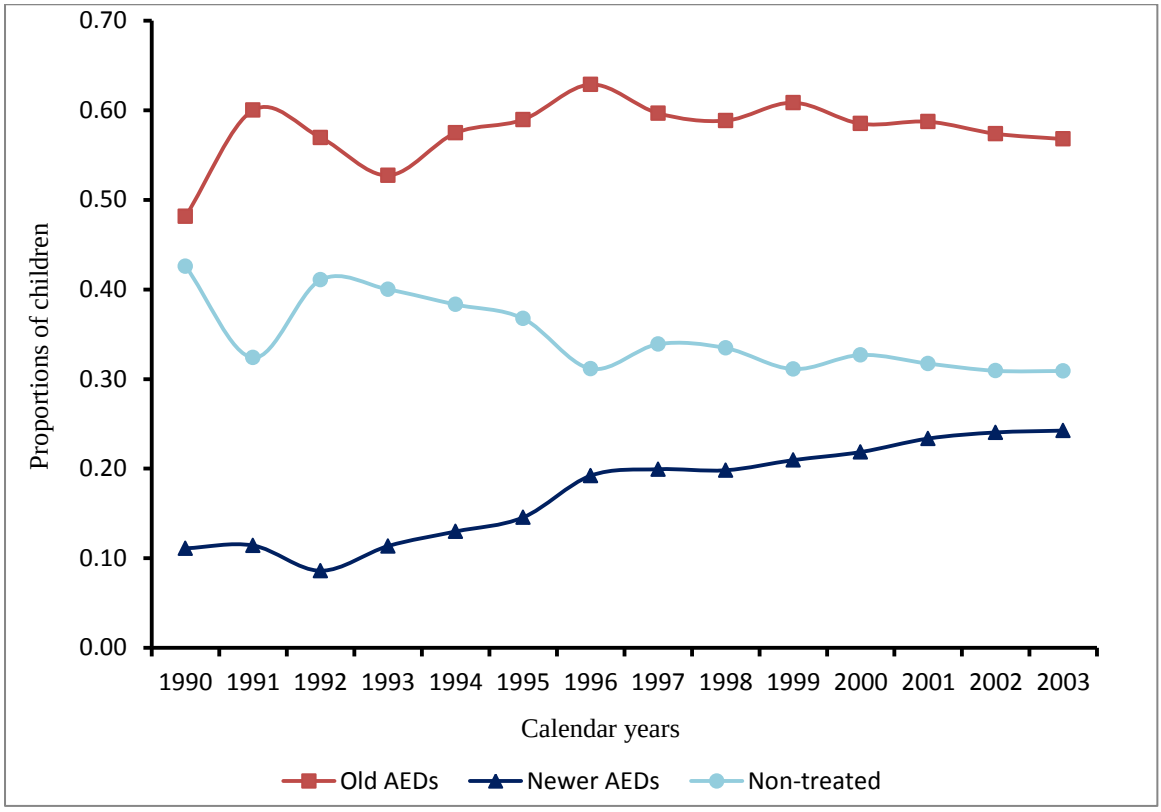


Figure 3-6: Proportions of CYP who were prescribed old and new AEDs each year

3.4.4 Frequency of prescribing of individual AEDs by calendar years over the study period

Cross-sectional per year analysis of the AED prescribing revealed that the number of prescriptions increased for many drugs such as sodium valproate, carbamazepine, lamotrigine and topiramate. There was also an increase in the total numbers of CYP who received individual drugs each year.

The total numbers of prescriptions per person-years of study cohort increased for sodium valproate and carbamazepine from the old AEDs (Figure 3-7). The total annual number of prescriptions per person-years decreased for phenytoin and phenobarbital. The mean numbers of prescription per person-years were 2.79 of sodium valproate, 1.83 of carbamazepine, 0.25 of Phenobarbital and 0.16 of phenytoin.

The annual numbers of prescriptions of the new AEDs per person years increased for lamotrigine (0.07 in 1992 to 2 per person-years in 2003) and topiramate (0.01 in 1996 to 0.63 per person-years in 2003) during the study period (Figure 3-7). An increase in number of prescriptions of vigabatrin, one of the new AEDs, was observed till the year 1998 followed by a decline. The mean numbers of prescription per person-years were 1.01 of lamotrigine, 0.44 of vigabatrin and 0.17 of topiramate per person-years.

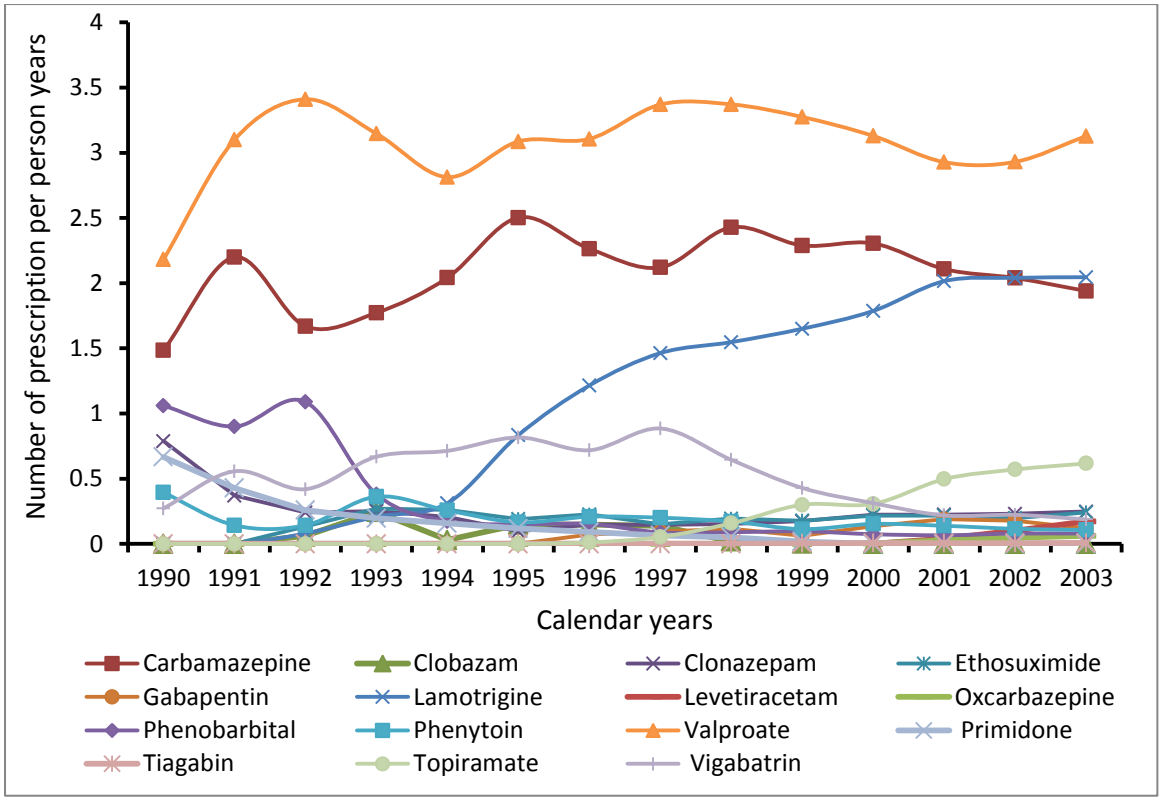


Figure 3-7: The annual numbers of prescriptions of individual AEDs per person-years

The proportions of CYP who were prescribed a particular AED type relative to the prevalent cases of study cohort each year (the probability of prescribing a particular AED type if a child was diagnosed with epilepsy) is shown in Figure 3-8. The overall prescribing remained higher for old AEDs during the study period. The proportions of CYP who were prescribed old AEDs almost unchanged for sodium valproate and carbamazepine after the year 1999. The proportions of CYP who were prescribed new AEDs such as lamotrigine and topiramate increased over the study period.

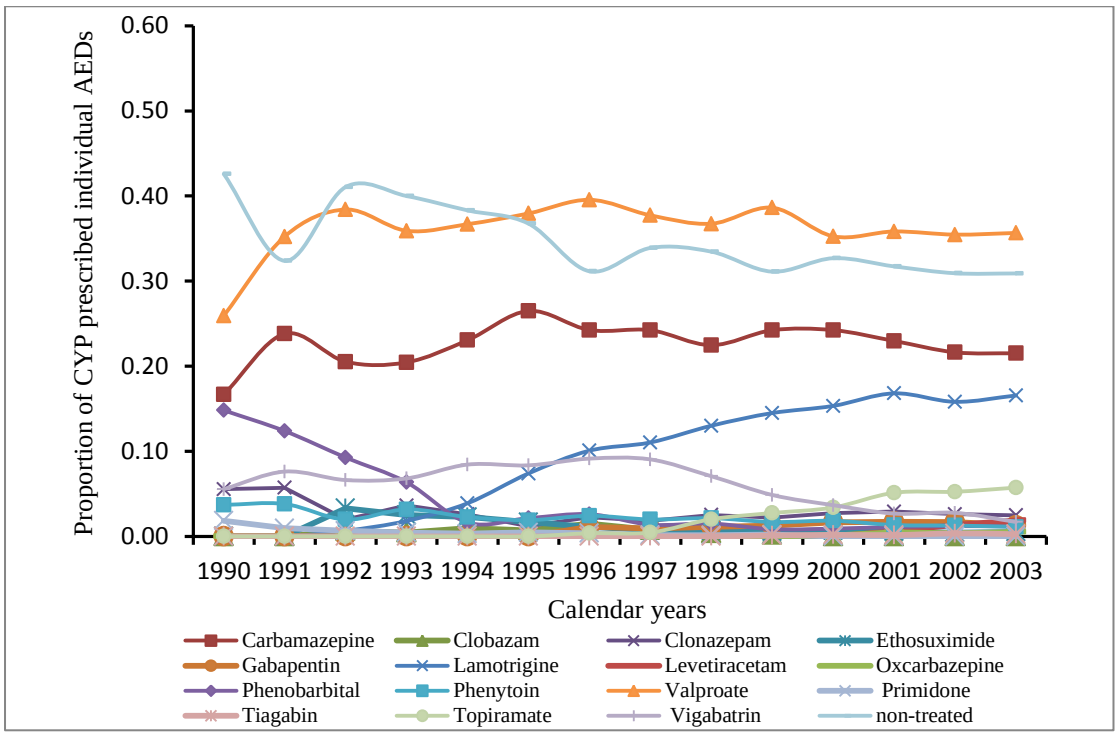


Figure 3-8: Proportions of CYP who were prescribed individual AEDs each year

3.4.5 Time to addition of or switching to a new drug type

The above-mentioned data in Table 3-3 of prescribing individual AEDs revealed that almost all AEDs were tried as first-line therapies to control epilepsy.

Although the majority of CYP were only prescribed one AED over the follow-up time (1042, 51.6%), 24 % were prescribed two drugs and 23% were prescribed three or more drugs. The maximum number of AED combinations taken as a single course was four drugs. The median time to add a new drug type to the course of therapy or to switch to a new AED is shown in Table 7. The median time to add or switch to a second type was 173 days (~0.5 year).

Table 7: Time to change the regimen (either by adding or switching to a new drug type)

Number of the added AED	Median time to add or switch to next AED in days (IQR)	Range (min	max)	Number of CYP
Second	173 (74-423)	5	1898	573
Third	203 (86-463)	8	2229	436

3.4.6 Results of calculating the daily dosage of prescribed AEDs

Table 3-5 shows a summary of available recorded data for the calculation and description of individuals' dosage regimens. Out of 2,020 CYP, 953 (47%) either had completely missing `unrecorded' dosage instructions and/or less than one year coverage of prescription records. Thus the data shown in Table 3-5 were for 1,067 CYP who had data for at least one follow-up year and at least one known dosage instruction. The daily dosage instructions were explicitly recorded for 45,779 (63.6%) out of 71,969 issued prescriptions. This means that the daily dosage instructions (and consequently the length of prescriptions) were unavailable for more than one-third (36.4%) prescriptions. Of the missing dosage instructions, 18,896 (26.3%) dosage instructions were completely unrecorded and 7,294 (10.1%) prescriptions carried non-specified instructions (e.g. `Take as directed'). The exact length of prescriptions in days was recorded for only 6% of the total prescriptions.

Table 3-5: Available data in THIN for calculation of dosage regimen for the study cohort

Variable (unit)	Missing data	Recorded data	Median (IQR)	Min	Max
Prescription quantity/package size (solid units or mls of liquid)	1.0 %	99%	112 (56-300)	1	1800
Calculated daily quantity/volume of dosage (solid units or mls liquid)	36.4%	63.6%	2 (2- 4)	0.5	40
Length of prescriptions (days)	94%	6%	28 (28-30)	1	84

mls=millimetres (unit measure of volume)

The extent of recording prescription instructions was examined during the three years before 2002 (the year where data collection in THIN started prospectively from contributing general practices) and three years from 2002 to 2004. Out of 23,229 prescriptions issued throughout 1999-2001, 10,318 (44%) prescription instructions were missing and out of 28,484 prescriptions issued throughout 2002-2004, 8,789 (31%) were missing prescription instructions. This suggests that the quality of recording data has improved since data collection started prospectively in 2002.

Similar analysis was carried out to investigate the quality of recording THIN-coded seizure outcomes before and after 2002 and the results were reported in section 4.5.2.

3.4.7 Results of imputation of missing dosage instructions

To calculate MPR for the study cohort, the available dosage data was utilised to impute missing dosage instructions. The overall MPR was calculated at each stage of executed assumption and the results are shown in Table 3-6. The MPR values shown in the table were calculated at each stage of assumption before executing the following assumption.

Table 3-6: Calculated MPR after each assumption for imputation of missing instructions

	No of CYP n=1067	No of imputed Rxdays	No of prescriptions with known instructions	Mean MPR (SD)* Median MPR [IQR]*
No assumptions	1067	0	45779	0.66 (0.24) 0.70 [0.48-0.86]
+Assumption 1 (using closest prescription dates)	1067	8949	54728	0.79 (0.20) 0.86 [0.70-0.95]
+Assumption 2 (using median time length between prescriptions)	1067	13649	68377	0.74 (0.22) 0.81 [0.62-0.92]
+Assumption 3 (using median recorded prescription length)	1067	3592	71969	0.74 (0.21) 0.81 [0.64-0.90]
* Overlap of prescription dates was accounted for before the calculation of the MPR				

Figure 3-9 illustrates different types of overlapping dates of issued prescriptions

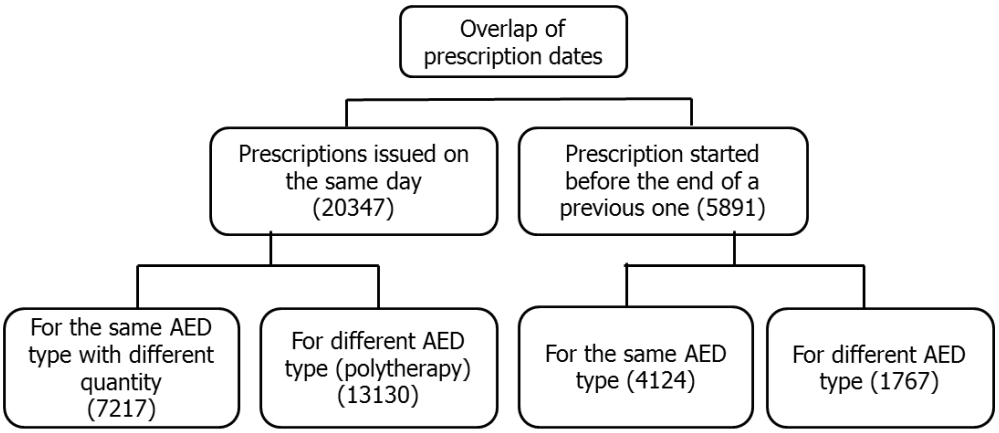


Figure 3-9: Different causes of overlapping of prescription dates

3.4.8 Distribution of the calculated overall MPR

The distribution of estimated MPR after data imputation but without accounting for overlapping of prescription dates is shown in Figure 3-10. The median calculated overall MPR was 1.06 (IQR= 0.83-1.53). There were 613 (57.4%) out of 1067 CYP had MPR > 1. The distribution of MPR suggested that more than one-half of CYP may have had oversupply of AEDs.

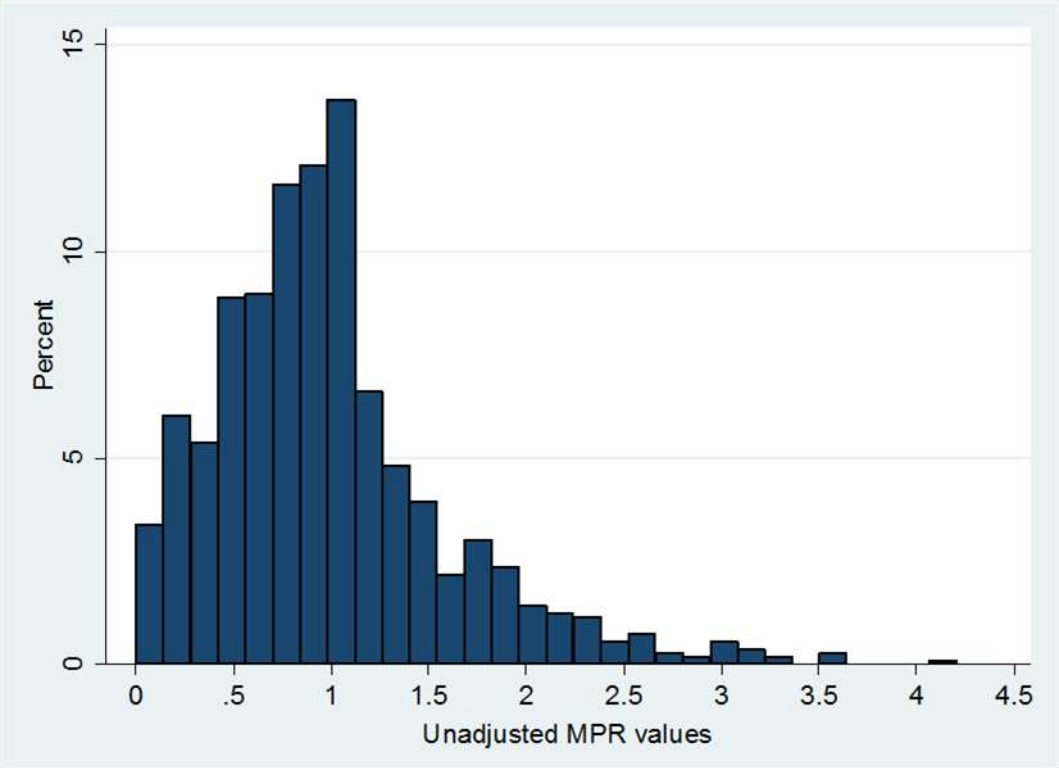


Figure 3-10: Overall calculated MPR without accounting for the overlapping prescription dates

The distribution of the calculated overall MPR after accounting for the overlapping prescriptions is shown in Figure 3-11. The distribution comprised a cohort of 1067 CYP who were issued a total of 71969 prescriptions. The overall MPR ranged from 0.05 to 1 (median=0.81, IQR=0.65-0.90). It can be observed that accounting for overlapping prescriptions markedly lowered the median overall MPR.

Calculated MPR values >1 were truncated to 1 (100%) adherence. Of the calculated MPR values, 555 (52%) CYP had MPR values ≥ 0.8 which means

that more than one-half of CYP had at least 80% AED coverage during the study period.

The calculated MPR after accounting for the overlapping prescriptions differed significantly from that before accounting for the overlapping prescriptions (Wilcoxon-rank sum (Mann-Whitney) test; $p<0.001$).

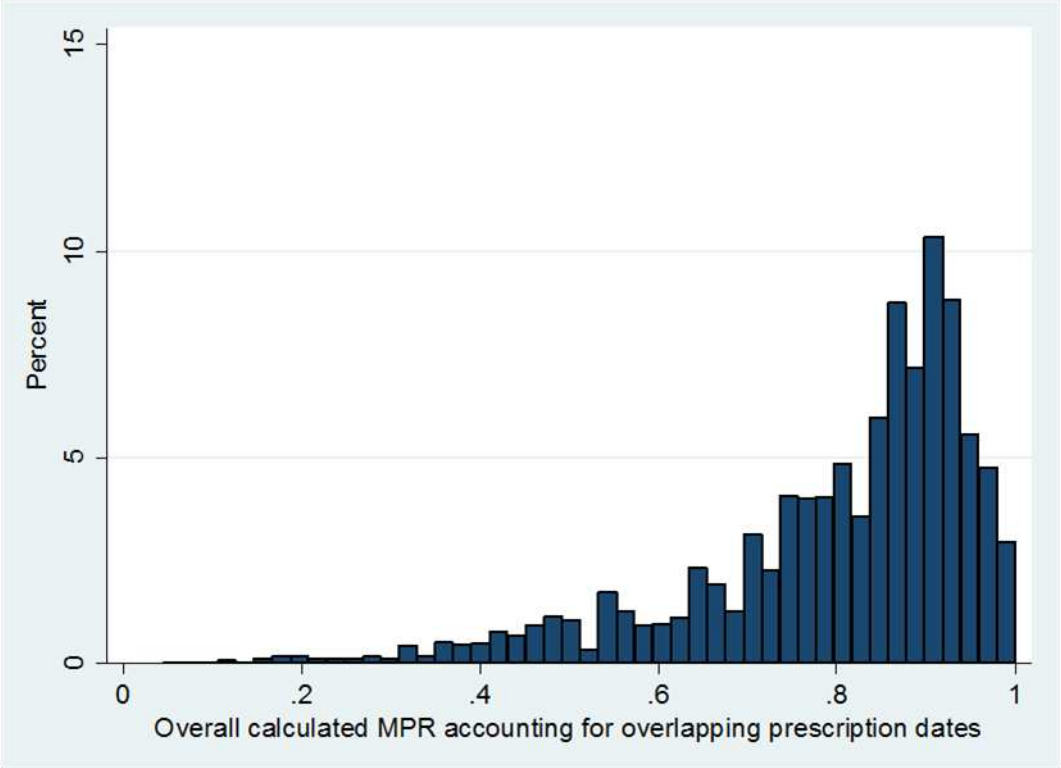


Figure 3-11: Distribution of calculated MPR after accounting for the overlapping prescription dates

Another method of dealing with overlapping days of AED prescriptions was carried out. When a prescription of the same AED was issued before the end of the last prescription (early refill), the total days' supply by the two prescriptions were summed based on the assumption that a child would not start taking AED doses of the second refill unless all doses of the first prescription finished. In such case, the overall MPR ranged from 0.06 to 1 (median=0.84, IQR=0.70-0.95) and 575 (54%) CYP had MPR values $\geqslant$ 0.8. This figure was considered similar to the above discussed one using the described methodology of dealing with prescription overlapping.

3.4.9 Description of overall MPR and bivariate analysis of factors influencing on adherence to AEDs

Adherence was measured as a function of measured MPR. Using median levels, the results of bivariate analysis are shown in Table 3-7 where adherence level was tested as a continuous outcome. Male children did not have a significantly higher adherence level compared to females (p=0.05). Adherence level was significantly increased with increasing age of CYP at the first diagnosis of epilepsy (p<0.001). It was higher among age groups of 7-12 years and more than 12 years old.

The data showed a non-significant difference in overall adherence level among CYP who lived with families of different family sizes (p=0.05).

There was a significant association between overall adherence levels and deprivation scores (P=0.03). CYP with higher deprivation scores showed lower adherence as compared to those of lower deprivation score.

More than one-half of CYP (55.3%) were on combined AEDs at time to control epilepsy and they showed significantly higher level of adherence (p<0.001). The distribution of the frequency of daily doses of AEDs showed that one-tenth of CYP (115; 10.7%) was on once daily regimen while the majority of CYP (893, 83.7%) were on twice daily regimen. Fewer number of CYP (59, 5.5%) were on thrice or more daily. Increased the frequency of daily doses to more than once daily did not significantly affect adherence level (p=0.87).

CYP who were treated for other co-morbid diseases such as asthma and mental health disorders did not differ from CYP with no co-morbidities with respect to overall adherence level (p=0.89 for asthma and p=0.07 for mental health disorder).

Table 3-7: Description of overall MPR, demographics and disease related factors

Character	Number of CYP n=1067	Median MPR (IQR)	Statistical test	p value
Sex			Wilcoxon rank sum (Mann-Whitney) test	0.05
Male	591	0.82 (0.68 -0.91)		
Female	476	0.79 (0.63 -0.90)		
Age at first diagnosis (Years)			Kruskal-Wallis test	<0.001
0-2	259	0.81 (0.64 -0.90)		
2-6	349	0.78 (0.59 -0.89)		
7-12	400	0.81 (0.69 -0.90)		
>12	59	0.88 (0.77 -0.93)		
Family size (members)			Kruskal-Wallis test	0.05
1-5	830	0.82 (0.67 -0.91)		
6-10	218	0.78 (0.60 -0.88)		
7-15	17	0.81 (0.72 -0.88)		
16-20	2	0.76 (0.62 -0.90)		
Townsend index			Kruskal-Wallis test	0.03
1 (least deprived)	200	0.84 (0.70 -0.91)		
2	156	0.83 (0.71- 0.91)		
3	208	0.80 (0.65 -0.91)		
4	224	0.79 (0.55- 0.89)		
5 (most deprived)	205	0.80 (0.66 -0.90)		
Missing	74	0.79 (0.64-0.88)		
Number of combined AED			Wilcoxon rank sum (Mann-Whitney) test	<0.001
No combination	467	0.77 (0.57 -0.88)		
Two or more drugs	591	0.84 (0.71 -0.91)		
Frequency of daily doses				0.87
Once daily	115	0.80 (0.62 -0.90)		
Twice or more daily	952	0.81 (0.65 -0.90)		
Asthma			Wilcoxon rank sum (Mann-Whitney) test	0.89
Yes	290	0.81 (0.65-0.90)		
No	777	0.81 (0.65-0.90)		
Mental disorders				0.07
Yes	145	0.78 (0.60-0.88)		
No	922	0.81 (0.66-0.90)		
Other co-morbidities				0.21
Yes	17	0.80 (0.70-0.91)		
No	1050	0.81 (0.65-0.90)		

3.4.10 Adherence to individual AEDs

The variation in adherence to different AEDs was examined on the group of CYP who were prescribed only one AED over the study period (Table 3-8). The CYP also had at least one year follow-up period and at least one known dosage instruction. The total number of CYP was 389 who were issued a total of 11854 prescriptions. The overall calculated MPR ranged from 0.07 to 1 (median=0.82; IQR 0.63-90).

The proportions of CYP who were prescribed monotherapy were higher for sodium valproate (60%) and carbamazepine (31%) than for other AEDs. A few number of CYP were on new AEDs (n=26; 6.7%) as monotherapy. The median MPR was higher for lamotrigine (0.87), carbamazepine (0.80) and sodium valproate (0.80). Adherence of CYP to new AEDs was higher but not significant as compared to old AEDs (P=0.65). The results showed that adherence to individual AEDs did not significantly vary among CYP (P=0.75).

Table 3-8: Variation of adherence to differnt AEDs among CYP on monotherapy

Character	Number of CYP n=389	Median MPR (IQR)	Statistical test	P value
Sex				
Male	215	0.80 (0.68 -0.90)	Wilcoxon rank sum (Mann-Whitney) test	0.20
Female	174	0.77 (0.59 -0.89)		
Age at first diagnosis (Years)				
0-2	38	0.81 (0.72 -0.90)	Kruskal-Wallis test	<0.001
2-6	115	0.75 (0.49 -0.88)		
7-12	195	0.79 (0.65 -0.90)		
>12	41	0.89 (0.73 -0.94)		
Type of AEDs*				
Sodium valproate	232	0.80 (0.66 -0.90)	Kruskal-Wallis test	0.75
Carbamazepine	121	0.80 (0.65 -0.90)		
Lamotrigine	22	0.87 (0.66 -0.93)		
Ethosuximide	6	0.63 (0.26 -0.90)		
Vigabatrin	4	0.70 (0.54- 0.79)		
AED class				
Old AEDs	363	0.80 (0.62- 0.90)	Wilcoxon rank sum (Mann-Whitney) test	0.65
New AEDs	26	0.86 (0.67-0.90)		

*Other individual AEDs were prescribed to less than 1% of CYP on monotherapy so they were not shown in this Table.

The results of bivariate analysis revealed that some potential factors, such as age of children and level of deprivation, significantly affected the measured adherence. All of these factors were tested simultaneously using multivariate regression.

3.4.11 Sensitivity analysis for the calculation of MPR before data imputation but accounting for overlapping prescription dates

The total number of CYP is 1067 who were issued 45,779 (63.5%) with clear dosage instructions out of a total number of 71,969 prescriptions. The number of prescriptions with clear dosage instructions was used to carry out the sensitivity analysis. The calculated MPR ranged from 0.01 and 1 (median=0.70; IQR=0.48, 0.86) and no CYP had MPR >1.

Table 3-9 shows that the median MPR values were often around 0.70 with different CYP's characteristics and regimen-related factors. The p values obtained from the bivariate analysis of the MPR and different CYP's demographics or regimen-related factors were similar to those obtained after imputation of missing data.

Table 3-9: Description of overall MPR before data imputation (overlapped prescriptions were accounted for); demographics and disease related factors

Character	No of CYP n=1067	Median MPR (IQR)	Statistical test	P value
Sex			Wilcoxon rank sum (Mann-Whitney) test	
Male	591	0.73 (0.49 -0.87)		0.07
Female	476	0.68 (0.46 -0.85)		
Age at first diagnosis (Years)			Kruskal-Wallis test	<0.001
0-2	259	0.67 (0.42 -0.85)		
2-6	349	0.68 (0.44 -0.86)		
7-12	400	0.72 (0.54 -0.87)		
>12	59	0.84 (0.62 -0.92)		
Family size (members)			Kruskal-Wallis test	0.77
1-5	830	0.70 (0.48 -0.87)		
6-10	218	0.69 (0.46 -0.84)		
7-15	17	0.76 (0.64 -0.83)		
16-20	2	0.67 (0.44 -0.90)		
Townsend index			Kruskal-Wallis test	0.05
1 (least deprived)	200	0.73 (0.52 -0.88)		
2	156	0.69 (0.52 -0.86)		
3	208	0.73 (0.54 -0.88)		
4	224	0.65 (0.44 -0.82)		
5 (most deprived)	205	0.74 (0.45- 0.86)		
Missing	74	0.68 (0.43- 0.84)		
Number of combined AED			Wilcoxon rank sum (Mann-Whitney) test	
No combination	467	0.70 (0.47 -0.86)		0.003
Two or more drugs	591	0.81 (0.59 -0.91)		
Frequency of daily doses			Wilcoxon rank sum (Mann-Whitney) test	
Once daily	115	0.73 (0.51 -0.90)		0.49
Twice or more daily	952	0.70 (0.46 -0.86)		
Co-morbidity				
Asthma			Wilcoxon rank sum (Mann-Whitney) test	
Yes	290	0.70 (0.52-0.86)		0.80
No	777	0.71 (0.47-0.86)		
Mental disorders				
Yes	145	0.67 (0.44-0.84)		0.07
No	922	0.71 (0.49-0.87)		
Other co-morbidities				
Yes	17	0.69 (0.56-0.86)		0.36
No	1050	0.70 (0.48-0.87)		

3.4.12 The MPR values without data imputation and without accounting for overlapping prescriptions

As above-mentioned the number of prescriptions which had clear dosage instructions was 45,779. These instructions were used to calculate MPR, however, without accounting for the overlapping dates of prescriptions. The range of calculated MPR is from 0.06 to 6.32 (median=1.09) with 603 (56.5%) CYP having MPR values >1. The calculated median MPR had higher values >1. The results suggested that the percentage of drug coverage was at least 100% for more than one-half of CYP. Similar to the main analysis of MPR, sex, family size and co-morbidity did not significantly affect the calculated MPR, whereas the calculated MPR significantly varied among age groups at diagnosis and by the number of concurrent AEDs. However, compared to the main analysis, the calculated MPR values did not significantly vary by different classes of socioeconomic status of CYP.

This sensitivity analysis showed that the majority of the examined factors showed similar bivariate associations with MPR, as those displayed between the factors assessed and corrected MPR in the principal analysis. This suggests that the assumptions used to correct the MPR did not change the relationship between the factors assessed and MPR.

Table 3-10: Description of overall MPR before data imputation without accounting for overlapped prescriptions; demographics and disease related factors

Character	Number of CYP n=1067	Median MPR (IQR)	Statistical test	P value
Sex			Wilcoxon rank sum (Mann-Whitney) test	0.15
Male	592	1.13 (0.83 -1.73)		
Female	475	1. 09 (0.80 -1.60)		
Age at first diagnosis (Years)			Kruskal-Wallis test	<0.001
0-2	259	1.31 (0.82 -2.03)		
2-6	349	1.04 (0.73 -1.66)		
7-12	400	1.06 (0.82 -1.09)		
>12	59	1.09 (0.98 -1.62)		
Family size (members)			Kruskal-Wallis test	0.54
1-5	830	1.11 (0.81 -1.71)		
6-10	218	1.04 (0.79 -1.47)		
7-15	17	1.19 (0.85 -1.45)		
16-20	2	1.56 (0.73 -2.38)		
Townsend index			Kruskal-Wallis test	0.73
1 (least deprived)	200	1.06 (0.82 -1.56)		
2	156	1.13 (0.87 -1.60)		
3	208	1.07 (0.76 -1.73)		
4	224	1.11 (0.71 -1.69)		
5 (most deprived)	205	1.12 (0.84 -1.64)		
Missing	74	1.01 (0.70 -1.47)		
Number of combined AED			Wilcoxon rank sum (Mann-Whitney) test	<0.001
No combination	467	1.07 (0.79 -1.60)		
Two or more drugs	591	1.97 (1.27 -2.50)		
Frequency of daily doses	115	1.25 (0.80 -1.77)		0.06
Once daily	952	1.07 (0.80 -1.64)		
Twice or more daily				
Asthma				
Yes	290	1.08 (0.77 -1.61)		0.42
No	777	1.09 (0.81 -1.69)	Wilcoxon rank sum (Mann-Whitney) test	
Mental disorders				
Yes	145	1.10 (0.81 -1.82)		0.81
No	922	1.09 (0.81 -1.69)		
Other co-morbidities				
Yes	17	1.28 (0.97 -1.95)		0.09
No	1050	1.08 (0.79 -1.66)		

3.4.13 MPR calculation before data imputation in CYP who were on monotherapy

The total number of CYP was 389 who had a total 8251 prescriptions with clear dosage instructions after overlapping prescriptions were removed. The statistical results showed that there was no significant difference of the MPR values by AED class or individual AED type which was similar to that examined after imputation of missing dosage instructions.

Table 3-11: Variation of adherence to different AEDs among CYP on monotherapy

Character	Number of CYP n=389	Median MPR (IQR)	Statistical test	P value
Sex			Wilcoxon rank	
Male	215	0.77 (0.51 -0.90)	sum	0.35
Female	174	0.71 (0.54 -0.86)	(Mann-Whitney) test	
Type of AEDs*				
Sodium valproate	232	0.74 (0.52 -0.89)	Kruskal-Wallis	0.84
Carbamazepine	121	0.72 (0.55 -0.87)	test	
Lamotrigine	22	0.85 (0.43 -0.90)		
Ethosuximide	6	0.63 (0.36 -0.87)		
Vigabatrin	4	0.70 (0.38- 0.79)		
AED class			Wilcoxon rank	
Old AEDs	363	0.74 (0.54- 0.88)	sum	0.60
New AEDs	26	0.85 (0.43 -0.90)	(Mann-Whitney) test	

*Other individual AEDs were prescribed to less than 1% of CYP on monotherapy so they were not shown in this Table.

3.4.14 Multivariate analysis of factors affecting adherence: GLM for overall adherence using aggregated data

The output of multivariate GLM regression shown in Table 3-12 is for factors that may affect the overall adherence using the aggregated data. The data showed that the overall MPR and hence adherence to AEDs did not significantly differ between male and female children (p=0.06). Older age children of 7-12 and >12 years showed significantly higher adherence levels (p=0.03 and p=0.01, respectively) controlling for other factors.

Adherence was negatively but insignificantly associated with families with larger family members. Compared to adherence levels of CYP who belonged to small family up to five members, CYP belonging to larger families showed lower adherence levels.

Adherence was negatively associated with higher deprivation quintiles. As compared with CYP with better socioeconomic status (quintile 1), CYP who had higher deprivation quintiles (score 4 and 5) were associated with significantly lower adherence levels (p=0.01 and p=0.04 respectively).

Complexity of AED regimens showed significantly higher adherence levels (p<0.01) in CYP who were prescribed two or more concurrent AEDs to control epilepsy. However, the frequency of daily dosage did not significantly affect adherence level (p= 0.49).

The existence of other co-morbid diseases such as asthma and mental behavioural disorders did not significantly affect adherence levels of CYP (p= 0.87 and 0.08, respectively)

Table 3-12: Potential factors affecting adherence: multivariate analysis using the aggregated data and GLM model

Explanatory variables (reference group)	Estimated coefficients [95% CI]	P values
Male sex	0.031 [-0.002, 0.064]	0.06
Age at first recoding of epilepsy (0-2 years)		
2-6	-0.041 [-0.088, 0.001]	0.42
7-12	0.049 [0.017, 0.082]	0.03
>12	0.119 [0.070, 0.169]	0.01
Family size (1-5 members)		
6-10	-0.037 [-0.078, 0.004]	0.07
11-15	-0.035 [-0.168, 0.098]	0.61
16-20	-0.019 [-0.399, 0.362]	0.92
Townsend index (quintile 1)		
2	0.014 [-0.043, 0.071]	0.63
3	-0.029 [-0.082, 0.025]	0.28
4	-0.073 [-0.126, -0.021]	0.01
5 (most deprived)	-0.057 [-0.107, -0.008]	0.04
Missing	-0.054 [-0.127, 0.018]	0.14
Number of combined AED (one drug)		
Two or more drugs	0.117 [0.082, 0.152]	<0.01
Frequency of daily doses (once daily)		
Twice or more	0.018 [-0.035, 0.072]	0.49
Comorbid diseases		
Asthma	-0.003 [-0.042, 0.035]	0.87
Mental disorders	-0.045 [-0.089, 0.005]	0.08
Other co-morbidities	0.072 [-0.060, 0.204]	0.28
Constant of regression	-0.289 [-0.361, -0.217]	<0.001

3.4.15 Results of post estimation diagnostic tests of GLM model

The results of post estimation statistics for GLM with family gamma distribution are shown in Table 3-13. The modified Park test showed that the gamma distribution family is accepted. The coefficient on the modified Park test was 1.75 is close to 2, that of gamma distribution. The Pearson residuals statistic indicates that the model was unbiased in predicting values of the outcome variable on raw scale. The p-value of Pregibon's link test is 0.78 and suggests that the link function is correct. The assumption of independence of error terms was not violated by GLM model as none of estimated coefficients of the residuals was significant; it means they are not correlated.

Table 3-13: GLM diagnostics on the refitted model

Fitted Model: Family Gamma; Link = Log		
Results of modified Park test (for Family) Coefficient=1.751		
Family	Chi2	P-value
Gaussian NLLS:	40.93	<0.001
Poisson:	8.63	<0.01
Gamma:	0.83	0.36
Inverse Gaussian or Wald:	20.83	<0.001
Pregibon's link test (goodness of link):		0.78
Pearson residuals test :		0.98
Independence of errors `autocorrelation':		1.00

The distribution of original MPR values was left skewed while that of reverse MPR was right skewed. Since the gamma has a probability density function (pdf) that can be either monotonically declining across the frequency axis or bell shaped, but skewed to the right [278], the GLM gamma family is assumed to fit better on reversed values of MPR. However, testing the significance of each coefficient of covariates revealed no difference predicting the values of outcome variable using GLM gamma link log on original and reverse values. The

hypothesised relationship between the mean and variance was specified with the Gamma distribution.

3.4.16 Longitudinal calculation of MPR

The results of biannual calculation of MPR for individual patients to track adherence levels over time starting from the individuals' index date are shown in Table 3-14. The MPR value of 0 was observed when CYP had intermittent periods of no therapeutic data (gaps) for 6-months or more and then reinitiated new episodes of AEDs prescriptions. These gaps in AEDs treatment may indicate medicines withdrawal due to remission of seizures (untreated intervals), non-adherence or registration gaps (i.e. in some cases, all medical files of CYP did have any recorded data during these gaps).

The table comprised two estimates of adherence levels over time. The first estimate showed the trend of the per-6-months calculated adherence of all registered CYP with epilepsy considering CYP with MPR=0 as non-adherent. This estimate shows that adherence levels started higher in the first two years after recording of epilepsy (up to biannual four) and then gradually decreased to rise again gradually at last few years of follow-up. The median values of MPR ranged from 0.77 to 0.33). The second estimate showed the median adherence levels of CYP after excluding CYP with MPR=0 (were considered untreated) at each interval of follow-up. The median values of MPR ranged from 0.80 to 0.93 which indicate little changes of the median MPR over time. There were a few numbers of CYP (14) who had therapeutic data up to 15 years.

Figure 3-12 is a graphical illustration of the trend of the calculated adherence over the follow-up time.

Because CYP had different follow-up durations and the number of CYP decreased each 6-month interval, changes in adherence levels would not be assessed over the whole period of follow-up for all CYP. A subgroup of CYP with reasonably long period of follow-up was chosen to assess their adherence levels over time. Figure 3-13 shows the values of MPR each 6-month interval for the 400 CYP who contributed to THIN for 14 biannual (7 years). The median MPR decreased over time and ranged from 0.65 (IQR=0.26-0.91) in the

first interval of follow-up to 0.31 (IQR=0.11-0.89) at the end of 7 years follow-up.

Table 3-14: Values of biannual calculation of MPR including the untreated CYP of each interval

Biannual after the index date	No of CYP[a]	Median MPR (IQR)	No of CYP[b]	Median MPR (IQR)	% of CYP with MPR≥0.8
1st biannual	1067	0.77 (0.33- 0.96)	956	0.80 (0.49- 0.97)	51
2nd biannual	1067	0.79 (0.41- 0.95)	889	0.85 (0.65- 0.97)	59
3rd biannual	1067	0.77 (0.45- 0.93)	914	0.84 (0.61- 0.95)	55
4th biannual	1026	0.77 (0.36-0.94)	854	0.84 (0.63- 0.97)	57
5th biannual	961	0.76 (0.27- 0.93)	777	0.84 (0.61- 0.96)	57
6th biannual	901	0.71 (0.11- 0.92)	679	0.83 (0.61- 0.95)	55
7th biannual	850	0.66 (0.0- 0.92)	627	0.82 (0.61- 0.96)	53
8th biannual	781	0.68 (0.0- 0.92)	555	0.84 (0.64- 0.97)	57
9th biannual	709	0.63 (0.0- 0.92)	494	0.83 (0.60- 0.97)	55
10th biannual	641	0.61(0.0- 0.91)	420	0.86 (0.62- 0.98)	57
11th biannual	588	0.58 (0.0- 0.90)	383	0.85 (0.61- 0.97)	56
12th biannual	518	0.58 (0.0- 0.91)	329	0.84 (0.61- 0.98)	57
13th biannual	447	0.49 (0.0- 0.90)	274	0.84 (0.61- 0.98)	57
14th biannual	400	0.31 (0.0- 0.90)	235	0.85 (0.51- 0.98)	58
15th biannual	370	0.33 (0.0- 0.91)	218	0.88 (0.59- 0.98)	59
16th biannual	336	0.47 (0.0- 0.91)	203	0.87 (0.63- 0.98)	61
17th biannual	300	0.49 (0.0- 0.90)	182	0.86 (0.61- 0.97)	58
18th biannual	267	0.35 (0.0- 0.89)	156	0.84 (0.54- 0.98)	58
19th biannual	227	0.40 (0.0- 0.87)	134	0.85 (0.56- 0.96)	60
20th biannual	198	0.43 (0.0- 0.89)	127	0.83 (0.46- 0.98)	52
21st biannual	164	0.50 (0.0- 0.87)	104	0.81 (0.59- 0.95)	52
22nd biannual	137	0.56 (0.0- 0.89)	87	0.82 (0.61- 0.95)	54
23rd biannual	112	0.54 (0.0- 0.91)	75	0.85 (0.54- 0.97)	55
24th biannual	88	0.62 (0.0- 0.93)	58	0.90 (0.63- 0.99)	66
25th biannual	74	0.50 (0.0- 0.88)	46	0.84 (0.57- 0.97)	61
26th biannual	63	0.64 (0.15- 0.99)	48	0.93 (0.47- 1.00)	63
27th biannual	45	0.73 (0.17- 0.93)	35	0.82 (0.52- 0.96)	51
28th biannual	33	0.61 (0.0- 0.80)	23	0.75 (0.51- 0.95)	35
29th biannual	22	0.73 (0.0- 0.92)	16	0.87 (0.62- 0.99)	63
30th biannual	16	0.87 (0.42- 0.99)	14	0.91 (0.56- 1.00)	71

a: number of CYP including untreated CYP each interval as non-adherent
b: number of CYP excluding untreated CYP each interval

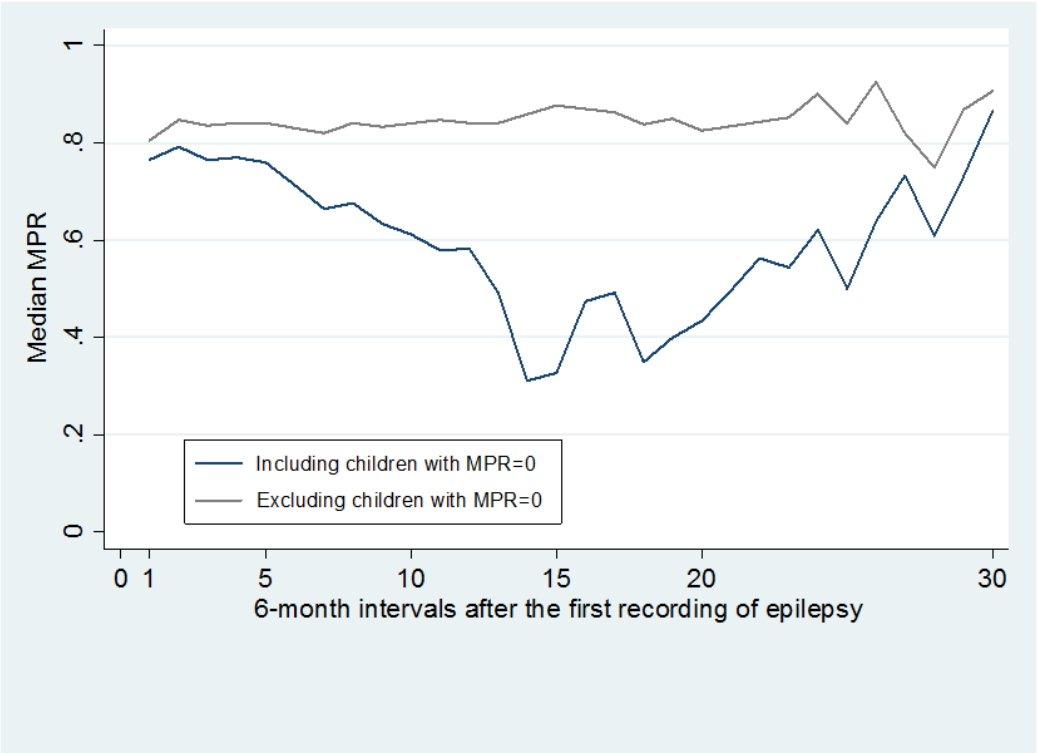


Figure 3-12: Median per-6months calculated MPR for individual CYP

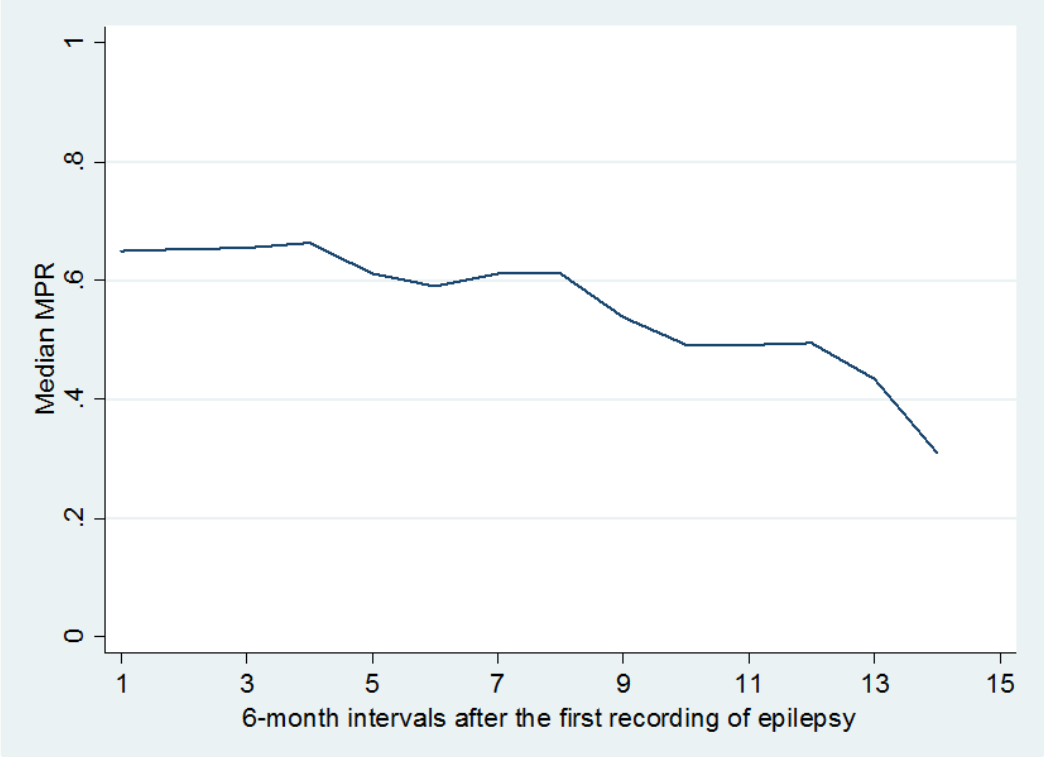


Figure 3-13: Median per 6-months calculated MPR for 400 CYP with 7 years of complete follow-up data

3.4.17 Multivariate analysis of factors affecting adherence over time (longitudinal data)

The results of multivariate analysis of factors affecting adherence levels over time based on average population response are shown in Table 3-15. In the GEE analysis, reporting the marginal effect (i.e., the population mean rate of change in adherence levels with respect to each the explanatory variables) is important than focusing on the coefficients of regressions from the GEE model [276].

The data showed that the predicted mean of the per-6-months calculated adherence levels for the study cohort was 60%. There was not a significant difference in the mean adherence between males and females. Adherence was positively associated with older age groups. Children of 2-6 and 7-12 years had 7% higher mean adherence levels than infants younger than 2 years and young people>12 years old had 8% higher mean adherence level than infants. It means that the mean per 6-months adherence levels of older children of 2-12 years were about 67% (0.60+0.068) and that of young people >12 years was about 68% (0.60+0.077)

Adherence levels were negatively but non-significantly associated with higher deprivation quintiles (low socioeconomic status). The size of effect of deprivation quintiles on the mean adherence levels was small (0.1-5%)

Adherence levels were negatively and significantly associated with the longer duration of antiepileptic drug treatment. CYP who had longer biannual intervals of follow-up time showed significantly lower mean adherence levels than those who had shorter follow-up time ($p<0.01$).

CYP who were prescribed at least two concurrent AEDs had 7% higher and significant adherence level ($p<0.001$) relatively to CYP who were on monotherapy.

Table 3-15: Marginal effects of explanatory variables on the biannual MPR; GEE model

Mean predicted longitudinal MPR=0.60

Explanatory variables (reference group)	Average-population rate of change [95% CI]	P values
Age at anniversary years (0-2 years)		
2-6	0.068 [0.003, 0.132]	0.04
7-12	0.069 [0.004, 0.135]	0.04
>12	0.077 [0.006, 0.149]	0.03
Male sex	0.024 [0.001, 0.054]	0.13
Family size (1-5 members)		
6-10	-0.026 [-0.063, 0.012]	0.18
11-15	0.007 [-0.047, 0.169]	0.66
16-20	0.082 [-0.091, 0.199]	0.46
Townsend index (score 1)		
2	-0.001 [-0.049, 0.048]	0.98
3	-0.021 [-0.069, 0.026]	0.38
4	-0.033 [-0.078, 0.012]	0.15
5 (most deprived)	-0.004 [-0.043, 0.039]	0.68
Missing	-0.054 [-0.119, 0.011]	0.11
Duration of follow-up	-0.005 [-0.007, -0.002]	<0.01
Number of combined AED (one drug)		
Two or more drugs	0.113 [0.080, 0.146]	<0.01
Frequency of daily doses (once daily)		
Twice or more	0.009 [-0.039, 0.058]	0.69
Comorbid diseases (yes/no)		
Asthma	0.004 [-0.022, 0.029]	0.78
Mental disorders	0.007 [-0.039, 0.042]	0.25
Other co-morbidities	0.055 [-0.090, 0.199]	0.46

3.4.18 Model diagnostics

Figure 3-14 shows the scatter plot of predicted residuals after the fitting of GEE model on longitudinal data against the follow up time. The residuals were a little left-skewed with mean, variance, skewness and kurtosis equal to -0.04, 0.15, -0.34 and 1.52, respectively. This scatter plot indicates that the current GEE model fitted the data satisfactorily.

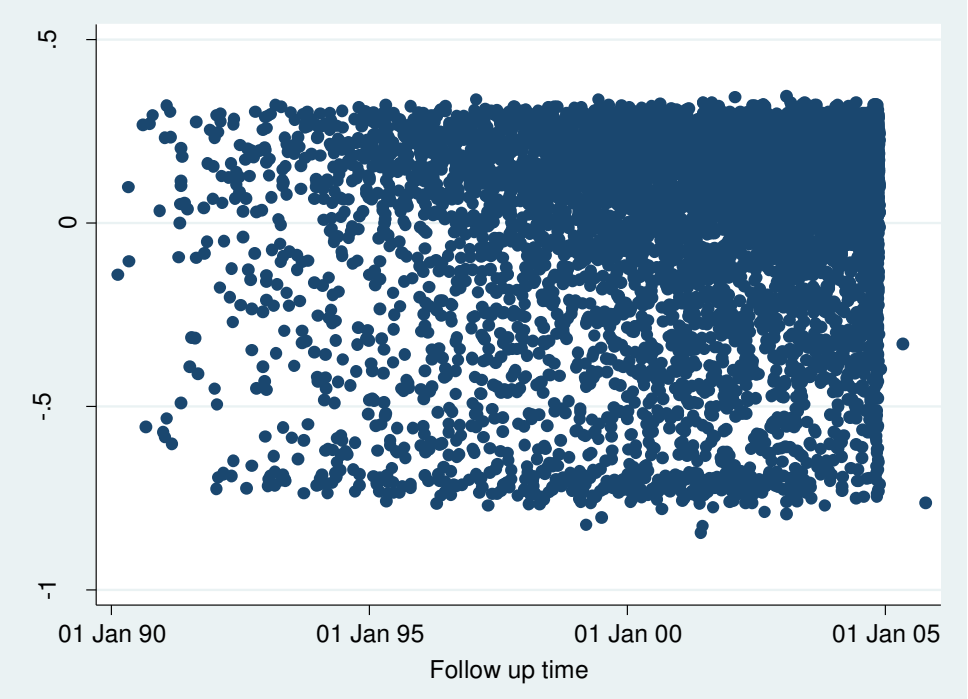


Figure 3-14: Scatter plot of residuals against the follow-up time after GEE fitting

3.5 Discussion

3.5.1 Prescribing pattern of AEDs

The analysis examined 2020 CYP diagnosed with epilepsy and prescribed at least one prescription for AED since their registration date at the general practice. During the study time, the results showed an increase in the overall number of prescriptions of AEDs between 1990 and 2003. This suggests that prescribing increased along with increasing number of prevalent cases of epilepsy each year in the study cohort as discussed earlier in Chapter 2.

More than one-half of CYP (51.6%) were only ever prescribed one AED type during the whole follow-up time and 58%-64% of treated CYP were prescribed monotherapy each year. This is in agreement with the literature which has shown that approximately 60-70% of CYP with epilepsy can be effectively controlled by a single AED [93, 94]. This is also in concordance with the late released NICE guidance recommendation that CYP should be treated with a single AED whenever possible [1].

Old AEDs such as carbamazepine and sodium valproate were most often tried as the first line of treatment. The overall number of prescriptions was higher for old AEDs during the study period. The findings showed that sodium valproate and carbamazepine were the most frequently prescribed old AEDs followed by lamotrigine and topiramate from the new AEDs. This finding was expected because carbamazepine and sodium valproate are considered the mainstay and first line pharmacological management of epilepsy in Europe and USA [288]. The higher prescribing frequency of carbamazepine and sodium valproate in this study is in line with the findings of an earlier study conducted in the Northern and Yorkshire region in England [117]. The authors examined the records of all registered patients from the Prescription Analysis and Cost (PACT) data across 16 health authority. The authors found an increase in prescribing of carbamazepine (up to 24%) and sodium valproate (up to 33%) between 1992 and 1995.

The proportions of CYP who were prescribed new AEDs increased by 13% between 1990 and 2003. However, the proportions of CYP who were prescribed old AEDs remained almost unchanged. This reflects that new AEDs were often tried as add-on therapy to control epilepsy and as monotherapy on few occasions as shown in the results. The straight rise in prescribing of new AEDs over time can be explained based on the approval time of these drugs in the UK market. At the beginning of this study period (1990), most of new AEDs were not launched in the market and even the approved drugs were still under head-to head trials with old AEDs. As more clinical trials were conducted, evidence of efficacy and/or tolerability of the new AEDs as add-on therapy or monotherapy became available.

The rise in prescribing of the new AEDs for this study cohort was consistent with the findings of an earlier study using primary care database [117]. The authors found that the number of prescriptions for AEDs increased by 15% between 1992 and 1995 in Northern and Yorkshire region, and that prescribing of the new AEDs, vigabatrin, lamotrigine and gabapentin, accounted for one-third of this rise. A study reported by the Office for National Statistics has found the number of AED prescription items in England increased by 33% and 42% part of this increase was attributed to increased prescribing of new AEDs between 1991 and 1999 [27]. The large paediatric study conducted using the UK GPRD reported a significant increase, up to fivefold, in the prescribing of new AEDs particularly lamotrigine, topiramate, and levetiracetam between 1993 and 2005 [118]. However, this study examined the utilisation of AEDs not only for epilepsy but for all other conditions such as mood disorders and pain.

Similar to this study, a more recent population-based study was conducted by Nicholas et al. (2012) on 63,586 patients with epilepsy of all ages identified from the UK GPRD data [289]. The authors reported that carbamazepine and sodium valproate were the most often used medications throughout 1993-2008 and lamotrigine prescribing was substantially increased between 1993 and 2008.

The rise in prescribing of new AEDs such as lamotrigine and topiramate may be due to the fact that both lamotrigine and topiramate are broad-spectrum new AEDs. The two drugs were licenced in the UK (1991 and 1995, respectively) as

monotherapy and adjunctive treatment in adults and children for different types of epilepsy including those which are classified as refractory (difficult-to-treat) [290-292]. Since this time, many randomised controlled studies have proven lamotrigine and/or topiramate to be effective treatment in childhood partial seizures [103, 293], absence seizures [294, 295] and generalized seizures associated with Lennox-Gastaut syndrome (one of refractory childhood-onset epilepsy syndromes) [69, 296].

This study showed an initial increase in the annual number of prescriptions and also number of children who were prescribed vigabatrin followed by a gradual decline after 1998. This finding was also reported by the two recent population-based studies using the UK GPRD data [118, 289]. Vigabatrin was launched in 1989 and has been proven effective as monotherapy in treatment of infantile spasms (West's syndrome) [79, 290]. It has been reported that long term-treatment with vigabatrin was associated with retinal toxicity (damage to the retina of the eye causing a visual-field constrictions) in children [297]. This side effect has been reported in 1 in 3 patients who received vigabatrin and was found to be irreversible [290, 297]. This adverse effect influenced its routine clinical prescribing and necessitates the assessment of risk to benefit ratio prior to use [69, 290]. This potential problem might also be the reason behind the refusal of the U.S. Food and Drug Administration to approve vigabatrin for epilepsy management in the United States until August 2009 [298]. This is likely to have been the reason which affected the prescribing trend of vigabatrin in this study.

The utilisation of AEDs in this study produced similar results to that of earlier European studies in Denmark and Italy [299, 300]. The study in Demark identified 15,604 patients of all ages including children from a local database between 1993 and 2002 [299]. The Italian study was a population-based study and used an Italian primary care database between 2000 and 2005 [300]. Both studies reported an increase in the prevalence of AEDs prescribing over time and that old AEDs were the most frequently prescribed particularly carbamazepine and sodium valproate. Moreover, the rise in AEDs prescribing was greater for new AEDs in epilepsy and other conditions such as mood disorders.

3.5.2 Adherence to AEDs and factors influencing on adherence level

The calculated median biannual adherence to AEDs in the study cohort was around 70% based on proportions of days supplied by medicines. By applying the 80% cut-off threshold for adherence, between 50% and 66% of CYP had at least 80% adherence per year. Previous paediatric studies have reported that adherence to AEDs ranges from 44% to 80% using different methods of measurement such as children/parents questionnaire and electronic monitoring devices [134, 135, 137, 141, 157]. There is a debate on the standard method of measuring adherence. However, the use of databases to measure adherence was found to be correlated with other direct and indirect methods [145, 146].

The calculated adherence to individual AEDs on CYP who were prescribed monotherapy revealed insignificant differences between individual drugs. It was not a surprising finding because 91% of CYP in this study were prescribed either carbamazepine or sodium valproate. These two drugs were recommended as the first-line and the mainstay for treatment of epilepsy. Adherence to these drugs was expected to be similar provided that CYP did not experience serious adverse effects.

Multivariate analysis using GLM with gamma distribution on the aggregated data revealed that CYP's demographics such as age and socioeconomic status and number of combined AEDs were likely to be potential factors affecting adherence levels. The long-term effects of these factors and other explanatory variables on adherence levels were examined using longitudinal regression analysis. The results showed that out of the demographic factors, adherence significantly varied only by age of CYP with older age groups were more adherent than infants up to 2 years. Sex, family size and deprivation levels had insignificant effects on the long-term calculated adherence. This finding was consistent with an earlier finding by Shope (1988) [177]. The author examined 15 demographic variables as correlates to adherence to AEDs in two paediatric populations with epilepsy (n=90, n=211) and concluded that demographic factors were of little significance in association with adherence [177]. Hazzard et al. assessed the AED blood levels of 35 CYP, aged 6-16 years, at three time

points over one year in the USA [134]. None of the demographic variables (age, sex, family income) were significantly related to adherence levels.

In this study, the higher adherence levels in older age groups of children, 7-12 years and older than 12 years, may reflect the fact that older children are able to self-manage their medicines whether supervised by their parents or school teachers, as compared to infants who are completely dependent on their caregivers to give them the medicines. Older children may also have taken their medicines based on self-perception of the impact of epilepsy on their daily lives and hence the necessity of medicines to control seizures. However it was not possible to qualitatively prove that. This may go against the current evidence for other chronic diseases that adherence declines as children take over their own care, and especially as they enter adolescence [181, 184]. However, this could be different in case of epilepsy where young people recognise that non-adherence to AEDs may result in an epileptic seizure which stigmatises them among their peers.

The deprivation levels (indicator of socioeconomic status) were not significantly associated with adherence. This may be attributed to the fact that all CYP up to 16 years old (age range of the study cohort) are entitled to free prescriptions in the UK health care system [301]. Thus inability to afford the cost of medicines may not be an issue with CYP in the UK and CYP belonging to either poor or rich families can have equal supply of medicines as they are recommended by clinicians. Socioeconomic status may represent an issue in other countries like the USA where patients have to pay for medicines or health insurance companies. Few studies have addressed the effect of socioeconomic status in CYP with epilepsy. No consensus conclusion could be drawn. Shope (1988) found that family income was not correlated to adherence, however, the level of social support was positively correlated ($P<0.05$) to adherence to AEDs [177]. In a another study, Mitchell et al. (2000) found that CYP from poorer families and those who reported stressful life events were more likely to adhere to prescribed regimens [135].

This study showed that adherence levels were negatively and significantly associated with duration of treatment. However, the size of effect was not high

(i.e. the estimated coefficient was small). This was a common feature in adherence to epilepsy and other chronic diseases such as asthma and diabetes[141, 203].

CYP who were prescribed two or more combined AEDs to control epilepsy had significantly higher levels of adherence than those who were on monotherapy. This may reflect how adherence was measured in this study. Adherence was calculated based on medication possession and hence the more prescribed medicines, the higher the ratio of days supplied with AEDs and thus the higher level of adherence. Another explanation is based on that the fact that epilepsy is most often treated by a single drug whenever seizures are controlled. Combined medicines may indicate severe or refractory epilepsy syndromes which may have motivated CYP to adhere to their medicines in order to achieve a state of controlled seizures. Seizure severity as disease-related factor was positively found correlated to adherence to AEDs in adults studies [121, 302]. The perceived severity of epilepsy by CYP and/or their parents could not be confirmed in this study

3.6 Strengths and limitations of this study

The present study provides a representative sample of CYP where generalisation of the results on the UK population could be achieved. Databases such as THIN offer a substantial advantage in providing information on patterns of medication prescribing in real-world practice that is not subjected to interventions or selection bias of other study designs. The prescribing information is linked to sex, age and deprivation levels of CYP which can describe the trends of AEDs use by CYP's demographics. This is the first population-based study in the UK that provided a longitudinal estimate of the adherence levels of individual CYP to AEDs up to 14 years of follow-up.

This study encountered some limitations. The study cohort comprised CYP who were born in or after 1988, so the prescribing pattern of AEDs did not include all CYP registered in THIN between 1990 and 2003. However, the study cohort was representative of all ages (i.e. infants, children and young people) as

indicated by the calculated prevalence of epilepsy which was comparable to the reported rates in epidemiological studies (Chapter 2).

The use of the number of prescriptions as a measure of prescribing volume of AEDs has some limitations such as it does not account for time periods in the average quantity prescribed per item. However, it can reflect the frequency and trends of prescribing of individual drugs and combined versus single prescribing of medicines.

The use of AEDs in treatment of different subtypes of epilepsy was not assessed because as a limitation of the data source, subtypes of epilepsy were not often reported in the primary care records. Therefore, it may be difficult to address the appropriateness of prescribing at the individual level. The focus of this analysis was therefore at the level of aggregated data for the population at risk.

The study cohort was most often prescribed liquid dosage forms with variable daily regimens according to age, AED type, and severity of illness. Because of the limitations of the general practice coding systems in THIN, about 37% of dosage instructions were missing which required careful imputation. However, assumptions on the length of prescriptions using the two thirds of known data were made and tested through sensitivity analysis.

The inherent limitation of measuring medication adherence using health database is that it is an indirect measure of adherence and does not guarantee the actual consumption of prescribed medications. However, medication possession is necessary for its consumption and adherence measured using databases has been validated against other direct and indirect methods (see Chapter 1).

This study was able to examine the effects of specific factors on adherence, whereas the effects of other factors such as parental education and ethnicity were not examined as these variables were not provided in this THIN version.

3.7 Conclusions

The results suggest that there was a higher frequency in prescribing of old AEDs over time particularly sodium valproate and carbamazepine that were dominantly prescribed as first-line treatment to the majority of study cohort. However, the rise of prescribing of new AEDs particularly for lamotrigine and topiramate during study period may suggest potential advantages in terms of higher effectiveness and/or tolerability.

The extent of paediatric adherence to AEDs as measured by the frequency of issued prescriptions was high in around one-half of CYP during the study period and tended to decrease over time.

The findings suggest that CYP's sociodemographics and coexisting morbidities were of little significance as correlates to long-term paediatric adherence to the prescribed AEDs. CYP who were on combined AEDs to control epilepsy had a higher level of adherence compared to those who were prescribed monotherapy.

Chapter 4: Estimation of epilepsy outcomes in CYP and assessing the relationship between adherence and outcomes

4.1 Introduction

4.1.1 Epilepsy outcomes in published literature

The short and long-term outcomes of treating epilepsy in CYP have been received much interest in the published literature in epilepsy [71, 74, 303]. Since childhood epilepsy has been demonstrated to influence a variety of life functions such as normal development and physical function, social functions and mental health [50, 51], the prognosis of epilepsy is commonly studied from various aspects. For example, some studies have concerned with cognitive outcomes, psychosocial outcomes and health related quality of life to address the long-term impact of epilepsy and its treatment on CYP [47, 50, 74, 304-306]. Other studies have focused on seizure control because optimal seizure control represents the principle goal of treating epilepsy and reduces the risk of other neuropsychological impairments [115, 307-309].

Since epilepsy is clinically defined as the recurrence of unprovoked seizures [3], the ability of a drug to prevent seizure recurrences or suppress seizure frequency is considered a direct outcome measure of drug efficacy in many RCTs [107, 310]. This kind of RCTs comprises, for examples, head-to-head trials of different AEDs and comparative studies of old versus new AEDs. With regards to seizures, the extent of seizure control in various childhood epilepsy syndromes can be categorised into three main groups. The first group is full remission of seizures without pharmacological intervention, e.g., in certain benign childhood epilepsy where seizures spontaneously resolve and drug treatment can be often avoided [16, 303]. The second group is remission of seizures on drug treatment where seizure control is achieved only by drugs and relapse of seizures often occur after drug withdrawal. The third group is drug-resistant seizures or refractory (intractable) epilepsy which

is characterised by poor prognosis. Drug-resistant seizures are usually defined as the failure to have a state of seizure remission within some period of follow-up [311].

The most common reported outcome measures of epilepsy and the methods of measurement are summarised in Table 4-1. A more detailed description of how these outcomes have been used to address the impact of epilepsy on various life functions was provided in Chapter 1.

By exploring THIN data, there were recorded data only for seizures; however, other outcomes such as psychosocial and HRQOL were not available for the study cohort. Thus this analysis focused on quantifying THIN-coded seizure outcomes as an indicator for the prognosis of epilepsy in the study cohort.

Table 4-1: Common outcome measures of epilepsy

Outcomes	Methods of measurement	comment
Seizure outcomes	Remission from seizures `duration of seizure freedom' (12 and 24 months)	This method represents the ultimate goal of treating epilepsy and assessing treatment efficacy in seizure control [312, 313].
	Suppression of seizure counts (frequency) from a baseline value over a defined period	It is a widely used outcome measure in clinical trials especially for refractory epilepsy syndromes [307, 314, 315].
	Proportion of patients maintaining 50-75% reduction in seizure frequency	In case of extreme variations of seizure counts between patients, percentage of subjects with 50-75% reduction in seizure frequency can be compared among groups [107].
AEDs	Time to discontinuation of allocated treatment due to side effects, poor seizure control or both [316].	This outcome can measure both the efficacy of treatment in controlling seizures and its tolerability as well
Cognitive outcomes	Interviewing CYP with epilepsy and their caregivers and then CYP are administered standard scale-measures and tests for intelligence score (IQ) and language skills [40, 317]	This outcome assesses the mental function of CYP diagnosed with epilepsy.
Psychosocial outcomes	Interviewing adults with childhood-onset epilepsy and/or prospectively observing CYP with epilepsy [47, 74, 304, 305].	This outcome assesses aspects such as educational and employment status, social maturation, eligibility for driving licence, marriage rates and mental health problems.
Health related quality of life (HRQOL)	Specific designed scales for CYP with epilepsy such as: - Epilepsy and Learning Disabilities Quality of Life Scale (ELDQOL) [306] -The HRQOL in CYP with Epilepsy measure [60] -Quality of Life for Adolescents with Epilepsy (QOLIE-AD-48) [318] -Quality of Life in Childhood Epilepsy Questionnaire (QOLCE) [319]	These scales address aspects of HRQOL such as seizure-related injuries, AED side effects, mood, physical functioning, cognitive functioning, social functioning, parental concern, communication, and overall health [58, 59]

4.2 Aim of the analysis

The aim of this analysis was to quantify THIN-coded outcomes of epilepsy for the study cohort and to examine the relationship between outcomes and adherence to antiepileptic drugs (AEDs)

4.3 Objectives

The objectives of this analysis were to:

1. Identify any recorded seizure outcomes in THIN database for the study cohort.
2. Calculate the incidence of medically-attended seizure events.
3. Examine the relationship between incidence of seizure events and sex, age as a time-varying variable, years since first diagnosis or treatment and number of AEDs prescribed to control epilepsy.
4. Examine the extent of seizure control in terms of remission of seizures for individual CYP based on incidence of medically-attended seizure events.
5. Determine the relationship between incidence of seizures and adherence to AEDs

4.4 Methods

4.4.1 Study cohort and study period

The incidence of seizure outcomes in THIN database were calculated for the subgroup of 1067 CYP with epilepsy defined in Chapter 3. This subgroup had to have at least one year of follow-up from the date of their first recoding of epilepsy diagnosis or treatment in THIN (index date). This subgroup of CYP also had at least one prescription with known dosage instruction and whose adherence to prescribed AEDs could be calculated using the method of MPR (Chapter 3).

The study period for exploring seizure outcomes started from the index date to the finish date for each child. The finish date was the date of death, the date where the child transferred out of the general practice, or the last date of data collection, whichever occurred first.

4.4.2 Definition of seizure outcomes in THIN data

The presented analyses to calculate the incidence of seizure outcomes were divided into two parts. The first part was to describe any recorded codes for seizure control by GPs during monitoring of epilepsy. For this part, seizure control was recorded by GPs on the basis of achieving seizure free periods (remission) or reporting the follow-up frequency (count) of seizures as described later in section 4.4.3.

Upon exploration of THIN database, codes for seizure control (Table 4-2) were not extensively recorded for all CYP in this sample, so the second part of this analysis was to calculate the incidence of medically-attended seizure events over time and use it as an indicator to describe the extent of seizure control. A medically-attended seizure was defined by either a Read code for seizure, convulsion and fit (Appendix 11) and/or a prescription for any of three drugs (diazepam, midazolam and paraldehyde). These three drugs are usually indicated for immediate control of prolonged seizures and life-threatening seizures (status epilepticus) and are prescribed as injection, rectal tubes or

buccal solutions [271]. These drugs were sometimes prescribed without a seizure code; however, their use suggested prolonged or cluster seizures (multiple repetitive seizures) [320].

4.4.3 Calculation of the incidence of THIN-coded seizure control

The medical file and the additional health data (AHD) file of THIN database were explored for any recorded episodes of seizure control by GPs. A number of codes which referred to extent of seizure control were identified (Table 4-2).

The main AHD code `1009200000' provided information on the extent of seizure control with an assigned description of `epilepsy check-fit details'. Further details on the frequency of seizures were provided by the subsequent `AHD value 1' code (Table 4-2). According to AHD value 1 codes, seizure control were recorded on the basis of achieving remission of seizures (e.g. Seizure free >12 months) or reporting the pattern of seizure occurrence for individual CYP from the date of epilepsy diagnosis. For example, CYP may have experienced seizure attacks in daily, weekly, monthly, quarterly, or yearly intervals.

Table 4-2: Recoded AHD codes of seizure outcomes in THIN database

AHD code	AHD value 1 code	Associated Read code	Code description (Seizure outcomes)
1009200000	FIT001/FIT006	6675.00	Fit frequency-Daily seizures
1009200000	FIT002/FIT007	6675.00	Fit frequency-Weekly seizures
1009200000	FIT003/FIT008	6675.00	Fit frequency-Monthly seizures
1009200000	FIT004/FIT009	6675.00	Fit frequency- Quarterly seizures
1009200000	FIT005	6675.00	Fit frequency- Yearly seizures
1009200000	FIT010/FIT011	667F.00	Seizure free >12 months
1009200000	--	667C.00	Epilepsy control good
1009200000	--	667D.00	Epilepsy control poor

The proportion of CYP who had any of THIN-coded seizure control was calculated and the total number of these codes was quantified for CYP.

4.4.4 Estimating the incidence of medically-attended seizure events

After medically-attended seizures were defined as described above, the interval between each two successive seizure events for each individual child was calculated. When the interval was less than 7 days, the two successive recorded seizures were considered one seizure event and only the first event was retained. This was done to account for overlapping dates of seizure codes and prescriptions of diazepam, midazolam and paraldehyde. On many occasions, a seizure event such as `grand mal status' was recorded in the medical file of CYP then a prescription for diazepam, midazolam or paraldehyde was prescribed in the same day or one or two days apart. In such cases, only the date of first seizure event was retained.

The incidence rates of medically-attended seizure events and 95% confidence intervals were calculated per person-years as the number of seizure events divided by the total follow-up time contributed by CYP. The method of survival analysis of multiple events `failures' was employed to calculate the incidence rate of seizure events and 95% confidence intervals. Survival analysis examines and models the time to the occurrence of an event [321]. In the multiple failure method, seizure events for each child were set as ordered events where the data were stratified by dates of occurrence of events.

The incidence of seizure events was stratified by a set of explanatory factors which were hypothesised to have effects on the frequency of seizures. These variables of interest are shown in Table 4-3.

Table 4-3: Factors associated with incidence of seizures

Explanatory variables (covariates)	Justification/ definition
Level of adherence to AEDs	The hypothesis was that high adherence levels to AEDs can lead to lower incidence of seizure events and better seizure control. The individuals' long-term measured adherence in 6-month intervals (biannual) from the Chapter 3 was divided into 5 levels; MPR=0-0.19, MPR=0.20-0.39, MPR=0.40-0.59, MPR=0.60-0.79, and MPR=0.80-1.00. A time variable which divided the duration of follow-up (started on the index date) of each child into 6-month intervals was generated. Then the biannual calculated adherence was compared to the seizure events using the generated time variable. It means that the incidence of seizures each 6-month was compared to the level of measured adherence during that 6-month interval.
Age and sex	Different types of childhood epilepsy syndromes have different age at onset. Some of these syndromes at infant age of onset are associated with poor prognosis and hence exhibit more frequent seizures. Sex was set as dummy variable; 0=female and 1=male. Age as time-varying variable which was categorised into four groups; < 2, 2-6, 7-12 and > 12 years old. This classification of age groups was used according to the BNF categorisation of age for indication as pointed in Chapter 3 [271].
Socioeconomic status	The database uses the Townsend deprivation index as a marker of socioeconomic status (as described in Chapter 2). Socioeconomic status of CYP was defined in quintiles of Townsend score where 1=least deprived and 5=most deprived.
Number of prescribed AEDs	Higher number of tried drugs to control epilepsy was assumed related to more frequent or sever seizures. Number of drugs ever prescribed to control epilepsy and by

	epilepsy subtypes was set as a dummy variable; 0=one drug and 1=two or more drugs.
Subtypes of epilepsy	Certain childhood epilepsy syndromes are associated more frequent seizure attacks. Different diagnostics subtypes of epilepsy were categorised into 5 groups; group 1 included unspecified epilepsy (no assigned epilepsy subtype), group 2 included focal epilepsy (all subtypes in which seizures are originated locally in brain), group 3 included generalised epilepsy (all subtypes in which seizures are originated from whole brain), group 4 included absence epilepsy (this subtype was withdrawn from generalised epilepsy into a separate class because of its absence seizure nature) and group 5 included refractory epilepsy (subtypes of epilepsy which are known in literature as difficult-to treat such as Lennox-Gastaut syndrome) [322, 323]. This categorisation of epilepsy subtypes was derived from the International League Against Epilepsy classification of epilepsy syndromes [324].

The incidence of seizure events was finally stratified according to years after the individuals' index dates.

The Mantel Haenszel method was used to examine the difference in incidence rate ratios of seizures between males and females, age groups, epilepsy subtypes and by unit increase in years of therapy.

For each group of CYP within all of the above-mentioned categorical covariates, estimates of the survival function (the probability of remission of seizures to time t) were illustrated using Kaplan-Meier curves. This was done to visually illustrate the difference in having seizure events between CYP of different groups. Kaplan-Meier estimate, also known as the product limit estimate, provides nonparametric estimates of overall survival function S(t) [321]. The Kaplan-Meier graph can plot multiple survival curves and enables visual comparison of the remission of seizures between various groups.

4.4.5 Multivariate modelling of factors affecting incidence of seizures using Cox proportional hazards regression

Cox proportional hazards regression model is the most widely used and feasibly computed method of survival analysis in medical research [321]. Survival modelling examines the relationship between survival time of group of subjects and one or more predictors, usually known as covariates in the survival analysis literature [325]. Cox models employ the hazard function or the log hazard and assume that covariates multiplicatively alter the baseline hazard (risk) function.

For this analysis, a Cox proportional hazards model was employed to examine whether the above-mentioned factors `covariates' had potential effects on the hazard of occurrence of seizures. The outcome measure was the occurrence of seizures. The recurrence of seizure events for each child cannot be assumed independent. So that the estimated hazard ratios of Cox model were adjusted to account for the possible within subject correlation of seizure events by allowing for clustering by child using the robust standard error option in STATA.

4.4.6 Tests of Cox proportional hazard assumptions

The key assumption of the Cox proportional hazards model is proportionality or a proportional hazards that is the covariates are multiplicatively related to the hazard [325]. The model allows for no assumption on the shape of the hazard over time that is it could be constant, decreasing or increasing. There are several methods to test whether the examined covariates satisfy the assumption of proportionality.

In this study, two methods were employed to test the assumption of proportionality. One method was a graphical plot and depended on the calculation of transformation of Kaplan-Meier curves. In this method, the examined covariate satisfies the proportional hazards assumption when the graphical plot of the ln [-ln(survival function)] versus ln of survival time results in a graph with parallel lines [321].

The second method is the log-rank test of equality across strata. It is a non-parametric test that compares estimates of the hazard functions of the groups of

a categorical covariate at each observed event time. The null hypothesis that there is no difference between groups in the probability of an event at any time point [326].

4.4.7 Exploring remission of seizures using the incidence of medically-attended seizure events

Remission of seizures (i.e., the duration of seizure-free period through which CYP did not experience any seizure events) is another way to describe seizure outcomes where the focus is to calculate the duration of seizure-free periods for individual CYP over time rather than reporting seizure events. Remission of seizures is considered the main interest in epilepsy literature to examine seizure outcomes [115, 308, 309].

Remission of seizures was calculated for intervals of 1, 2, 3, 4 or more years using the method of multiple failures survival analysis of medically-attended seizure events both from the index date and from each seizure event. This analysis is similar to calculating the interval between two starting points to calculate the seizure-free period. A Life-table estimate of the probability of remission of seizures out of the entire CYP at risk (i.e., cumulative probability) was computed.

The life table technique (also known as the actuarial method) is one of the oldest methods for analysing survival data [327, 328]. This table is considered as an `enhanced' frequency distribution table and makes use of the data from all subjects. In this method, the distribution of length of data contribution of each child (remission times) is divided into yearly intervals. For each interval, the number and proportion of CYP that remained without seizures and entered the respective interval, the number and proportion of CYP that failed in the respective interval (i.e., number of CYP that experienced seizures), and the number of CYP that were lost or censored (CYP lost to follow-up or seizures occurred outside the range of a measured interval) in the respective interval can be calculated. The probability of seizure remission was then calculated by dividing the number of CYP who did not experience seizures in that interval by the number at risk at the beginning of that interval. Therefore, life table provides

a good indication of the distribution of remission rates in population at risk over time [321].

The main difference between the life-table method and Kaplan-Meier approach is that with the life-table method, the cumulative probability of seizure remissions can be calculated at fixed times (depending on the interval), whereas with the Kaplan–Meier approach it is calculated only when seizures occur (at the exact time of seizures) [329].

4.5 Results

4.5.1 Study population

Of the 1067 CYP with epilepsy, more than one-half were males, 591(55.4%) and the age at first recording of epilepsy ranged from one day to 15.2 years (mean age was 3.9 years). The sex and age distribution of this subgroup of CYP were similar to that of the overall population of 2020 CYP with epilepsy. The total contribution of person-years was 6467.1 years and ranged from 1.0 to 16.8 years per child (mean=6 years).

4.5.2 Frequency of THIN-coded seizure control for the study cohort

Of the 1067 CYP, 276 (26%) had recorded data on extent of seizure control during the follow-up time which are shown in Table 4-4. The majority of these codes (85%) were recorded at least one year after the index date. The degree of seizure control showed that 6% had daily seizures, 5% had weekly seizures, 3.6 % had monthly seizures and 4.5% had quarterly seizures. Nine percent of CYP achieved at least one year free of seizures. However, the majority of CYP, 792 (74%) were not assigned any codes for seizure control in this sample.

Out of the 380 events of THIN-coded seizures, 39 (10%) were recorded before 2002 and 341 (90%) were recorded from 2002 onwards. This may suggest better quality of recording clinical outcomes since data collection started prospectively in THIN in 2002.

Table 4-4: Recorded seizure control within THIN database for the study cohort

Seizure outcomes	Number of CYP (%) n=1067	Frequency of recorded seizure-control (%) n=380
Fit frequency-Daily seizures	63(6)	83 (22%)
Fit frequency-Weekly seizures	50 (5)	57 (15%)
Fit frequency-Monthly seizures	38 (3.6)	42 (11%)
Fit frequency- Quarterly seizures	47 (4.5)	55 (14%)
Fit frequency- Yearly seizures	21 (2)	22 (6%)
Seizure free >12 months	93 (9)	112 (30%)
Epilepsy control good	6 (0.4)	6 (2%)
Epilepsy control poor	3 (0.3)	3 (0.8%)
No assigned codes	791(74)	0

4.5.3 Overall incidence of medically-attended seizure events for the study cohort

During the study period, there were 2440 recorded seizure codes and 3027 prescriptions for prolonged and life-threatening seizures giving a total of 5467 codes. After accounting for codes of seizures occurred within less than 7 days, the total seizure events were 4704 for 1067 CYP over 6467 person-years (Figure 4-1).

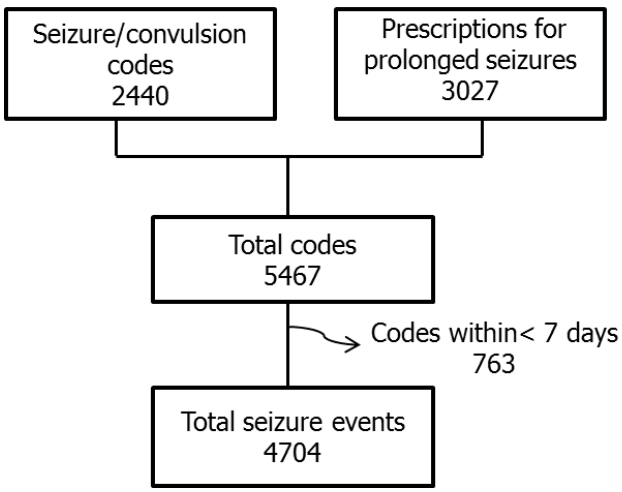


Figure 4-1: Identification of medically-attended seizure events

The overall distribution of medically-attended seizure events for CYP is illustrated in Figure 4-2. Over 6467person-years, the number of seizure events for individual CYP ranged from 0 to 97 (median=2; IQR; 3-25). Out of 1067 CYP, 307 (29%) did not have any records for seizure events, 183 (17%) had only one seizure event, 458 (43%) had 2-10 seizure events and 119 (11%) had more than 10 seizures.

When compared to THIN-recorded codes of seizure control, the distribution of medically-attended seizure events did not reflect the extent of the recorded seizure control. For example, CYP who had codes of poor seizure control (such as daily or weekly seizures) did not necessarily have high frequency of medically-attended seizures.

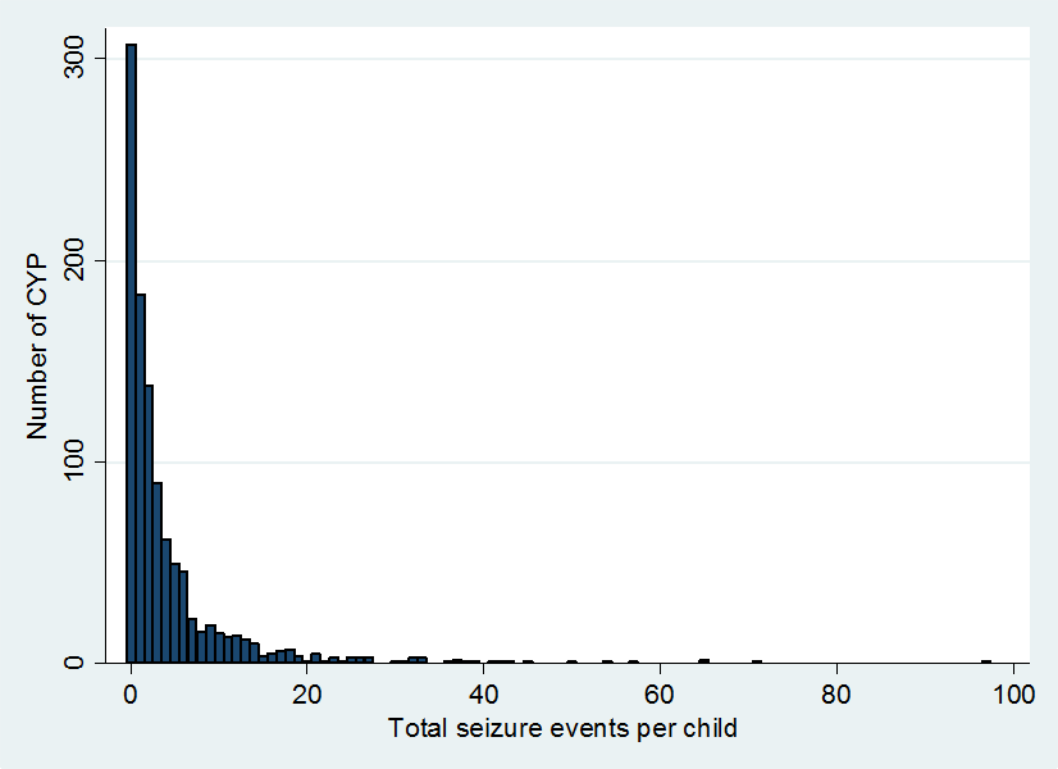


Figure 4-2: The distribution of medically-attended seizure events over the whole follow-up years

The overall incidence rate of medically-attended seizures was 0.73 [95% CI 0.71-0.75] per person-year (Table 4-5). Incidence of seizure events was not significantly different between males and females (Mantel Haenszel test; p=0.68). Incidence of seizure events stratified by age as time-varying variable was higher, 1.64 [95% CI 1.64-2.01], in the age group under 2 years compared to older age groups. The incidence rate of seizure per person-year was significantly lower by each category increase of CYP age group [Mantel Haenszel test; p<0.001].

Incidence of seizures was lower in highest deprived CYP (Townsend quintile=5) as compared to least deprived CYP (Townsend quintile=1).

Incidence of seizures was lower in CYP who were diagnosed with absence epilepsy subtype, 0.35 [95% CI; 0.32-0.40] per person-year, compared to other subtypes where incidence was higher in generalised subtype, 0.94 [95% CI 0.87-1.02], and refractory epilepsy, 1.03 [95% CI 0.93-1.15] per person-year.

Incidence of seizure events was significantly higher, 0.97 (95% CI 0.94-1.00), in CYP who prescribed more than one drug type to control epilepsy [Mantel Haenszel test; p<0.001]. The incidence rate of seizures was significantly higher in CYP who had higher calculated MPR values (higher drug adherence levels) as compared to CYP with lower MPR values [Mantel Haenszel test; p<0.001].

Table 4-5: Incidence of medically-attended seizure events for the study cohort (N=1067)

Character	No of CYP with epilepsy	Seizure counts	Person-years	Incidence per person-years [95% CI]
Total	1067	4704	6467.1	0.73 [0.71-0.75]
Sex				
Male	591	2527	3510.8	0.72 [0.70-0.75]
Female	476	2177	2956.3	0.74 [0.71-0.77]
Age (time-variant)*				
0-2	218	449	274.5	1.64 [1.49-1.79]
2-6	566	1596	1600.1	1.00 [0.95-1.05]
7-12	903	1894	3329.9	0.57 [0.54-0.60]
>12	59	765	1261.7	0.61 [0.57-0.65]
Townsend quintiles				
1	200	785	1122.3	0.70 [0.65-0.75]
2	156	718	938.8	0.76 [0.71-0.82]
3	208	933	1284.9	0.73 [0.68-0.77]
4	224	1284	1456.8	0.88 [0.83-0.93]
5	205	722	1231.2	0.60 [0.55-0.63]
Missing	74	262	433.0	0.61 [0.54-0.68]
MPR (adherence levels)				
0	506	168	354.1	0.47 [0.41-0.55]
>0-0.19	284	205	498.0	0.41 [0.36-0.47]
0.20-0.39	336	242	890.0	0.27 [0.24-0.31]
0.40-0.59	502	395	806.6	0.50 [0.45-0.55]
0.60-0.79	812	858	1070.5	0.80 [0.75-0.86]
0.80-1.00	1046	2836	2848.0	0.99 [0.95-1.03]
No of prescribed AEDs				
One drug	476	454	2064.9	0.22 [0.20-0.24]
Two or more drugs	591	4250	4402.2	0.97 [0.94-1.00]
Subtypes of epilepsy				
Unspecified	711	3158	4177.8	0.76 [0.74-0.78]
Absence	137	310	881.0	0.35 [0.32-0.40]
Focal	70	266	407.1	0.65 [0.58-0.74]
Generalised	109	642	682.9	0.94 [0.87-1.02]
Refractory	40	328	318.2	1.03 [0.93-1.15]
Years after first recording of epilepsy				
1	1067*	971	1067.0	0.91 [0.85-0.97]
2	1067	716	1023.7	0.70 [0.65-0.75]
3	961	614	903.7	0.68 [0.63-0.74]
4	850	572	780.0	0.73 [0.68-0.80]
5	709	451	644.8	0.70 [0.63-0.77]
6	588	350	516.9	0.68 [0.59-0.74]
7	447	239	404.8	0.60 [0.56-0.72]
8	370	224	335.9	0.67 [0.60-0.80]
9	300	161	262.7	0.61 [0.58-0.81]
10	227	116	194.3	0.60 [0.54-0.80]
11	164	104	136.0	0.76 [0.63-0.97]
12	112	71	89.3	0.80 [0.54-0.95]
13	74	47	60.7	0.77 [0.58-1.03]
14	45	49	32.3	1.52 [1.14-2.08]
15	22	18	13.0	1.38 [0.87-2.22]

* The number of CYP in age groups and each year does not add to the total as over time a child may have contributed to more than one age group and more than one year of follow-up.

4.5.4 The incidence of medically-attended seizure events stratified by years after the first recording of epilepsy

The incidence of recorded seizure events stratified by years after first recording of epilepsy-related diagnosis or prescription is shown in Table 4-5. The incidence per person-year was 0.91 [95% CI 0.84-0.96] for the first year and then showed a lower value in the second year 0.70 [95% CI 0.65-0.75]. The incidence of seizures slightly changed over time. Figure 4-3 illustrates the incidence of seizure per person-years over time. The data for years 13 to 15 are not illustrated due to few numbers of CYP followed-up and lower values of person-years. The incidence rate was not significantly changed by unit increase in years of follow-up [Mantel Haenszel test; p=0.11].

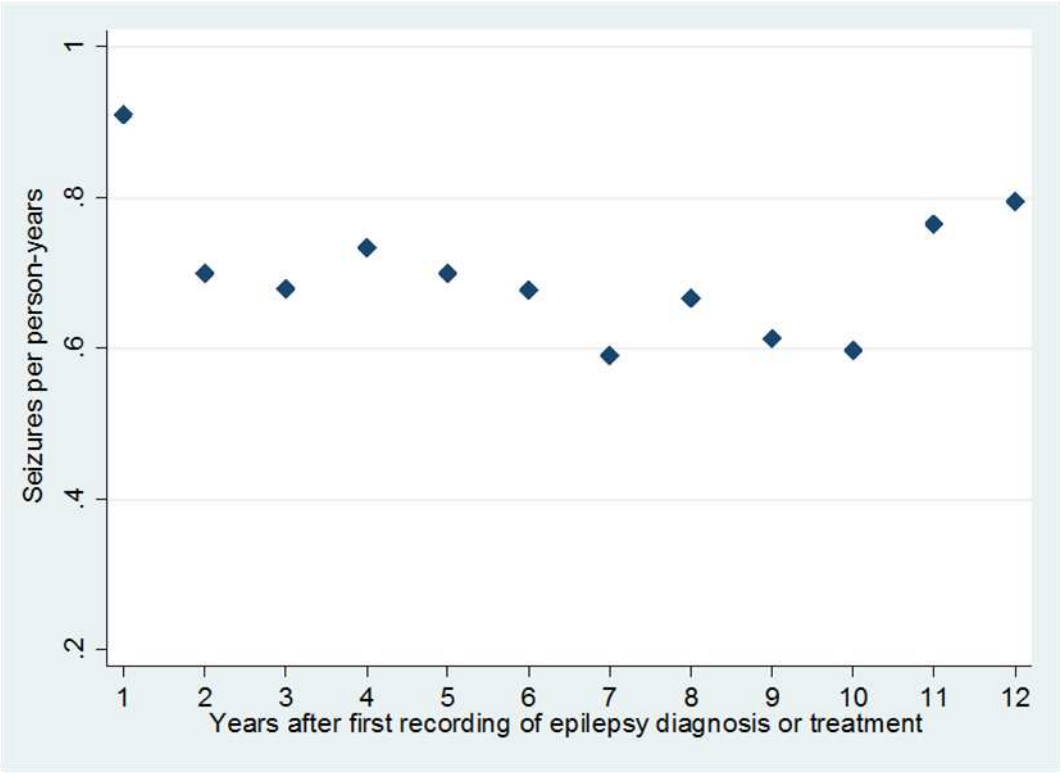


Figure 4-3: Incidence of medically-attended seizure events per person-years

4.5.5 Kaplan-Meier estimates of the probability of seizure remission

The Kaplan-Meier graphs (Figure 4-4) showed almost overlapping curves of males and females which may indicate that no significant difference in the hazard of seizures between males and females. However, Kaplan-Meier estimates for different age groups showed parallel curves with younger age CYP, <2 years, had a lower hazard of seizure incidence (higher remission of seizures). Similar results to that of age groups were found in Kaplan-Meier estimates across the calculated MPR quintiles (biannual adherence). Higher MPR quintiles were associated with higher remission of seizures.

CYP who were prescribed at least two drugs to control epilepsy were associated with lower remission of seizures than CYP who were prescribed only one drug.

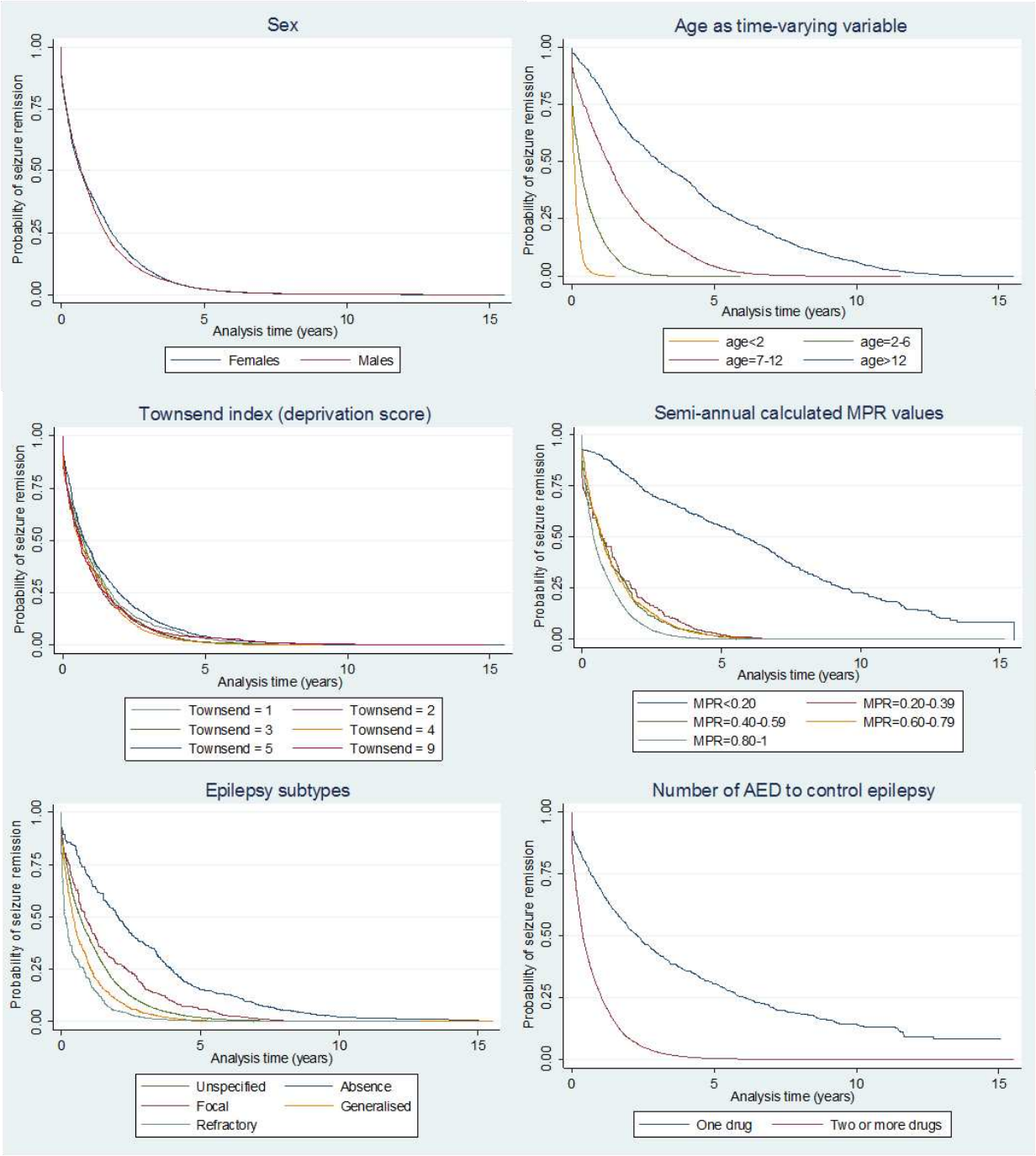


Figure 4-4: Kaplan-Meier curves of remission of seizures

4.5.6 Factors affecting incidence of seizures using Cox regression

The values of the unadjusted hazard ratios from the univariate Cox proportional hazards regression for the effect of explanatory variables on incidence of seizure events are shown in Table 4-6.

The data showed that the hazard of seizures was significantly lower with older age groups >2 years. The hazard of seizures was significantly higher in CYP who were prescribed more than one drug to control epilepsy and by higher levels of adherence (MPR>0.59). However, the hazard of having seizures did not significantly differ between males and females, different quintiles of deprivations or different epilepsy subtypes.

The hazard ratios of the fully-adjusted Cox model are shown in Table 4-6. The data showed that the hazard of seizure events was associated with higher levels of biannual measured adherence. Compared to MPR=0-0.19, the hazard of seizures, adjusted to other covariates, was higher but insignificant for MPR=0.20-0.39 (HR=1.04, 95% CI 0.78, 1.11) and MPR=0.40-0.59 (HR=1.19, 95% CI 0.90, 1.56); significant for MPR=0.60-0.79 (HR=1.54, 95% CI 1.16, 2.04) and for MPR ≥0.8 (HR=1.83, 95% CI 1.40, 2.38).

The hazard of seizures was not significantly different (p=0.40) between males and females (HR=0.92, 95% CI 0.76, 1.12). Older age CYP had a significantly lower hazard and hence a longer survival without seizures than younger CYP. As compared to the reference age group <2 years, the hazard of seizures decreased for age group 2-6 years (HR=0.35, 95% CI 0.27, 0.43); for 7-12 years (HR=0.13, 95% CI 0.09, 0.17) and for CYP >12 years old (HR=0.04, 95% CI=0.03, 0.06). The p-values were highly significant in all age groups ($p<0.001$).

Compared to CYP who were only ever prescribed one AED type, the hazard of seizures increased more than twofold for CYP who were prescribed at least two AEDs to control epilepsy (HR=2.18, 95% CI 1.78, 2.66).

Epilepsy subtypes had little and insignificant effect on the hazard of seizures than other factors. Compared to the unspecified epilepsy subtype, the hazard of

seizures was lower by 37% for absence seizures subtype (p=0.01); lower by 8% for focal subtype (p=0.67); higher by 5% for generalised (p=0.69) and unchanged for refractory subtypes of epilepsy (p=0.88).

Table 4-6: Factors affecting incidence of seizures: unadjusted and adjusted hazard ratios from Cox regression

Potential factor affecting incidence of seizures	Hazard ratio [95% CI] Unadjusted model	p values	Hazard ratio [95% CI] Adjusted for age, sex, Townsend index	p values	Hazard ratio [95% CI] Fully adjusted model	p values
Adherence levels						
0-0.19	1.00		1.00		1.00	
0.20-0.39	1.08 [0.80, 1.36]	0.53	1.11 [0.93, 1.42]	0.10	1.04 [0.78, 1.11]	0.15
0.40-0.59	1.17 [0.84, 1.64]	0.38	1.23 [0.95, 1.62]	0.16	1.19 [0.90, 1.56]	0.22
0.60-0.79	1.89 [1.34, 2.68]	<0.01	1.62 [1.21, 2.16]	<0.01	1.54 [1.16, 2.04]	<0.01
0.80-1.00	2.37 [1.71, 3.27]	<0.01	1.92 [1.47, 2.50]	<0.01	1.83 [1.40, 2.38]	<0.01
Sex						
Female	1.00		1.00		1.00	
Male	0.98 [0.78, 1.21]	0.84	0.94 [0.77, 1.13]	0.50	0.92 [0.76, 1.12]	0.40
Age at follow-up years						
<2	1.00		1.00		1.00	
2-6	0.34 [0.28, 0.42]	<0.001	0.33 [0.26, 0.41]	<0.001	0.35 [0.27, 0.43]	<0.001
6-12	0.10 [0.07, 0.12]	<0.001	0.10 [0.07, 0.13]	<0.001	0.13 [0.09, 0.17]	<0.001
>12	0.03 [0.02, 0.04]	<0.001	0.03 [0.02, 0.04]	<0.001	0.04 [0.03, 0.06]	<0.001
Townsend index						
1	1.00		1.00		1.00	
2	1.09 [0.75, 1.56]	0.64	0.96 [0.68, 1.36]	0.82	0.94 [0.66, 1.33]	0.73
3	1.04 [0.75, 1.45]	0.81	0.94 [0.70, 1.27]	0.71	0.93 [0.70, 1.25]	0.64
4	1.26 [0.91, 1.76]	0.17	1.15 [0.85, 1.56]	0.35	1.13 [0.84, 1.53]	0.35
5	0.84 [0.61, 1.15]	0.28	0.77 [0.57, 1.05]	0.10	0.73 [0.53, 0.99]	0.04
Missing	0.86 [0.52, 1.41]	0.55	0.81 [0.50, 1.30]	0.38	0.87 [0.50, 1.30]	0.57
Number of prescribed AED						
One drug	1.00		--	--	1.00	
Two or more drugs	4.46 [3.72, 5. 35]	<0.001	--	--	2.18 [1.78, 2. 66]	<0.001
Subtype of epilepsy						
Unspecified	1.00		--		1.00	
Absence	0.45 [0.32, 0.65]	0.01	--	--	0.63 [0.47, 0.83]	0.01
Focal	0.86 [0.50, 1.47]	0.58	--	--	0.92 [0.54, 1.49]	0.67
Generalised	1.25 [0.94, 1.66]	0.12	--	--	1.05 [0.84, 1.31]	0.69
Refractory	1.37 [0.99, 1.90]	0.05	--	--	1.01 [0.89, 1.14]	0.88

4.5.7 Test of proportionality assumption

Using the log-rank test, sex showed a non-significant proportional hazard (p=0.62) which means that incidence rate of seizures did not differ between males and females (Table 4-7). The log-rank test across age groups showed significant proportional hazards (p<0.001). Similar to that of age was the log-rank test across adherence quintiles, number of AEDs to control epilepsy and epilepsy subtypes.

Table 4-7: log-rank test for proportional hazard assumption

Covariate	P-values of log rank test
Sex	0.62
Age at follow-up years	<0.001
Townsend index	<0.001
Adherence (MPR quintiles)	<0.001
Number of AEDs to control epilepsy	<0.001
Epilepsy subtypes	<0.001

The graphical plot of ln [-ln(survival)] versus ln of survival time confirmed the results of the log-rank test. Figure 4-5 illustrates almost overlapping curves for sex and parallel curves for the rest of the examined covariates.

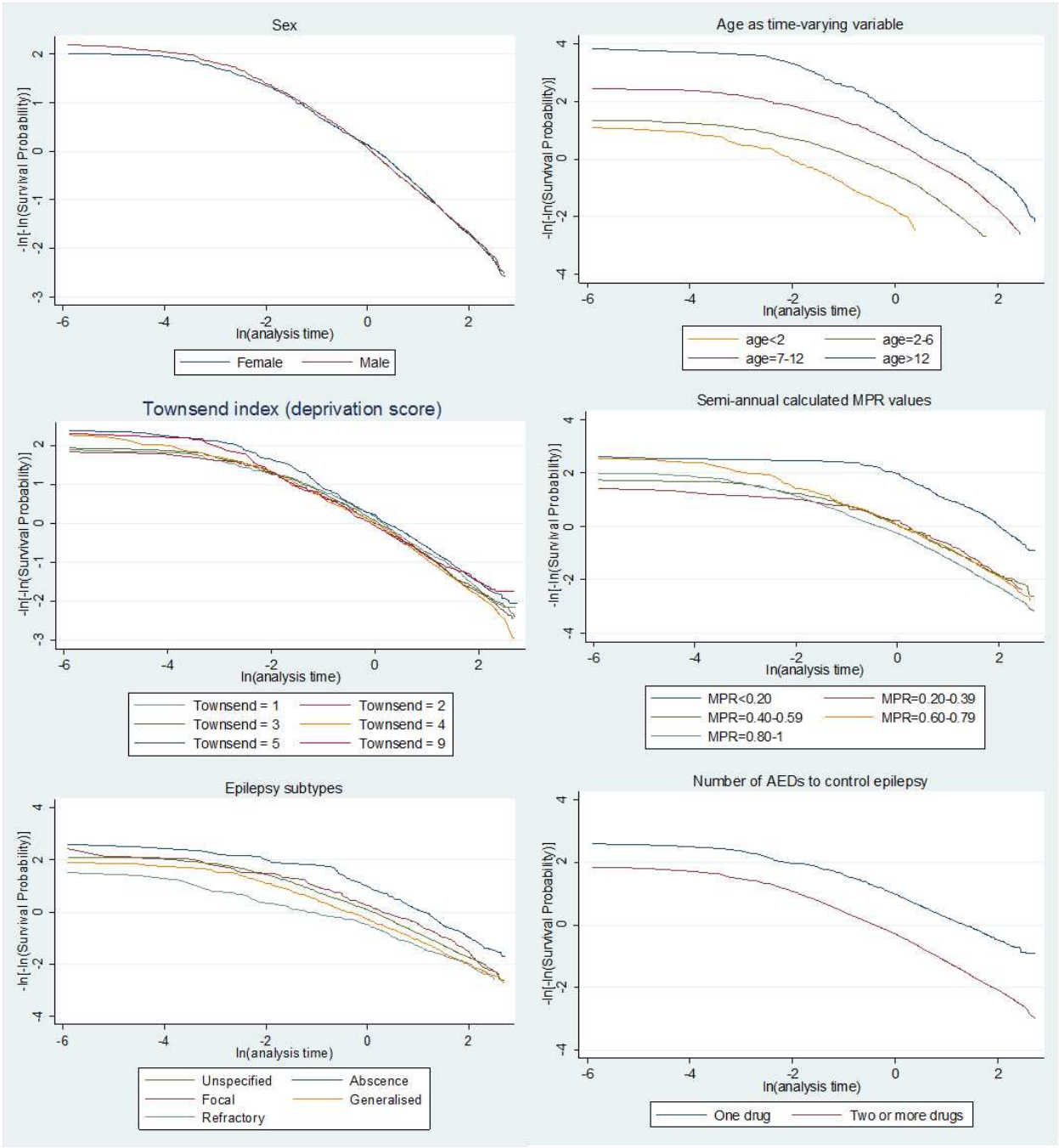


Figure 4-5: Test of proportional hazard assumption for covariates

4.5.8 Duration of seizure remission

The probability of seizure remissions out of the total number of CYP at risk, with 95% CI using life table estimates is shown in Table 4-8. The table describes the remission rates of the study cohort over time. Remission rates were reported at the end of the interval. For example, of the 1067 CYP at the beginning of the analysis, 976 CYP achieved at least 1 year remission of seizures by the end of the follow-up time. A year after the index date, the proportion of CYP with seizure remission was 94% [95% CI= 93%, 96%], whereas 59 CYP failed to achieve 1 year remission and 18 CYP were censored.

The proportions of CYP who achieved 2-year and 3-year remissions by 15 years follow-up period were 80% [95% CI 78%, 83%] and 68% [95% CI 65%, 71%]. The proportion of CYP who entered long-term remission, for example, 5-year and 10-year remissions out of the entire study cohort were 47% [95% CI 43%, 50%] and 27% [95% CI 22%, 31%], respectively. Figure 4-6 illustrates the proportions of CYP with remission of seizures over time.

Table 4-8: Life table estimates of cumulative probability of seizure remission over time

Interval of remission (years)	Total CYP at risk	Number of CYP with seizures	Number censored	Probability of remission	95% Confidence interval
0-1	1067	59	18	0.94	[0.92-0.95]
1-2	990	140	70	0.80	[0.78-0.83]
2-3	780	119	67	0.68	[0.65-0.71]
3-4	594	67	69	0.60	[0.56-0.63]
4-5	458	47	56	0.53	[0.50-0.56]
5-6	355	38	62	0.47	[0.43-0.50]
6-7	255	25	35	0.42	[0.38-0.46]
7-8	195	24	34	0.36	[0.33-0.40]
8-9	137	9	36	0.34	[0.30-0.37]
9-10	92	7	23	0.31	[0.27-0.35]
10-11	62	7	16	0.27	[0.22-0.31]
11-12	39	3	10	0.24	[0.20-0.29]
12-13	26	2	12	0.22	[0.17-0.27]
13-14	12	3	5	0.15	[0.09-0.23]
14-15	4	0	3	0.15	[0.09-0.23]

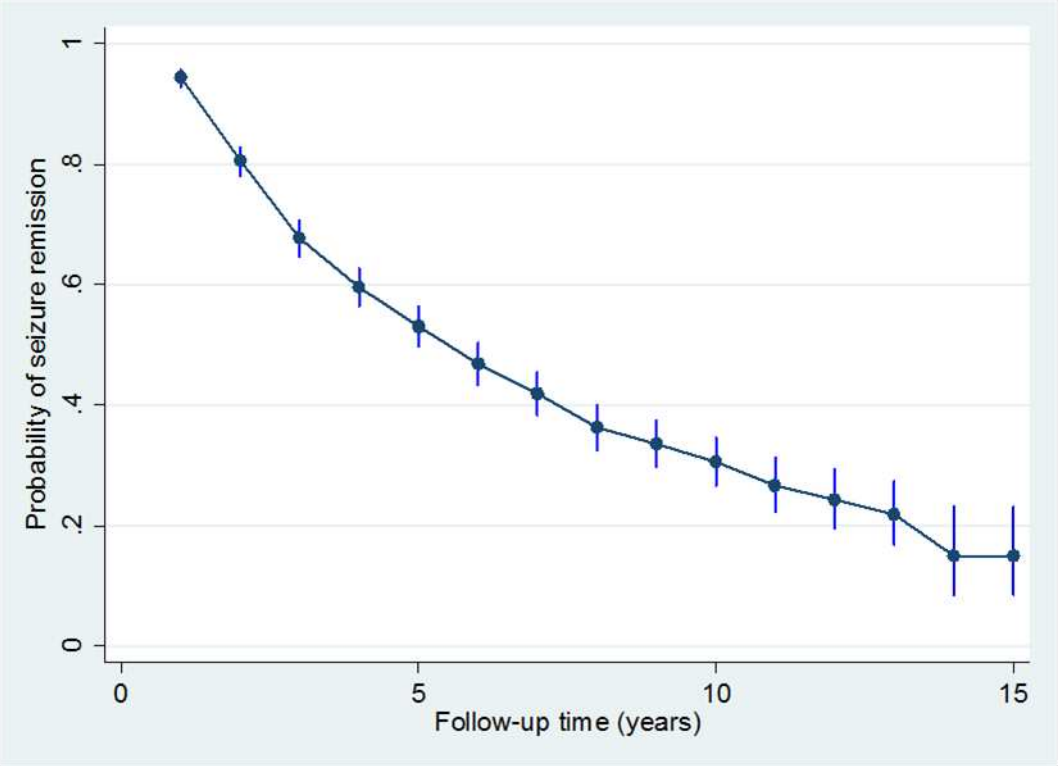


Figure 4-6: Cumulative probability of remission of seizures over time

4.6 Discussion

The main aim of this chapter was to use UK primary care data to quantify long-term seizure outcomes of epilepsy in CYP and additionally to assess the effect of level of adherence on outcomes. Of 1067 CYP who were included in this analysis, 276 (26%) CYP had THIN-coded records for the extent of seizure control. The extent of seizure control after initiation of therapy was recorded in terms of the follow-up frequency of seizure attacks such as daily, weekly, monthly, or yearly seizures. CYP who achieved better seizure control were recorded to have `seizure free >12 months' or `epilepsy control good'. This may indicate that seizure control was an important measure to monitor the response to AED treatment and prognosis of epilepsy. However, the fact that only around one-quarter (26%) of the study cohort have had records for seizure control suggests that GPs did not regularly record seizure state for all CYP within medical files of THIN database.

4.6.1 Overall incidence of medically-attended seizure events compared to previous studies

Since not all CYP of the study cohort had records of seizure control, the incidence of medically-attended seizure events over years of study time was employed to explore seizure control. The overall incidence of seizures was 0.73 [95% CI 0.71-0.75] per person-years. Over 6467 person-years, the number of seizure events for individual CYP ranged from zero to 97 (median=2; IQR 3-25). The incidence of medically-attended seizures was poorly correlated to THIN-coded seizure control. This may be because the incidence of seizures was calculated using only the events presented on the dates of visiting the GPs. It means that a child may have experienced daily seizures; however, it was counted as just one medically-attended event on the day the child visited the GP.

The frequency of seizures per person-year is much lower if compared to the distribution of seizure frequency from published data on the frequency of seizures. This study reported only seizures that were recorded at the time of

physician visits. However, the design of the published studies was different than this study where the data were based on self-reported seizure frequency and not only the medically-attended. It was not clear if patients/caregivers kept diary of seizure attacks or just recalled information. For example, a previous survey was conducted by Moran et al. (2004) to describe the clinical characteristics of epilepsy in terms of seizure frequency and severity for patients with epilepsy in the UK [330]. The authors analysed returned postal questionnaires of 1630 patients with epilepsy recruited through 80 primary care practices across different areas in the UK. The sample included 127 (7.8%) patients aged up to 17 years. The questionnaire requested information on the number of seizures in the last 12 months of the study. The authors presented data of the seizure frequency within the last 12 months by age groups. The seizure frequency of the age group <17 years were that 28.3% of participants reported zero, 3.1% reported one, 28.3% had 2-9 and 40.2% had >10 seizures.

Another community-based survey was carried out by Hart et al. (1995) to assess the severity of epilepsy and to address the issue of medical care in the UK community [114]. Questionnaires were distributed by 119 participating GPs to patients with epilepsy identified from 58 general practices. Out of 1628 responding patients, 14% were under the age of 20 years. Separate data were not presented about CYP. The seizure frequency in the last 12 months before study were that 46% had zero, 33% had 1-12, 12% had 13-50 and 8% had >50 seizures.

The incidence of seizure events in this study was significantly higher, 1.64 [1.49-1.79], in CYP who had their first recording of epilepsy at younger age, i.e. age group up to 2 years old, compared to other age groups. It can be explained on the basis that 36 (14%), out of 259 CYP of this age group had experienced "infantile spasms" compared to no one in other age groups. This subtype of epilepsy is characterised by more frequent manifestation of seizure attacks (tonic or myoclonic seizures) and is classified as difficult-to-treat or refractory epilepsy syndrome [322, 323]. Another possible explanation is that this age group is highly dependent and much more supervised by their parents/caregivers which may suggest more reporting of seizure attacks if any.

Incidence of seizure events in this study varied across different epilepsy subtypes. Incidence was lower in absence epilepsy as compared to other subtypes which was expected as this subtype is characterised by absence manifestation of seizures. Incidence was higher in generalised epilepsy subtypes and difficult-to-treat subtypes including Lennox-Gastaut syndrome and infantile spasm. Generalised epilepsy subtypes manifest different forms of seizures such as tonic, clonic, myoclonic and tonic-clonic with widespread convulsive activity [7]. Difficult- to-treat epilepsy subtypes are usually resistant to treatment and manifest poor seizure control [322, 323].

4.6.2 The incidence of seizure events stratified by years of follow-up time

Higher incidence of medically-attended seizure events in the first year of diagnosis may be expected because at the first year after starting therapy, GPs would be seeking seizure reports from CYP or their caregivers to monitor the chosen first-line drug treatment and to reach a steady state treatment for CYP. For further follow-up years, some CYP were probably seizure-controlled provided that the treatment was monitored for them. The incidence of seizures was again higher in the year 14 and 15 after starting therapy where obviously the person-years contribution of CYP was very small with some CYP experiencing higher seizure frequency. The nature the study cohort was that CYP were entered the database sequentially as the study progresses. Consequently, CYP have been followed for varying lengths of time where some CYP have dropped out of the study and become lost to follow-up, some have experienced seizures being evaluated, and the rest have not had seizures by the time the study was ended.

4.6.3 Regression analysis of factors affecting incidence of seizure events using Cox model

The Cox proportional hazard model revealed that the hazard of seizure events significantly decreased with older age of CYP compared to infants less than 2 years old. The hazard was much lower in the age group >12 years. This could be explained on the different epilepsy subtypes of onset at young ages as described above. This may also suggest that infants and pre-school age children were

much supervised by their parents or caregivers and hence reporting of seizure events was higher than older age children. A previous study by Arts et al. (2004) reported that children ≥6 years achieved significantly better seizure control compared to <6years old using multivariate analysis [odds ratio (OR) 0.62, 95% CI 0.39-0.99].

There was not a significant difference in the risk of seizures between males and females.

The interesting finding was that adherence was positively associated with incidence of seizures where the hazard of seizures significantly increased with higher adherence levels. It can be explained on the basis of the nature of managing epilepsy in primary care and how adherence was calculated. Epilepsy is an episodic disease that manifests seizures as the main symptoms. More frequent occurrence of seizures is a sign of poor control of epilepsy which encouraged more GP's visits and hence more prescribed medicines. As MPR was used as a proxy measure of adherence and was calculated as the sum of the days' supply for all prescriptions during a defined period of time, the more issued prescriptions to control seizures, the higher the MPR values. This was also revealed by significantly higher hazard of seizures ($p<0.001$) in CYP who were treated with at least two AEDs compared to those on one drug.

Another reason behind positive association of incidence of seizures and adherence could be the severity of illness and medicine's necessity. As more severe epilepsy syndromes manifest more frequent seizures which may have motivated CYP to adhere to the prescribed medicines. The perceived susceptibility for the negative consequences of poor seizure control such as injuries and hospitalisation may also have driven CYP and parents to adhere to prescribed medicines. However, the causality conclusion is difficult to be drawn because the prompt consequence of lower adherence in epilepsy is manifesting seizures where the time frame is very short. Thus it could be that lower adherence levels led to higher incidence of seizures then CYP immediately sought their medicines to reduce the risk of seizures. Perhaps the pharmacological expectation was that incidence of seizures may decrease with higher adherence levels but the results suggested that the behavioural effect was

dominant that is adherence was correlated to the frequency of uncontrolled seizures. Measurement of adherence was very challenging in this study and it was encountered by some limitations such as poor level of recoding of prescription instructions. Thus the analysis of factors predicting seizures was to estimate an approximate association between seizure outcomes and adherence.

This relation between adherence and seizures supported earlier finding by Shope (1988) who examined predictors to adherence by assessing serum levels of AEDs in two paediatric populations with epilepsy (n=90, n=211) [177]. The author concluded that among factors correlated to adherence, adherence increased in the group of CYP who had more frequency of occurrence of seizures ($p<0.025$). Another study was conducted by Jones et al. (2006) in the UK on 54 adult patients with epilepsy to examine the associations between self-reported adherence and seizure control and perceptions of illness and medication [121]. The authors reported that patients with poorly controlled epilepsy had a greater belief in the necessity of medication than well-controlled patients and were prescribed significantly more medications ($p< 0.01$).

Epilepsy subtypes apart from absence seizures subtype did not significantly affect the hazard of seizure incidence. However, epilepsy subtypes in this study were not specified for the majority of CYP (67%). The numbers of CYP with focal and refractory epilepsy were relatively small. By referring to previous paediatric studies, univariate analysis of predictors of seizure prognosis has showed that seizure control was significantly worse for infantile spasms and myoclonic/atonic seizure types as compared to generalised tonic-clonic seizure type [309]. Berg et al. (2001) reported that two-year remission of seizures was significantly higher for absence seizures type as compared to focal and generalised seizure types [313] which was supported by the current analysis where the hazard of seizures was significantly lower for absence seizures.

4.6.4 Duration of seizure remission

The multiple events survival analysis of seizure remission showed comparable results to what has been published on long–term prognosis of seizures in CYP with epilepsy. The study findings showed that 94% [95% CI 92%, 95%] of CYP achieved 1-year remission of seizures, 80% [95% CI 78%, 83%] achieved 2-year remission and 68% [95% CI 65%, 70%] achieved 3-year remission and 47% [95% CI 43%, 50%] achieved 5-year remission by 15 years follow-up. The findings at 3-year and 5-year remission periods were comparable to a population-based study conducted by Cockerell et al. (1997) to examine the seizure prognosis in patients with epilepsy in the UK [115]. The authors identified and prospectively followed 792 patients newly diagnosed with epilepsy (including 295 (37%) patients aged up to 19 years) from 275 general practices in the UK between 1984 and 1987. Patients were followed up to 9 years from the index seizure. The authors calculated cumulative remission of seizures as the cumulative proportions of patients with seizures ever attaining a 3 or 5-year remission from the index seizure. The results of follow up revealed that in the age group <16 years, 85% (CI 77,93) and 57% (CI 48-66) achieved 3 years and 5 years cumulative remission rates by 9 years follow up. While the 3-year and 5-year terminal remission rates at 9 years for the age group <16 years were 66% (CI 56, 76) and 46% (CI 36, 56), respectively.

The study findings also showed comparable results at 2-year remission with some worldwide studies which examined seizure remission in CYP in Europe and the United States. For example, in a Dutch study, a cohort of 453 CYP, aged 1 month to 15 years, was prospectively followed up to 5 years to examine the prognosis of epilepsy [309]. Seizure outcomes were examined based on 2 and 5 years terminal remission. At the end of 5 years, the results showed that 345 (76%) attained at least one year remission, 290 (64%) at least 2 years remission and 248 (55%) achieved more than 2 years remission.

Berg et al. (2001) prospectively followed a cohort of 594 CYP newly diagnosed with epilepsy in the USA and examined seizure outcomes in terms of seizure remission [313]. The CYP, aged 1 month and 15 years at the first (index) seizure, were observed for a median followed-up of 5 years. About 90% of CYP were

treated with AEDs. The authors reported that 442 (74%) of CYP achieved 2 years remission.

The proportion of CYP who entered long-term remission, for example, more than 5-year remission was 42% [95% CI 38%, 46%]. This proportion of CYP was lower than previous studies which reported that around 65-75% of both CYP and adults with newly diagnosed epilepsy had a chance of entering long-term remission [46, 115]. However, a few numbers of CYP in this study were followed-up to 15 years as above-mentioned

4.7 Strength and limitations of the analysis

The study is one of the large studies on CYP with epilepsy in the UK to quantify clinical outcomes of treating epilepsy in general practices in terms of seizure frequency and remission of seizures.

A potential limitation to this analysis was that the estimated seizures frequency and seizures free periods (remission) were based on the incidence of medically-attended seizure events and not the actual seizure attacks. It is high likely that seizure events were underestimated because they were not reported by CYP/caregivers or were not comprehensively recorded by the GP for the whole study cohort. Research has found that clinicians cannot monitor patients continuously and they mostly rely on the patients' and/or caregivers' reports of seizure activity [331, 332]. Some studies suggested under-reporting of seizures by patients or caregivers [333, 334]. However, the proportions of CYP who achieved seizure remission in this analysis were compared to some cohort studies which were prospectively conducted and showed comparable results as previously discussed.

4.8 Conclusions

The calculated incidence of medically-attended seizures was higher in infant and young children as compared to adolescents. This either suggests different severity of epilepsy subtypes in infant and young CYP or lower reporting of seizure events for adolescents. Length of calculated seizure-free periods suggest that approximately half of CYP can have good prognosis of epilepsy in terms remission of seizures for 5 years or more. Regression analysis demonstrated positive association between the AED adherence and seizure frequency which suggest that CYP were more likely to adhere to prescribed regimens when their condition were less controlled.

Chapter 5: Estimating the costs of treating epilepsy in CYP in primary care in the UK

5.1 Introduction

Epilepsy has been demonstrated to be associated with economic burden at individual, family, health services, and societal level in the UK and Europe [65]. Assessment of health resource utilisation (HRU) and the costs associated with treating epilepsy is important to understand its economic impact on individuals and health care providers. Estimating the cost of illness is also important when assessing the cost-effectiveness of interventions to manage epilepsy such as drugs, medical procedures or surgery, and also to assist decision makers to set priorities for resource allocation within the health care system. Examining the cost of illness includes three main elements; direct costs, indirect costs and intangible costs[335]. Direct costs are the costs of medical (e.g., drug treatment, outpatient appointments and inpatient hospital admissions, diagnostic tests and laboratory investigations and general and specialists' visits) and non-medical heath care resources (e.g., patient/family out-of-pocket costs for treatment-related travel and time off work and costs for taking care of dependents). Indirect costs usually refer to the associated productivity loss due to illness in terms of underemployment, unemployment and increased mortality. Intangible costs are difficult to measure and value such as the associated psychological disorders and reduction in quality of life due to illness.

Little is known about the costs of treating epilepsy in CYP in the UK and previous studies estimating the costs of treating epilepsy in adults are over 14 years old [67, 336]. Recently, Beghi et al. (2005) reviewed published studies on the cost of epilepsy in childhood and concluded that the knowledge of economic impact of epilepsy in CYP is limited due to the scarcity, inconsistency and poor comparability of the published articles [68]. A search was carried for more recent studies that may have been published since this review. No study was found estimating the total direct costs of treating epilepsy in the UK or Europe.

In a study by Cockerell et al. (1994), children were included as part of large survey study and another longitudinal prospective study [67]. The study was conducted on two populations; one population of 1628 patients was identified from general practices throughout the UK and 14% patients were less than <20 years. The second population included a longitudinal prospective follow-up of 602 patients of whom 25% were less than 15 years. However, separate data were not provided about the cost of epilepsy in children and only combined data for the adults and children were presented. The annual direct costs of epilepsy were estimated to be in the first year of diagnosis. Ninety three CYP aged 5-15 years were also included as part of another prevalence survey study by Jacoby et al. (1998) to investigate the direct and indirect cost of epilepsy in the UK [336]. The authors estimated the total annual health care cost to be £689 per patient. The later study had a limitation in that the bulk of information was based on patient and parent questionnaires which might lead to an underestimate or overestimate of the medical services utilised by patients (recall bias). Morgan and Kerr (2004) investigated only the hospital care-related costs for 3,892 people with epilepsy in Cardiff and the Vale of Glamorgan- UK in 1999 [337]. The study was not representative of the whole UK population and no separate cost data were presented for children.

The economic aspects of epilepsy should be studied separately in CYP because children and adults are different in terms of incidence and prognosis of epileptic syndromes, hospital care, referrals to specialists, and the age licence of antiepileptic drugs (AEDs) [68]. For example, Morgan and Kerr (2004) reported that children younger than 15 years were more frequently admitted to hospitals than adults [337]. Similar findings were reported by Jette et al. (2008) who analysed HRU by patients with epilepsy for the year 2001 using a Canadian database. The authors revealed that children less than 18 years were more likely to see neurologists, visit emergency departments and admitted to hospitals [338].

Sub-optimal adherence to AEDs has been associated with more frequent hospitalisations, emergency room visits and higher associated direct costs of epilepsy in adults studies (See Chapter1) [156, 170].

To the researcher's knowledge no population-based study has focused on investigating the cost of treating epilepsy in CYP in the UK.

Epilepsy is one of the chronic conditions for which drug prescribing and monitoring are primarily managed in general practices in the UK in collaboration with secondary care settings. Thus the primary aim of this analysis was to use THIN database to provide estimates of the costs of drug treatments and investigations associated with epilepsy on a large and representative sample of CYP in the general population. Applying longitudinal analysis in this chapter enables understanding of the HRU by CYP with epilepsy and the associated cost of treating epilepsy over the study time.

5.2 Aim of the study

The aim of this cost analysis was to describe the health resource utilisation and associated direct costs in CYP with epilepsy from the Primary care Trust (PCT) perspective and to determine the relationship between resource utilisation and adherence to AEDs.

5.3 Objectives

The objectives of this cost analysis were to:

1. Extract primary health resource utilisation data from THIN database
2. Define the unit cost of the resource using Department of Health (DH) - NHS Reference Costs Database, the Personal Social Services Research Unit (PSSRU) and the British National Formulary (BNF).
3. Estimate the total costs of resource use by multiplying the unit costs by resource use in THIN.
4. Determine whether there were any variations in HRU and costs by age, sex, socioeconomic status of children and adherence to AEDs.

5.4 Methods

5.4.1 Study population and study time

Assessment of the cost of epilepsy was conducted on a subgroup of CYP with epilepsy between January 1st, 1988 and November 30, 2004. This cohort of children had at least one year of follow-up data after the date of their first recording of epilepsy diagnosis in THIN database. The follow-up time ended at the finish date of each child. The finish date was the date of death, the date where the child transferred out of the general practice, or the last date of data collection, whichever occurred first.

To estimate the costs of HRU, this cohort was again divided into newly diagnosed CYP with epilepsy (incident group) and CYP with established epilepsy (prevalent group). The incident group met the criteria discussed in Chapter 2 where CYP were either registered from the date of birth, so the date of the first diagnosis of epilepsy was known or children had at least 6 months registration data before the date of first recording of epilepsy (Figure 5-1).

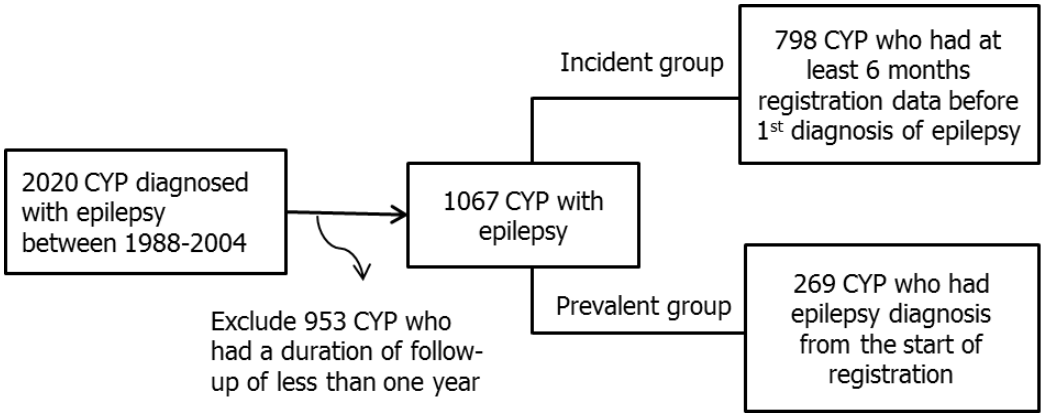


Figure 5-1: Study population for cost analysis

The date of first recording of epilepsy was the date of first diagnosis code or the date of first prescription of AED, whichever occurred first as described in Chapter 2. Dividing the study cohort into incident and prevalent groups was done to compare the overall costs of epilepsy in newly diagnosed cases to the

established cases and also to compare the cost during the first year of epilepsy diagnosis with subsequent follow-up years.

The HRU and the associated costs were estimated from the date of first diagnosis of epilepsy. However, since there are procedures as part of the diagnosis process of epilepsy such as general practitioners (GP) consultations, specialists' appointments and diagnostic imaging which often occurred before assigning the diagnosis of epilepsy, the analysis time was extended to 6 months before the date of first diagnosis of epilepsy for the subgroup of newly diagnosed children. For the study cohort, a suspected child with epilepsy was usually assigned a tentative code (on examination code) for symptoms such as seizure or convulsion before the diagnosis of epilepsy and/or epilepsy syndrome.

This was considered normal procedure as it was also recommended by the NICE guideline 2004 and its update in January 2012 to verify the diagnosis and determine subtypes of epilepsy[26]. The recommendations stated that CYP with a first suspected seizure should be referred as soon as possible to a specialist in the management of the epilepsies to provide accurate and early diagnosis and initiation of appropriate therapy. Alongside the clinical features and history of seizure, an electroencephalography (EEG) should be performed to support a diagnosis of epilepsy in CYP. If necessary, an EEG should be performed after the second epileptic seizure or as assessed by the specialist, it may be performed after a first epileptic seizure.

5.4.2 Extraction of primary health resource utilisation from THIN database

The main outcome measure was the total cost of HRU recorded in THIN database. The categories of resource use included costs of GP consultations, outpatient such as referrals to paediatric neurologists or other specialists, inpatient and emergency hospital care medications for epilepsy, diagnostic imaging, and laboratory investigations. The methods of identifying each element of HRU are described in Table 5-1:

Table 5-1: Identification of categories of cost related to epilepsy from THIN database

Category of cost	Definition/identification
General practitioner consultations	The number of GP visits were extracted from THIN medical and AHD files using the dates the CYP were assigned diagnosis codes for epilepsy, seizure events and codes for epilepsy monitoring and medication review
Outpatient hospital care	Codes for outpatient attendances including referrals to paediatric neurology (specialists for diagnosis of epilepsy) were extracted from the medical files of CYP using the code list in Appendix 17. Outpatient neurologists' appointments were recorded for only 95 (9%) of the study cohort.
Inpatient hospital care	Data for inpatient hospital admissions and other accident and emergency (A&E) visits were extracted from the medical files of CYP using the code list in Appendix 18. The primary care coding system did not provide whether the procedures were elective (planned patient's admission) or non-elective (unplanned patient's admission) admission. So non-elective admission was defined in this analysis to include codes of urgent and emergency admissions. Other extracted codes were categorised into elective admissions or non-admitted accident and emergency visits [339].
Diagnostic imaging	Diagnostic imaging for CYP with epilepsy principally included EEG (EEG is a main diagnostic tool for epilepsy via recording of electrical brain activity along the scalp), computerised tomography (CT is used to generate a three-dimensional image of the inside of an organ and it markedly increases the

	ability to determine an aetiology for epilepsy) [340]and magnetic resonance imaging (MRI) which uses radio waves and a magnetic field to show the physical structure of the brain. Codes for diagnostic imaging were recorded in the medical and additional health data (AHD) files of THIN (Appendix 19)
Laboratory investigations	Laboratory investigations included biochemistry tests for monitoring of serum level of AEDs. Codes for laboratory investigations were listed in Appendix 19
Medications for epilepsy	All AED types prescribed in THIN for the study cohort including information on the quantity prescribed, formulation and dosage strength of each drug.

The categories of HRU were extracted from THIN and the number of events was quantified separately for the newly diagnosed CYP with epilepsy (incident group) and the prevalent group. For each group of children, the HRU was stratified by sex, age as time-varying variable, socioeconomic status (Townsend deprivation quintiles) and years of follow-up since the date of first diagnosis or the date of first recording of epilepsy in THIN for the prevalent group. The overall percentage of CYP who consumed each element of health resources was calculated. HRU was also calculated per child per year.

5.4.3 Define the unit cost of the health care resource

The mean unit cost of HRU in CYP with epilepsy were obtained using PSSRU-Unit Costs of Health and Social Care[341], the DH-Reference Costs database[339]. The costs were calculated for the year 2011. The costs of prescribed AEDs were obtained from the BNF for children 2011[271]. Table 5-2 summarises the unit cost of each element of health resources and the data source of each cost.

Within the DH-Reference Costs database, the unit costs of health care resource were classified into Health Resource Group (HRG) codes. The HRG codes are

standard groupings of patients' events or treatments that have been defined by clinicians as consuming a similar level of resource[339]. The latest version, HRG-4, has been used in reference costs database since the year 2006-07. The patients' events in HRG-4 codes are sometimes grouped by diagnosis, age, body areas or body systems, length of stay or a combination of factors. For example, EEG and electromyography (EMG) scans had the same HRG-4 code which was DA14. Thus the unit cost of a diagnostic EEG scan was defined by searching its HRG-4 code within the DH-Reference Costs database.

The unit cost of a GP consultation was obtained from the PSSRU using the average unit cost per surgery consultation lasting 11.7 minutes without qualifications and including direct care staff cost. Qualifications are specific types of pre-registration and post-graduate medical education and training. The assumption was that not all GPs have had these medical qualifications.

The costs of hospital care events were obtained from the DH-Reference Costs database. The cost of epilepsy specialist was obtained using the cost of outpatient attendances at paediatric neurology. The medical files of CYP did not provide any data for other specialists' visits except 5 visits to psychiatrists which were excluded from the total cost analysis. The unit cost for other outpatient hospital care was attached using the average unit cost of all outpatient episodes within DH-Reference Costs database.

It was not recorded in THIN for the extracted inpatient and emergency hospital care data whether they were epilepsy-related. So the unit costs of elective and non-elective hospital admissions were attached using the average unit cost of all elective or non-elective episodes within the DH-Reference Costs database. For emergency admission, the cost was attached as non-elective inpatient short stay. The emergency short stay was chosen based on the online Hospital Episodes Statistics (HES) Database for the year 2011which reported that the median length of hospital stay of 120,271 admitted patients with epilepsy and other episodic disorders (including 18,253 CYP less than 15 years) was 1 day[342].

The costs of diagnostic imaging and blood chemistry tests were obtained from the DH-Reference Costs database.

The costs of AEDs for individual children were calculated for each issued prescription by multiplying the price guidance obtained from the BNF for children 2011[271] for each drug formulation by the quantity prescribed for each child. For example, if a child was prescribed 600 ml of sodium valproate liquid and the unit price in the BNF was £6.13 for 300ml-pack, so the cost of this prescription was calculated as 2x £6.13=£12.26.

Formulations (1% of the total number of prescriptions) for the four AEDs clobazam, clonazepam, midazolam and paraldehyde did not have price guidance in the BNF because these formulations are extemporaneous preparations and are usually provided by special order. The costs of these formulations were obtained from the NHS Electronic Drug Tariff 2011[343].

Table 5-2: Unit cost of health care resource

Health care resource	Number	Cost (£)	Source
GP consultation	1	30	PSSRU 2011
Hospital care episodes			
Paediatric neurology outpatient attendances	1	354	DH Reference Costs 2011
Other outpatient attendances	1	101	DH Reference Costs 2011
Elective inpatient admissions	1	3091	DH Reference Costs 2011
Non-elective admissions (e.g. emergency)	1	568	DH Reference Costs 2011
A&E visits (not admitted)	1	108	DH Reference Costs 2011
Diagnostic imaging			
CT	1	95	DH Reference Costs 2011
EEG	1	93	DH Reference Costs 2011
MRI	1	163	DH Reference Costs 2011
Blood chemistry tests	1	1	DH Reference Costs 2011
Cost of AEDs	Pack size	Cost (£)	
Old AEDs			
Sodium valproate capsules 150mg	100 cap	5.70	BNF for children 2011
Sodium valproate crushable tab 100mg	100 tab	5.60	
Sodium valproate EC tablet 200mg	100 tab	5.35	
Sodium valproate EC tablet 500mg	100 tab	11.31	
Sodium valproate MR tablet 200mg	100 tab	11.65	
Sodium valproate MR tablet 300mg	100 tab	17.47	
Sodium valproate MR tablet 500mg	100 tab	29.10	
Sodium valproate liquid 200mg/5ml	300 ml	6.13	
Carbamazepine chewable tablet 100mg	56 tab	3.72	BNF for children 2011
Carbamazepine chewable tablet 200mg	56 tab	6.92	
Carbamazepine MR tablet 200mg	56 tab	4.88	
Carbamazepine MR tablet 400mg	56 tab	9.63	
Carbamazepine tablets 200mg	28 tab	6.02	
Carbamazepine liquid 100mg /5ml	300 ml	7.20	
Ethosuximide capsule 250mg	56 cap	38.23	BNF for children 2011
Ethosuximide syrup 250mg/5ml	200 ml	6.60	
Phenobarbital elixir 15mg/5ml	100 ml	0.77	BNF for children 2011
Phenobarbital tablet 30mg	28 tab	1.06	
Phenytoin capsule 50mg	112 cap	0.67	
Phenytoin suspension 30mg/5ml	500 ml	4.27	
Phenytoin tablets 50mg	28 tab	7.38	
Primidone tablets 250mg	28 tab	12.60	BNF for children 2011

Diazepam injection 5mg/ml	2ml	0.45	BNF for children 2011
Diazepam rectal tube 5mg	2.5ml	1.67	
Clobazam tablet 10mg	30 tab	4.68	
Clobazam suspension 5mg/5ml	100ml	120.25	NHS Electronic Drug Tariff
Clonazepam oral drops 2.5 mg/ml	20ml	125.62	NHS Electronic Drug Tariff
Clonazepam suspension 500µg /5ml	100ml	133.94	NHS Electronic Drug Tariff
Clonazepam tablets 500µg	100 tab	3.77	BNF for children 2011
Midazolam buccal solution 10mg/ml	25 ml	97.51	NHS Electronic Drug Tariff
Paraldehyde injection	10ml	111.65	NHS Electronic Drug Tariff
New AEDs			
Lamotrigine dispersible tablet 25mg	56 tab	3.41	BNF for children 2011
Lamotrigine dispersible tablet 100mg	56 tab	6.50	
Lamotrigine tablet 25mg	56 tab	2.77	
Lamotrigine tablet 50mg	56 tab	3.73	
Lamotrigine tablet 100mg	56 tab	5.39	
Lamotrigine tablet 200mg	56 tab	9.63	
Topiramate capsule 15mg	60 cap	15.09	BNF for children 2011
Topiramate capsule 25mg	60 cap	22.63	
Topiramate capsule 50mg	60 cap	37.18	
Topiramate tablet 25mg	60 tab	19.68	
Topiramate tablet 50mg	60 tab	32.33	
Topiramate tablet 100mg	60 tab	57.91	
Topiramate tablet 200mg	60 tab	112.46	
Vigabatrin sachet 500mg	50 sach	17.08	BNF for children 2011
Vigabatrin tablet 500mg	100 tab	30.84	
Levetiracetam tablet 250mg	60 tab	29.70	BNF for children 2011
Levetiracetam tablet 500mg	60 tab	52.30	
Levetiracetam tablet 1000mg	60 tab	101.10	
Gabapentin capsule 100mg	100 cap	3.94	BNF for children 2011
Gabapentin capsule 300mg	100 cap	5.52	
Gabapentin capsule 400mg	100 cap	5.91	
Gabapentin tablet 600mg	100 tab	41.06	
Gabapentin tablet 800mg	100 tab	54.19	
Oxcarbazepine tablet 150mg	50 tab	9.91	BNF for children 2011
Oxcarbazepine tablet 300mg	50 tab	20.14	
Oxcarbazepine tablet 600mg	50 tab	40.18	
Tiagabine tablet 5mg	100 tab	41.68	

5.5 Estimation of the total costs of health resource utilisation

For individual children, the unit cost of each element of health resources was attached. The total costs of the health resources were then estimated by multiplying the quantities of each resource per year by the fixed unit cost values. The total costs of all observed HRU were aggregated and estimated for individual child per year. Finally the mean total costs per child per year were estimated and presented. The total costs of actual recorded HRU in THIN were presented first. Referrals to outpatient paediatric neurologists were recorded for few CYP (9%). The NICE guideline 2004 and its update 2012 [26] have recommended that the diagnosis of epilepsy should be established by a neurologist or a paediatric specialist of expertise in managing epilepsy to avoid misdiagnosis of cases. So the recorded data in THIN for outpatient specialist attendances were considered an underestimate of what would have been performed under the new practice recommendations. Therefore, the costs of HRU in first year of diagnosis was re-estimated after assigning one visit to paediatric neurology for each child with newly diagnosed epilepsy during the first year of epilepsy diagnosis.

The annual total direct costs per child were estimated and stratified by sex, age, Townsend deprivation quintiles and adherence groups as a function of the calculated MPR. With regards to adherence, CYP were categorised into two groups; adherent (MPR$\geqslant$0.8), non-adherent (MPR<0.8). The threshold of 0.8 (80%) has been commonly used in the adherence literature including two recent previous studies assessing the association between costs and non-adherence in adult populations with epilepsy [156, 170]. Some CYP may not have constant supply of AEDs during the follow-up time as because of remission of seizures or other medical reasons. So CYP without any drug prescription for 180 days or more were classified as untreated during this period.

The arithmetic mean of cost data provides information about the total costs required to treat all patients and so it is considered the most useful measure for health care policy decisions. Common methods of skewed data (common for

cost data)transformation such as the natural log transformation and square root transformation to achieve approximate normal distribution do not enable comparison of arithmetic means [344]. Nonparametric bootstrapping is an adopted method to compare arithmetic means of cost data [344]. Therefore, nonparametric bootstrapping was performed using Stata software. On the data generated by bootstrapping, t-test was used to compare the annual total cost between sex and adherence groups. Analysis of variance (ANOVA) was applied to compare the total costs between age groups and deprivation quintiles.

5.6 Results

5.6.1 Study population

The analysis of the direct medical costs of HRU was conducted on 1067 CYP with epilepsy of whom 798 were newly diagnosed CYP (incident group) and 269 CYP were prevalent cases. Of the incident group, 444 (56%) were male and the mean age at first diagnosis of epilepsy was 5.6 years and ranged from 1 day to 15.2 years (Table 5-3). Age of CYP varied over the follow-up years and the proportions of age are shown in Table 5-3. About 18% had the lowest deprivation score (Townsend =1) and 17% had the highest deprivation score (Townsend=5).

The prevalent group had similar characteristics to that of the incident group where out of 269 children, 147 (55%) were males. The mean age at first recording of epilepsy in THIN was 5.2 years and ranged from 1 day to 15 years. The proportions of age over the follow-up years are shown in Table 5-3. One-fifth (20%) had the lowest deprivation score (Townsend quintile=1) and 26% had the highest deprivation score (Townsend quintile =5). The total person years of registered data of the whole study cohort were 6467 years and the mean follow-up years was 6 and ranged from 1.0 to 15.9 years.

Table 5-3: basic characterics of CYP with epilepsy

Characters	Number of CYP (%)	
	Incident group n=798	Prevalent group n=269
Sex		
Male	444 (56)	147 (55)
Female	354 (44)	122 (45)
Age time-varying* (years)		
0-2	192 (24)	67 (25)
2-6	441 (55)	155 (58)
7-12	663 (83)	227 (84)
>12	338 (42)	154 (57)
Townsend quintiles		
1	147 (18)	53 (20)
2	123 (15)	33 (12)
3	168 (21)	40 (15)
4	170 (21)	54 (20)
5	135 (17)	70 (26)
Missing	55 (7)	19 (7)

*A child may contribute to more than one age category over time so the number of CYP does not add to total

5.6.2 Health resource utilisation by the newly diagnosed CYP with epilepsy (incident group)

The overall HRU by the newly diagnosed CYP with epilepsy in the sample is shown in Table 5-4. Each child in this sample had at least one GP consultation during the follow-up time which varied for each child. The total number of GP consultations was 4629 of which 2041(44%) occurred during the first year after diagnosis.

Thirty one percent of CYP (250) were treated at hospital as outpatients including 25 (3%) paediatric neurology attendances, 147(18%) of CYP had inpatient hospital admissions and 122(15%) had emergency visits.

Twenty two (3%) of CYP had CT scans, 185(23%) had EEG scans and 116 (15%) had MRI scans. The blood drug levels of AEDs were monitored for 98 CYP (12%). All CYP were treated with AEDs (one of the inclusion criteria of identifying CYP with epilepsy) and the total number of prescriptions was 50,506. Thirty eight percent (306) of CYP were on one drug whereas

492(62%) were prescribed at least two drugs to control epilepsy. A detailed description of the number and the most commonly prescribed drugs was discussed in Chapter 3.

The HRU per year following diagnosis is described in Table 5-5. The data showed that in the first year of epilepsy diagnosis, the mean number of GP consultations was 2.56, 0.45 outpatient attendances, 0.16 inpatient admissions, 0.33diagnostic imaging and laboratory tests and 11.41 drug prescriptions per child. A wide variation in the HRU was observed between CYP during the follow-up years. For example, in the first year of epilepsy diagnosis, 93% of CYP were treated with AEDs, 11% admitted to hospital, 4% had accident and emergency visits, 15% had EEG, 7% had MRI and 2% had CT scans. This figure decreased in the eighth year of follow-up at which point 90% of CYP were treated with AEDs, 5% admitted to hospital, 7% had accident and emergency visits, 2% had EEG, 2% had MRI and 0% had CT scans. The mean number of drug prescriptions remained almost unchanged over time.

Table 5-4: Health resource utilisation by the incident group (n=798); total episodes in THIN data

Characters	No of CYP (%)	GP visits	Hospital care episodes				Diagnostic imaging			Blood drug tests	Prescriptions
			Sp visits	Outpatient	Inpatient	A&E	CT	EEG	MRI		
Total	798	4629	30	951	368	253	25	245	154	156	50506
Sex											
Male	444 (56)	2552	19	617	228	133	18	141	74	86	29065
Female	354 (44)	2077	11	434	140	120	7	104	80	70	21441
Age time-varying*											
0-2	192 (24)	754	1	159	69	42	9	32	15	5	3784
2-6	441 (55)	1409	3	362	167	85	10	70	39	32	15365
7-12	663 (83)	1860	15	432	118	81	5	118	70	79	24639
>12	338 (42)	606	11	98	14	45	1	25	30	40	6718
Townsend index											
1	147 (18)	894	4	85	40	53	6	45	28	25	8241
2	123 (15)	688	8	204	62	44	5	39	30	30	7909
3	168 (21)	820	8	229	59	59	4	41	40	40	10491
4	170 (21)	1161	3	233	100	52	8	54	25	32	12534
5	135 (17)	800	6	137	64	34	2	41	21	27	8311
Missing	55 (7)	266	1	163	43	11	0	25	10	2	3020

Spvisits=paediatric neurology attendances, A&E= accident and emergency visits

*A child may contribute to more than one age category over time so the number does not add to total of CYP.

Table 5-5: Health resource utilisation by the incident group; mean per child per year

Years after diagnosis	No of CYP	GP visits	Hospital care			Diagnostic imaging			Blood drug tests	Prescriptions
			All outpatient	Inpatient	A&E	CT	EEG	MRI		
1	798	2.56	0.45	0.16	0.13	0.03	0.17	0.08	0.05	11.40
2	755	0.94	0.25	0.07	0.08	0.00	0.03	0.03	0.05	12.45
3	647	0.83	0.18	0.08	0.09	0.00	0.04	0.01	0.03	12.03
4	514	0.77	0.23	0.06	0.05	0.00	0.04	0.04	0.04	12.18
5	381	0.73	0.21	0.11	0.09	0.01	0.04	0.02	0.02	12.29
6	288	0.64	0.13	0.05	0.09	0.00	0.02	0.03	0.03	12.06
7	201	0.65	0.19	0.05	0.15	0.00	0.05	0.04	0.01	12.05
8	162	0.78	0.15	0.05	0.13	0.00	0.03	0.03	0.03	12.00

5.6.3 Health resource utilisation for the prevalent group of CYP with epilepsy

To compare with the incident group, the HRU by CYP with established epilepsy (prevalent group) is shown in Table 5-6. The total number of GP consultations was 1571, of which 559 (36%) occurred in the first year of recording epilepsy in THIN data. Each child in the group had at least one GP consultation during the follow-up time.

One-fourth of CYP (68) were treated at hospital as outpatients including a few of CYP (6) had records of referral to paediatric neurology with a total of 9 visits during the whole follow-up time, 41 (15%) CYP had inpatient hospital admissions, and37 (14%) had accident and emergency visits.

Ten CYP (4%) had CT scans, 43(16%) had EEG scans and 25 (9%) had MRI scans. The blood drug levels of AEDs were monitored for 23 CYP (8%). All CYP were treated with AEDs and the total number of prescriptions was 20790. Eighty three (31%) CYP were on one drug whereas 186 (69%) were prescribed at least two drugs to control epilepsy. A detailed description of the number and the most common prescribed drugs was discussed in Chapter 3.

The HRU per child per year during 8 years of follow-up are shown in Table 5-7. The mean number of GP consultations per year was approximately 1 except for the first year where it was 2.08. Outpatient attendances ranged from 0.09 to 0.18, 0.01-0.09 inpatient admissions, 0.04-0.14accident and emergency visits, 0.05-0.13 diagnostic imaging and laboratory tests and 11.67-15.56 drug prescriptions per child.

Table 5-6: Health resource utilisation by the prevalent group (n=269); total episodes in THIN data

Characters	No of CYP (%)	GP visits	Hospital care			Diagnostic imaging			Blood drug tests	Prescriptions
			Sp visits	Outpatient	Inpatient	A&E	CT	EEG	MRI		
Total	269	1571	9	193	75	67	10	50	30	42	20790
Sex											
Male	147 (55)	815	3	98	39	37	2	24	15	17	11836
Female	122 (45)	756	6	95	36	30	8	26	15	25	8954
Age time-varying*											
0-2	67 (25)	228	0	9	12	1	1	7	2	1	953
2-6	155 (35)	488	2	42	27	12	9	20	7	4	5922
7-12	227 (36)	591	5	110	29	33	0	14	13	26	10498
>12	154 (4)	264	2	32	7	21	0	9	8	11	3417
Townsend index											
1	53 (20)	246	3	28	21	8	2	9	8	3	3770
2	33 (12)	171	2	11	7	5	2	6	2	3	2278
3	40 (15)	309	4	22	11	23	1	5	5	7	3680
4	54 (20)	282	0	46	7	12	2	15	6	17	3650
5	70 (26)	461	0	79	24	17	2	10	7	8	6018
Missing	19 (7)	102	0	7	5	2	1	5	2	4	1394

Spvisit=paediatric neurology attendances, A&E= accident and emergency visits

*A child may contribute to more than one age category over time so the number does not add to total of CYP.

Table 5-7: Health resource utilisation by CYP with established epilepsy (prevalent group); mean per year

Years after first recording of epilepsy	No of CYP	GP visits	Hospital care			Diagnostic imaging			Blood drug tests	Prescriptions
			outpatient	Inpatient	A&E	CT	EEG	MRI		
1	269	2.08	0.16	0.07	0.05	0.01	0.08	0.02	0.02	11.67
2	222	1.00	0.11	0.09	0.05	0.01	0.01	0.03	0.01	14.46
3	192	0.75	0.12	0.05	0.04	0.02	0.04	0.01	0.01	13.82
4	166	0.98	0.09	0.04	0.11	0.00	0.03	0.01	0.03	14.87
5	143	0.70	0.13	0.05	0.06	0.00	0.02	0.01	0.02	13.92
6	119	0.77	0.13	0.05	0.04	0.00	0.02	0.02	0.05	12.99
7	90	0.98	0.16	0.01	0.08	0.00	0.03	0.03	0.05	13.50
8	74	0.94	0.18	0.04	0.04	0.00	0.01	0.03	0.01	15.65

5.6.4 The total annual direct costs of epilepsy per child for the incident group

The total direct costs of epilepsy per child over the first 8 years of follow-up after the diagnosis of epilepsy for the incident group are illustrated in. The figure showed the mean costs per child of the actual recorded events in THIN data. The mean cost per child was higher (£811(SD= £1,718); range £30-16,305) in the first year of diagnosis compared to a mean of £458 (SD=£1,633); range £368-587) in consecutive follow-up years principally due to higher inpatient hospital care costs. The total hospital care costs comprised 75% of the total costs in the first year and ranged from 45% to 67% of the total cost per year, AED costs ranged from 21% to 47% and the costs of GP consultations from 4% to 10%. The highest contribution of hospital care costs was principally the cost of inpatient admissions which ranged from 34% to 61%.

Figure 5-3 illustrates an example of the distribution of total costs of HRU for individual CYP in the first four years after epilepsy diagnosis. The distribution was right-skewed with a few CYP (4%-11%) consumed high levels of health resource and had a total cost of more than £2000 each year of follow-up period.

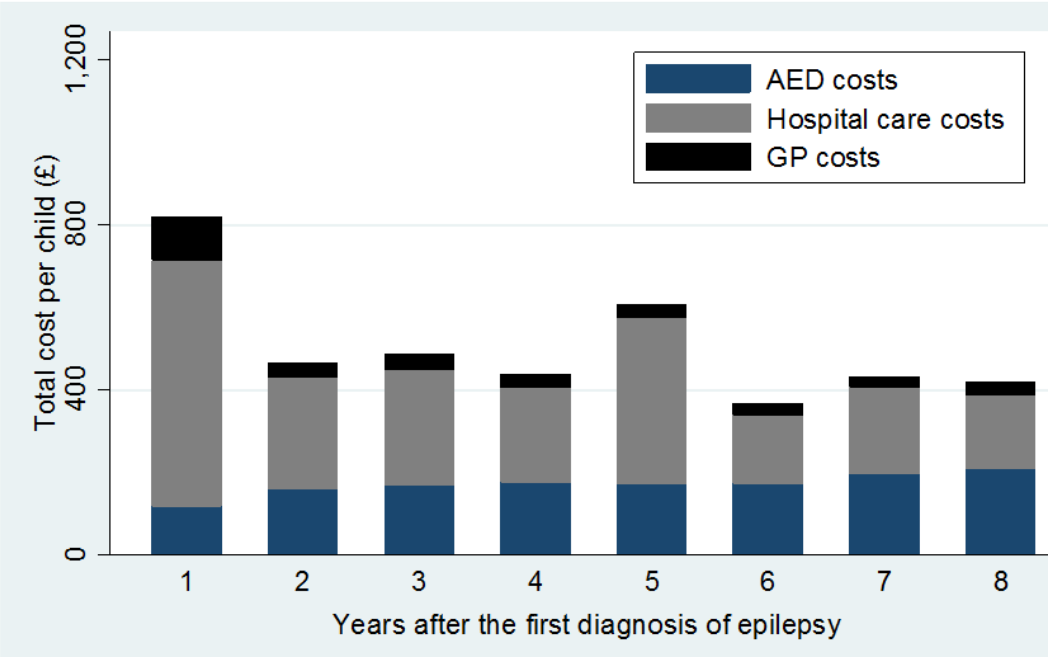


Figure 5-2: Actual calculated total annual direct medical costs per child for newly diagnosed CYP with epilepsy (incident group)

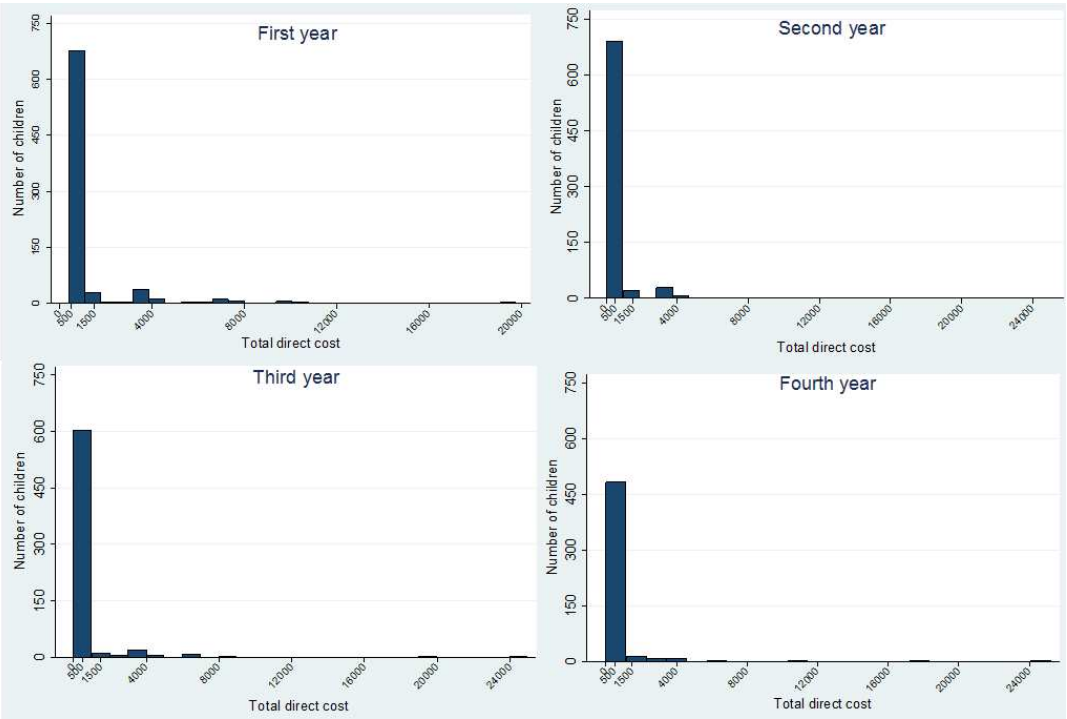


Figure 5-3: The distribution of total medical costs in the first four years after diagnosis

Under the new practice recommendations for the diagnosis of epilepsy, the costs of HRU were re-estimated in first year of diagnosis after adding one outpatient visit to paediatric neurology. The new total direct costs of epilepsy per child over the first 8 years of follow-up after the diagnosis of epilepsy for the incident group are shown in Table 5-8. The mean cost per child was higher (£1,153 (SD=£1,808); range £384-16,659) in the first year of diagnosis compared to a mean of £458 (SD=£1,633), range £368-587) in further follow-up years principally due to the costs of referrals to paediatric neurologists.

Each year the largest contribution to the total health care cost was made by the costs of hospital care followed by the costs of AEDs. Figure 5-5 illustrates the contribution of the elements of the health resource to the total direct cost per child. The hospital care costs comprised 82% of the total costs in the first year and ranged from 45% to 67% in further years, AED costs ranged from 20% to 47% and the costs of GP consultations ranged from 4% to 7%. The highest contribution of hospital care was principally the cost of inpatient admissions which ranged from 34% to 59%.

During the first 8 years after diagnosis, the mean cost of all AEDs per child increased from £118 (SD=£267) in the first year to £208 (SD=£325) in the eighth year (Figure 5-4).The increase in the annual mean costs of AEDs was due to increased costs of new AEDs, whereas the costs of old AEDs slightly decreased.

The recently published population estimates for UK by the ONS indicated that there were 11.6 million CYP younger than 16 years in mid-2010 accounting for 18% of the total UK population [28]. From this study, the estimated prevalence of epilepsy in CYP was 4.5/1000 population in 2004. If epilepsy has the same prevalence for the year 2010, there would be 51,040 CYP with epilepsy in the UK. The mean annual direct cost per child for prevalent cases of epilepsy was estimated at £458 (SD=£1,633). This would suggest that, from the perspective of the healthcare provider, the total direct cost of treating CYP with epilepsy was £23,019,040 in the year 2010.

Table 5-8: The mean direct cost of epilepsy per child per annum for the incident group (n=798)

Cost category	Year1 No of CYP=798		Year 2 No of CYP=754		Year 3 No of CYP=653		Year 4 No of CYP=530	
	No of events	Mean cost (SD) range	No of events	Mean cost (SD) range	No of events	Mean cost (SD) range	No of events	Mean cost (SD) range
GP consultations	2041	81(77); 30-900	711	28 (46); 0-360	549	24 (43);0-330	408	22 (41); 0-330
Hospital care								
Outpatient								
Paediatric neurology	798	354 (0); 354-354	0	0	0	0	0	0
Other outpatient	354	45 (143);0-1515	191	25 (94); 0-808	110	17 (76); 0-1212	123	23 (93);0-1111
Inpatient	127	492 (1713); 0-15455	56	230 (1223);0-21637	50	241 (1487); 0-24728	32	187 (1423);0-24728
Emergency	101	32 (207); 0-2840	61	11 (76); 0-1136	57	17 (102); 0-1244	28	11 (74);0-676
Diagnostic imaging								
CT	20	2 (16); 0-190	0	0	1	0.2 (4);0-95	2	0.4 (6); 0-95
EEG	136	16 (41);0-279	24	3 (17); 0-186	28	4 (21); 0-186	19	3 (18); 0-186
MRI	66	14 (53); 0-489	26	6 (33); 0-326	10	2 (20); 0-326	23	7 (49); 0-815
Blood chemistry tests	43	0.1 (0.3); 0-2	41	0.1 (0.3) 0-5	20	0.1 (0.2); 0-2	20	0.1 (0.2); 1-2
Cost of AEDs								
Old AEDs	7574	94 (250); 0-6369	7026	108 (168); 0-2250	5606	110 (250); 0-4720	4352	107 (202); 0-2383
New AEDs	1514	24 (84); 0-1004	2457	50 (132); 0-1056	2353	61 (158); 0-1621	2199	70 (166); 0-1509
Total cost of hospital care per child		955 (1776); 0-16377		276 (1254); 0-22142		281 (1503); 0-24930		232 (1465); 0-25132
Total cost of drugs per child		118 (267); 0-6369		157 (228); 0-2971		170 (297); 0-4720		177 (274); 0-2383
Total direct cost per child		1153 (1808); 384-16659		461 (1281); 2-22154		475 (1548);2-24946		430 (1529); 3-25215
Total cost per year		637,868		347,584		310,722		228,353

All estimated costs were rounded to nearest whole UK£.

Table 5-8: Continued

Cost category	Year 5 No of CYP=400		Year 6 No of CYP=319		Year 7 No of CYP=223		Year 8 No of CYP=175	
	No of events	Mean cost(SD) range	No of events	Mean cost (SD) range	No of events	Mean cost (SD) range	No of events	Mean cost (SD) range
GP appointments	292	21 (32); 0-180	200	18 (34); 0-240	138	17 (42); 0-480	137	21 (48); 0-480
Hospital care episodes								
Outpatient	83	21 (73); 0-505	42	13 (59); 0-606	42	19 (69); 0-606	24	16 (50); 0-303
Inpatient	45	349 (2848);0-40183	15	136 (838); 0-9273	12	166 (1085);0-12364	9	141 (727); 0-6182
Emergency admission	35	13 (76); 0-568	26	13 (88); 0-1136	33	20 (108); 0-1136	25	16 (79); 0-568
Diagnostic imaging								
CT	2	0.5 (7); 0-95	0	0	0	0	0	0
EEG	17	4 (18); 0-93	6	2 (15);0-186	10	4 (23); 0-186	4	2 (12); 0-93
MRI	7	3 (23);0-326	9	5 (32);0-326	7	5 (28); 0-163	5	5 (27); 0-163
Blood chemistry tests	9	0.1(0.2); 0-1	8	0.1 (0.2);0-2	3	0.1(0.1); 0-1	4	0.1 (0.2); 1-2
Cost of AEDs								
Old AEDs	3094	102 (175); 0-2020	2303	93 (159);0-2022	1608	87 (100); 0-753	1238	92 (119); 0-724
New AEDs	1903	71 (176); 0-1493	1626	82 (203);0-1959	1110	108(258); 0-1959	893	117(298); 0-2533
Total cost of hospital care per child		393 (2874);0-43275		177(885); 0-9459		217(1115); 0-12364		184 (754); 0-6750
Total cost of drugs per child		173 (253); 0-2187		174 (260); 0-2173		194 (269); 0-1959		208 (325); 0-2533
Total direct cost per child	--	587(2914); (2-41192)		368 (949);1-9842		429 (1160);3-12487		413 (863); 1-7003
Total cost per year	--	259,227		113,495		104,485		73,801

All estimated costs were rounded to nearest whole UK£.

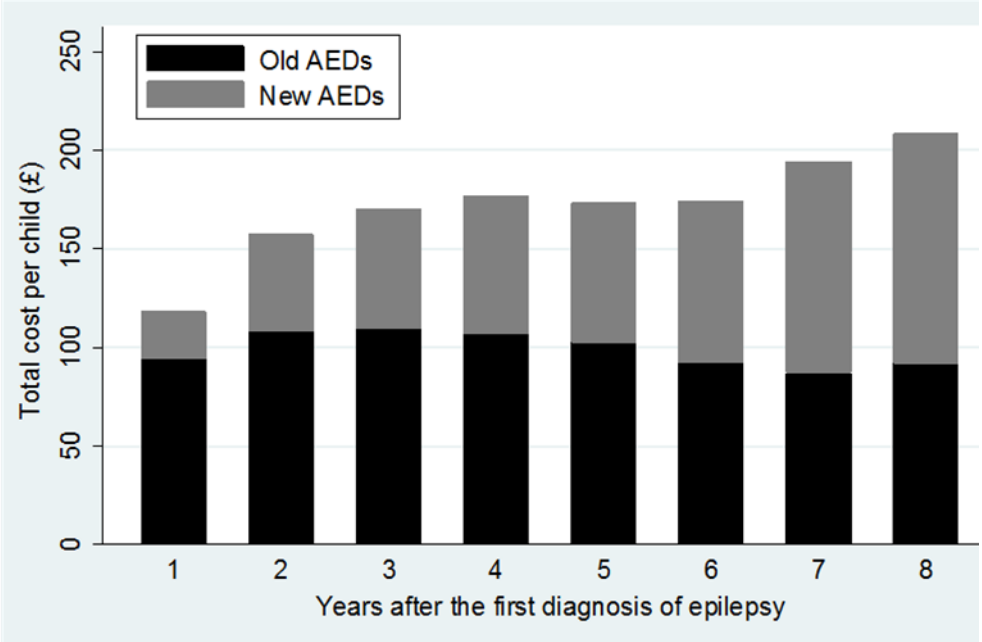


Figure 5-4: Total annual costs of old and new AEDs per child (incident group)

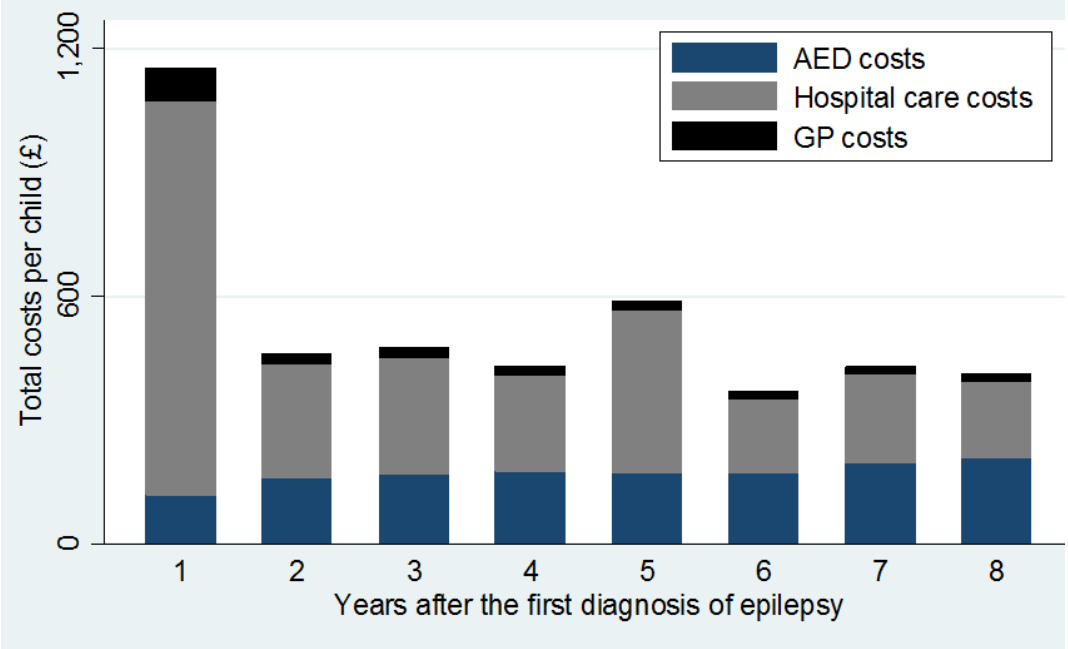


Figure 5-5: Total annual direct costs per child for newly diagnosed CYP with epilepsy (incident group) after re-estimating the cost of the first year

Table 5-9 shows the variation of the costs of HRU by children's demographics and adherence to AEDs. Compared to that of female children, the mean total costs per child were non-significantly higher in male children during the first four years of follow-up except for the first year (bootstrapped t-test, annual p values are shown in Table 5-9)

The mean total direct costs per child were higher in younger age groups (<2 years) of CYP and tended to be lower in older age groups (>12 years) during the first four years after diagnosis. The variation of the total direct costs was significantly different between age groups (ANOVA test, annual p values are shown in Table 5-9). The total direct costs did not significantly vary by Townsend deprivation quintiles (ANOVA test, annual p values are shown in Table 5-9).

The association between the total direct costs and adherence to AEDs are shown in Table 5-9. The percentage of non-adherent CYP was approximately 50% in each year of the first four years of follow-up. In the first year following diagnosis, the non-adherent group consumed more hospital care resource and had higher associated hospital care costs (£1072; SD=2033) than the adherent group (864; SD=1485). However, the mean total direct cost was not significantly different for non-adherent group (bootstrapped t-test p=0.56) principally because the adherent group consumed higher drug costs. The mean total direct costs remained non- significantly different during consecutive years of follow-up.

Table 5-9: The mean of the annual total direct costs and children's demographics and adherence to AEDs

	First year (n=798)						Second year (n=754)					
	No of CYP (%)	Hospital costs (SD)	Drug costs (SD)	GP cost (SD)	Total costs (95% CI)[a]		No of CYP (%)	hospital costs (SD)	Drug costs (SD)	GP cost (SD)	Total costs (95% CI) [a]	
Sex						p						p
Male	444 (56)	1119 (2116)	113 (170)	81 (74)	1313 (1141-1546)	0.01[b]	420 (56)	318 (1450)	163 (254)	26 (45)	507 (399-712)	0.36[b]
Female	354 (44)	748 (1194)	125 (353)	80 (79)	952 (840-1124)		334 (44)	214 (857)	151 (189)	30 (48)	395 (324-528)	
Age time-varying (years)												
< 2	192 (24)	1266 (2279)	136 (473)	102 (99)	1504 (1209-1877)	0.01[c]	102 (14)	823 (2683)	149 (229)	35 (51)	1007 (619-1705)	0.01[c]
2-6	255 (32)	997 (1906)	92 (99)	79 (68)	1168 (962-1457)		248 (32)	298 (1060)	150 (230)	31 (55)	478 (371-659)	
7-12	303 (38)	789 (1355)	125 (183)	69 (53)	983 (846-1153)		321 (43)	112 (599)	161 (236)	22 (36)	296 (236-383)	
>12	48 (6)	525 (473)	146 (166)	76 (58)	747 (634-920)		83 (11)	134 (580)	124 (145)	32 (44)	290 (179-438)	
Townsend quintiles												
1	147 (18)	811 (1387)	119 (112)	85 (79)	1015 (819-1291)	0.67[c]	143 (18)	184 (676)	168 (214)	27 (45)	379 (275-513)	0.29[c]
2	123 (15)	1258 (2275)	101 (97)	76 (56)	1435 (1062-1887)		113 (15)	410 (1456)	134 (117)	26 (46)	577 (352-911)	
3	168 (21)	949 (1598)	150 (511)	69 (54)	1167 (942-1447)		157 (21)	231(860)	156 (211)	31 (45)	419 (303-619)	
4	170 (21)	612 (1849)	117 (219)	86 (83)	1170 (920-1490)		159 (21)	268 (1086)	180 (291)	29 (47)	477 (338-686)	
5	135 (17)	548 (1882)	106 (117)	86 (100)	1095 (846-1485)		129 (17)	222 (876)	155 (271)	28 (50)	405 (255-562)	
Missing	55 (7)	388 (1406)	91 (65)	80 (78)	913 (625-1424)		53 (7)	467 (3038)	126 (140)	22 (37)	615 (169-1869)	
Adherence groups (MPR)												
Adherent (MPR≥0.8)	317 (40)	864 (1485)	183 (401)	80 (66)	1127 (974-1322)	0.56[b]	377 (50)	252 (1132)	222 (284)	31 (49)	512 (425-641)	0.21[b]
Non-adherent (MPR<0.8)	411 (1)	1072 (2033)	88 (93)	86 (88)	1247 (1069-1474)		355 (47)	260 (1378)	99 (123)	26 (44)	388 (288-636)	
Non-treated (MPR=0)	70 (9)	676 (1259)	0	48 (30)	724		22 (3)	738 (2129)	0	22 (30)	760	

a: bootstrapped bias corrected and accelerated confidence intervals b: boot-strapped t-test p-value c: boot-strapped one way ANOVA p-value

Table 5-9: continued

	Third year (n=653)						Fourth year (n=530)					
	No of CYP (%)	Hospital costs (SD)	Drug costs (SD)	GP cost (SD)	Total costs (95% CI)[a]		No of CYP (%)	hospital costs (SD)	Drug costs (SD)	GP cost (SD)	Total costs (SD) (95% CI)[a]	
Sex						P						P
Male	363 (55)	323 (1859)	174 (331)	24 (42)	521 (375-794)	0.64[b]	292 (55)	241 (1593)	177 (255)	22 (39)	440 (329-766)	0.18[b]
Female	290 (45)	225 (923)	165 (250)	25 (43)	415 (324-567)		238 (45)	215 (1296)	176 (297)	23 (44)	414 (295-721)	
Age time-varying (years)												
< 2	0	0	0	0	0		0	0	0	0	0	
2-6	259 (40)	635 (1906)	202 (384)	25 (50)	743 (508-1083)	0.02[c]	175 (33)	311 (1079)	229 (345)	28 (51)	697 (428-1173)	0.05[c]
7-12	306 (47)	133 (688)	150 (217)	24 (38)	306 (244-407)		264 (50)	143 (812)	158 (220)	18 (33)	318 (236-449)	
>12	88 (13)	96 (470)	150 (231)	24 (33)	270 (170-373)		91 (17)	77 (475)	131 (248)	25 (40)	233 (144-382)	
Townsend deprivation score												
1	119 (18)	106 (642)	198 (465)	27 (41)	329 (215-503)	0.71[c]	91 (17)	224 (805)	135 (145)	11 (34)	376 (234-571)	0.93[c]
2	102 (15)	246 (1001)	109 (134)	24 (45)	397 (233-645)		82 (15)	82 (419)	167 (215)	25 (45)	275 (195-415)	
3	133 (21)	200 (880)	182 (244)	19 (35)	411 (256-585)		113 (22)	297 (1576)	202 (327)	19 (33)	518 (290-945)	
4	143 (22)	385 (1828)	194 (326)	30 (55)	608 (394-1030)		115 (22)	164 (1024)	216 (339)	27 (54)	407 (265-688)	
5	111 (17)	316 (1173)	144 (190)	26 (38)	486 (293-708)		93 (18)	130 (594)	144 (202)	25 (39)	299 (190-448)	
Missing	45 (7)	388 (1406)	157 (254)	17 (28)	808 (203-2400)		36 (7)	828 (4198)	186 (368)	16 (27)	1030 (239-3070)	
Adherence groups (MPR)												
Adherent (MPR≥0.8)	312 (48)	317 (1467)	251 (364)	28 (48)	590 (458-814)	0.13[a]	256 (48)	204 (1113)	280 (350)	25 (44)	512 (410-760)	0.45[b]
Non-adherent (MPR<0.8)	316 (48)	263 (1621)	104 (197)	21 (38)	387 (260-691)		254 (48)	255(1786)	86 (112)	20 (40)	362 (218-755)	
Non-treated (MPR=0)	25 (4)	52 (66)	0	23 (20)	72		20 (4)	226 (815)	0	20 (22)	249	

a: bootstrapped bias corrected and accelerated confidence intervals b: boot-strapped t-test p-value c: boot-strapped one way ANOVA p-value

5.6.5 The total annual direct costs of epilepsy per child for the prevalent group

The total direct costs of epilepsy per child over the first 4 years of follow-up since the first recoding of epilepsy in THIN for the prevalent group are shown in Table 5-10. The mean direct cost per child slightly changed over the 4 years of follow-up and ranged from £405(SD 817) in the first year to £368 (SD=£772) in the fourth year.

The mean costs of all AEDs slightly changed over the 4 years with the cost of old AEDs almost unchanged and remained of higher mean cost than that of new AEDs (Figure 5-6). Each year the largest contribution to the total health care cost was made by the costs of hospital care and AEDs. Figure 5-7 illustrates the contribution of the elements of resources to the total direct cost per child. The hospital care costs ranged from 42% to 58% of the total direct cost per year, AED costs ranged from 32% to 50% and the costs of GP consultations ranged from 6% to 15%.

Table 5-10: The mean direct cost of epilepsy per child per annum for the prevalent group (n=269)

Cost category	Year1 No of CYP=269		Year 2 No of CYP=222		Year 3 No of CYP=192		Year4 No of CYP=166	
	No of events	Mean cost(SD) range	No of events	Mean cost (SD) range	No of events	Mean cost (SD) range	No of events	Mean cost (SD) range
GP consultations	596	63 (75); 0-540	223	30 (58); 0-450	141	22 (40); 0-270	157	29 (49); 0-330
Hospital care episodes								
Paediatric neurology	0	0	0	0	3	6 (57); 0-708	0	0
Other outpatient	39	15 (60); 0-404	23	10(45); 0-404	23	12 (50); 0-404	12	8 (35); 0-202
Inpatient	20	150(765); 0-6182	19	265(1236); 0-9273	9	145(727); 0-6182	7	130 (710); 0-6182
Emergency admission	13	14 (98); 0-1136	12	12 (77);0-568	8	8 (60); 0-568	20	12 (73); 0-568
Diagnostic imaging								
CT	2	0.7 (8); 0-95	3	1 (11); 0-95	4	2 (14); 0-95	1	0.6 (7); 0-95
EEG	21	7 (28); 0-186	3	1(11); 0-93	7	3(16); 0-93	5	3 (19); 0-186
MRI	6	4 (34); 0-489	7	5 (33); 0-326	1	0.9 (12); 0-163	1	1 (13); 0-163
Blood chemistry tests	5	0.1 (0.2); 1-2	2	0.1(0.1); 0-1	2	0.1(0.1); 0-1	4	0.1(0.1); 0-1
Cost of AEDs								
Old AEDs	2360	97 (161); 0-1549	2215	110 (135); 0-862	1790	109 (151); 0-1225	1583	108 (129); 0-770
New AEDs	809	55 (187); 0-1738	1025	72 (203); 0-2087	905	69 (156); 0-1118	907	76 (144); 0-744
Total cost of hospital care per child		190 (772); 0-6182		296 (1249); 0-9374		176 (749); 0-6586		156 (723); 0-6275
Total cost of AEDs per child		152 (247); 0-1762		182 (238); 0-2111		178 (225); 0-1858		184 (200); 0-1050
Total cost per child	--	405 (817); 1-6207		508 (1281); 5-9625		376 (824); 5-6968		368 (772); 6- 6366
Total cost per year	--	113,035		110,661		70,107		58,705

All estimated costs were rounded to nearest whole UK£.

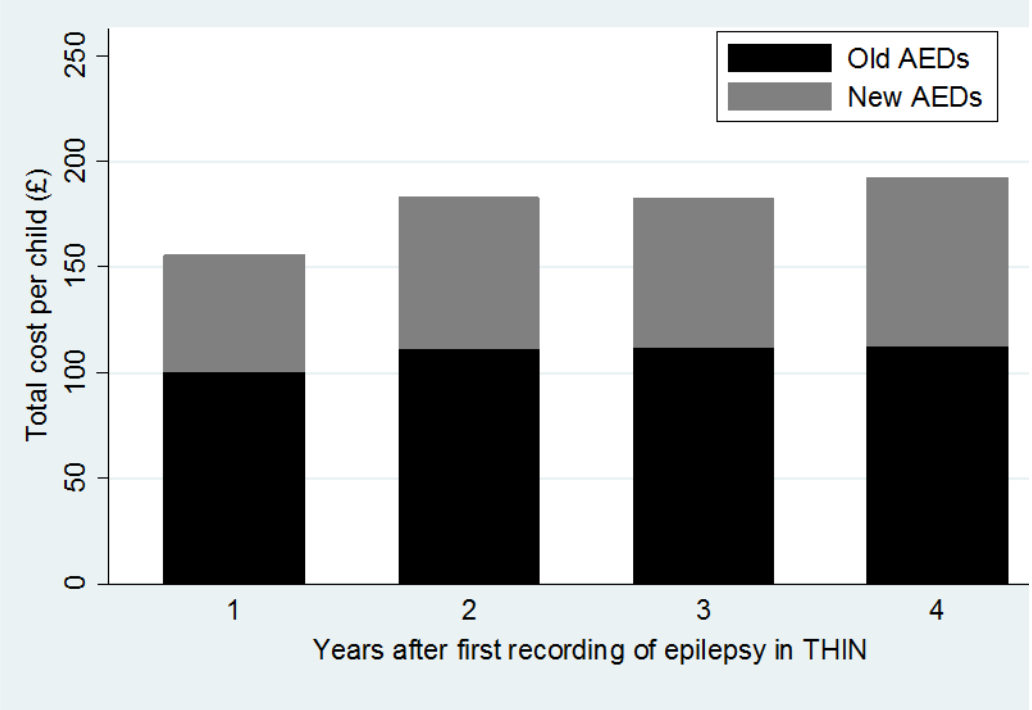


Figure 5-6: Total costs of old and new AEDs per child up to 4 years (prevalent group)

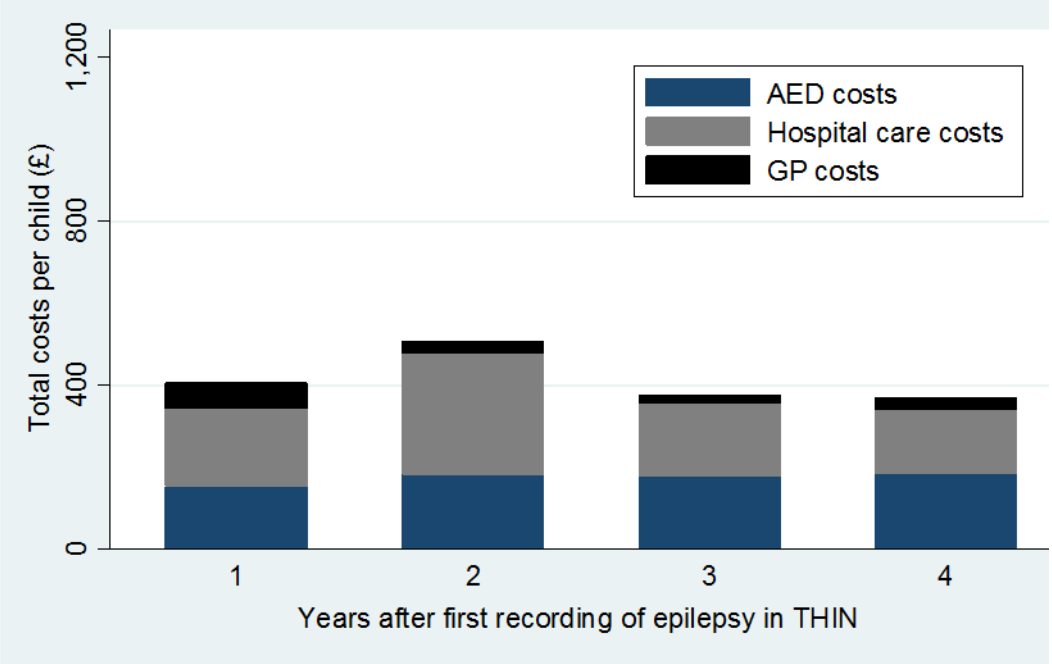


Figure 5-7: Total annual direct medical costs per child for CYP with established epilepsy (prevalent group)

5.7 Discussion

5.7.1 The of cost health resource utilisation by the CYP

The direct cost of treating CYP with epilepsy was examined based on the recorded HRU in THIN primary care database. To examine whether there was any difference between the cost of epilepsy in newly diagnosed CYP and those with established epilepsy, the data were reported separately for the incident and prevalent groups of the study cohort. There was a wide variation within the overall direct cost of treating epilepsy between individual children based on the variety of investigations required, hospital care and drug treatment choices. For example, the right-skewed distribution of the total direct costs, in the first four years after epilepsy diagnosis, reflects that a few CYP consumed high levels of health resources that increased the mean annual costs of the whole cohort.

The data also showed that CYP with newly diagnosed epilepsy consumed higher health care resources and consequently higher associated mean cost in the first year, compared to consecutive years of follow-up or that consumed by the prevalent group. Higher total cost of healthcare in the first year was expected because of investigations and specialists' consultations. The variation in the costs of resource use between individual children may reflect the heterogenic nature of epilepsy in terms of clinical severity and response to treatment. As each year, some CYP may have had uncontrolled (drug-resistant) seizures which may lead to consumption of more hospital care services and/or higher drug costs. It was not possible to assess the cost by epilepsy subtypes as they are not well-recorded in THIN for the majority of the study cohort. The association between the cost and severity of seizures was reported by Jacoby et al. (1998) who conducted a large cross-sectional prevalence survey study in the UK on a total of 789 people with epilepsy and included 93 CYP <16 years [336]. Data were obtained from GP records and from patient questionnaires to investigate the cost of HRU in the previous 12 months. The authors reported that patients with more frequent seizures consumed more than one-half of total combined costs of direct and indirect care for epilepsy.

The present findings revealed that the highest contribution to the direct costs of epilepsy per year was that of hospital care where the cost of inpatient admissions ranged from 34% to 59%, followed by AED costs ranged (20%-47%), GP consultations (4% -7%) and outpatient attendances (4-5%). The same pattern was obtained for CYP with established epilepsy (prevalent group).

To date, few studies have been examined the cost of treating epilepsy in the UK. The differences in study design, data collection, definition of epilepsy, and including aggregated adults data in the cohort have made it difficult to compare the study findings. For example, previous published data on the cost of epilepsy in the UK were performed using prospective longitudinal cohort study [67], survey design [336] and local data confined to certain geographical area [337]. Despite these differences, the contribution of HRU to the mean direct cost of epilepsy was consistent with the previous studies of adult and children with epilepsy in the UK. Similar to this analysis, Cockerell et al. (1994) estimated higher cost in the first year of prospective follow-up of 602 patients (including 25% under 15 years) from primary care settings [67]. The estimated cost of hospital inpatient admissions in 1-year period that was 59% of the total medical costs followed by AEDs (20%), outpatient attendances (13%) and GP consultations (6%).

Jacoby et al. (1998) estimated similar contribution of HRU to the total direct cost. The estimated cost of inpatient hospital admissions was 58%, followed by AEDs (23%), outpatient attendances (7%) and GP consultations (2%) in 12 months period [336].

The percentage of AEDs cost per year was higher in this study (ranged from £118 to £208) than estimated in previous stdies which may be attributed to the introduction of more expensive new AEDs especially in later follow-up years. Jacoby et al. (1998) reported a mean cost of £161 of AEDs per patient per year [336].

The comparison of the direct costs of treating epilepsy to different countries is difficult because of monetary differences and the nature of health care systems. However, a review of European studies to estimate the costs of treating

epilepsy was conducted by Pugliatti et al. (2007) [65]. The review included studies which had different study designs, age ranges and health care settings. Some of these studies have conducted on children [345] and others included children as a part of the cohort [346-348]. The estimated costs of health resource use were converted to Euro and were inflated to the year 2004. Of these studies, an Italian study reported higher rates of hospitalisations and investigations than the present study [345]. The authors identified a total of 189 Italian children and adolescents with epilepsy from secondary care settings who were followed prospectively for 12 months. The authors showed that the annual HRU such as investigations (mean EEG ranged 1.8-3.5) and hospital admissions were higher in newly diagnosed children with epilepsy and children with drug-resistant epilepsy. The annual cost per patient was estimated at €1635 which corresponds to £1349.

5.7.2 The costs of HRU and CYP's demographics and adherence to AEDs

The total direct costs per child revealed higher but no significant difference between males and females. The possible principal reason is that there is no clinical epilepsy subtype difference that affects males and females and hence the same health resource was consumed. The direct costs per child were significantly different among age groups of CYP and tended to be lower in older age groups (6-12 and >12 years) which may be attributed to more frequent hospitalisations and visits to the emergency departments in young ages. This probably because the age of onset of some drug-resistant epilepsy subtypes (e.g. West syndrome and Dravet's syndrome) which manifest more frequent seizures is at infancy and early childhood [16]. Similar findings were reported by Morgan and Kerr (2004) who estimated the costs of hospital care using a local database of 3892 patients with epilepsy in Cardiff and the Vale of Glamorgan-UK [337]. The authors estimated higher inpatient costs in children younger than 5 years than the other age groups. No statistics were presented.

The association between the mean costs of treating epilepsy and adherence showed non-adherence was associated with higher hospital care utilisation in the first year which led to a higher value of the mean total cost per child. This was similar to an earlier study by Faught et al. (2009) who reported that non-

adherence to AEDs was associated with higher incidence of inpatient admissions, total inpatient days and emergency room visits and consequent higher costs in 33,658 adult populations with epilepsy [170]. Similar findings were reported by Davis et al. (2008) in a large population study which examined AED non-adherence in adult population in the USA. The authors reported that non-adherence was associated with higher inpatient and ED services and costs [156]. Both studies analysed databases and adherence was measured using the method of MPR. However, the mean total costs did not significantly vary between adherent and non-adherent groups which reflect that higher drug costs consumed by the adherent group outweighed lower hospital care cost.

From the second year after diagnosis, adherent and non-adherent groups consumed similar mean hospital care costs. It is difficult to draw an explanation as because some of hospital care may not have related to epilepsy in both groups; however, this may suggest that non-adherent group may have had less severe epilepsy subtypes or they achieved remission of seizures.

5.7.3 The health resource utilisation recorded in THIN

Although the distribution of direct cost in this analysis was similar to previous studies, the recorded HRU were slightly different. For example, CYP of the incident group had a mean of 2.6 GP consultations and 93% of CYP were treated by AEDs (mean=11.6 prescriptions) in the first year. These findings were similar to that reported by Jacoby et al. (1998) who reported that 41% of CYP had epilepsy-related consultations with GP (mean=2.9) and that 87% of CYP were treated by AEDs [336].

However, the recorded hospital care services in THIN were lower than that reported in previous studies in the UK. This probably because of the completeness and accuracy of recording hospital events in THIN were not much high. Another cause was the different method of data collection and study design. For instance, during the first year of diagnosis, 14% of CYP had outpatient attendances (mean=0.46), 11% admitted to hospital (mean 0.16), 4%

had emergency visits, 15% had EEG, 7% had MRI and 2% had CT scans (mean=0.33 for all diagnostic imaging).

Compared to the present findings, Cockerell et al. (1994) reported higher percentage of consumed hospital care [67]. For the prospectively followed cohort of patients, 92% of patients had initial hospital assessment as inpatients or outpatients in the first year. Jacoby et al. (1998) reported higher percentage (86%) of children attended hospital as outpatients and 18% had epilepsy-related inpatient hospital admissions [336]. However, the bulk of data were collected using patients' questionnaires which can be subjected to recall bias. Compared to the present findings, Morgan and Kerr (2004) reported higher utilisation of hospital services that were a mean of 0.6 outpatient attendances and 1.8 inpatient admissions in 1999 for 3892 patients with epilepsy [337]. However, Morgan and Kerr collected their data from secondary care settings.

Since the previous cost studies in the UK had different study designs to the present study, the HRU in present study were compared to some worldwide studies which used databases. Kurth et al. (2010) conducted a large retrospective cohort study in the USA by using insurance claim databases of 14 million persons between 2005 and 2007 to investigate HRU in patients with active epilepsy [349]. The authors identified 46,857 patient with active epilepsy included 8,671CYP under 18 years old. As compared to the present study, the authors reported a lower mean of epilepsy-related GP consultations (1.8 per year) and a lower mean of drug prescriptions for epilepsy (7.6 per year). However, the authors reported higher utilisation of hospital care that was a mean of 10.1 outpatient attendances, 0.8 emergency room admissions and 24.8 diagnostic tests and procedures per year of which 1.1 a year were related to epilepsy [15].

In a Canadian study, Jette et al. (2008) investigated the HRU over 1 year period in patients with epilepsy using three administrative databases from secondary care (inpatient, emergency and physician claim) [338]. The authors identified 1431 prevalent cases with epilepsy with a mean age of 37.3(SD=17.3) years. The authors reported the means of HRU per patient in

the year 2001 that were 1.6 GP visits, 2.5 outpatient physician visits, 0.8 neurology visits, 0.2 inpatients and 0.1 emergency room visits [338].

5.8 Strength and limitations of the present analysis

To the researcher's knowledge, this was the first study in the UK that has focused on estimating the direct costs related to epilepsy in CYP. The study group was a representative sample to CYP with epilepsy in the general population of the UK so the findings of HRU and associated cost can be generalised. This study estimated the direct costs on an incident group initially and over time and not only in the first year like some studies where the costs have been reported higher in the first year than for subsequent years.

A number of limitations have been encountered in this study. First due to the retrospective nature of data analysis, a number of assumptions have been made to estimate the cost of treating epilepsy. These assumptions were used to correct for lower recording of neurologists' appointments and categorisation of elective and non-elective hospital admissions. These assumptions included, for example, the cost of one paediatric neurology visit per child in the first year; however, it was considered reasonable based on recommendation made by NICE guideline 2004 and its update 2012 for better diagnosis of epilepsy in children. However, it is likely that actual specialists' visits were underestimated in subsequent years of diagnosis.

The costs of hospital care were estimated from the average costs per episode from the DH reference cost data 2011 as it was not possible to distinguish between epilepsy-related and non-epilepsy related hospital care. The cost of hospital care including diagnostic imaging was based on the recorded data in THIN and it was not possible to ascertain using secondary care data. However, the hospital care comprised the highest contribution to the direct cost of epilepsy as reported in previous studies.

Prospective data collection on the specialists' appointments and hospital care may be required for future analysis of the direct cost of treating epilepsy.

5.9 Conclusions

The mean direct costs of treating epilepsy in CYP were higher in the first year of diagnosis than the following years due to diagnostic process. The cost of inpatient hospital care was the major contributor to the total direct costs of epilepsy followed by the costs of AEDs. The total direct costs did not significantly vary by sociodemographic characteristics of CYP. No significant difference in the total direct costs was observed among higher adherent and less adherent groups due to higher costs of drugs themselves.

Chapter 6: Conclusions and implications for practice and policy

6.1 Summary of findings

This thesis investigated the pattern of AED use to manage epilepsy in CYP, the long-term adherence to medication, the clinical outcomes of epilepsy and health resource utilisation with associated direct costs for treating epilepsy in primary care in the UK.

The background from the literature review on epilepsy demonstrated that epilepsy is a heterogeneous set of serious neurological disorders that has a higher incidence in children than adults. About one-half of epilepsy syndromes have age of onset in CYP that have been shown to have different aetiologies and prognosis than adults. In addition, some AEDs are not approved for use in younger children less than 6 years. Epilepsy has serious adverse educational, developmental, psychosocial and vocational consequences in CYP. The negative impacts of epilepsy on physical, psychosocial functions and HRQOL of CYP were discussed. The literature review has shown that there is limited information about the patterns of prescribing AEDs and long-term adherence to AEDs, although poor medication adherence is suspected. Limited data are available about the clinical consequences of improper use of medications in CYP with epilepsy. Common methods of measuring medication adherence and possible causes of non-adherence to AEDs were described. The additional role related to parents/caregivers in medication adherence of CYP was also discussed. Considering the potential population impact of poor management of epilepsy in this age group, there was a clear rationale for exploring this further using population-level data.

This thesis identified CYP who were born on or after 1st January 1988 and diagnosed with epilepsy before the age of 18 from THIN database, to allow investigation of the profiles of four main areas; prescribing of AEDs, medication adherence, clinical outcomes and associated costs in primary care. This study estimated annual incidence rates of epilepsy ranged from 42 to

61/100,000 person-years and annual prevalence of 2-4.6/1000 CYP that were in concordance with previous population-based epidemiological studies in the UK and Europe and provided assurance that the study cohort was representative of CYP in the general population. The incidence of epilepsy was higher in the first year of life [83 /100,000 person-years (95% CI, 73-95)] and in children aged less than 5 years [54/100,000 person-years (95% CI, 51-59), p=0.05]. However, the prevalence showed increasing trend with increasing age. Relatively higher incidence of epilepsy in CYP living in areas of high socioeconomic deprivation ($p<0.01$) suggests that there is a potential link between living in areas of greater socioeconomic deprivation and development of epilepsy. However, it was not possible to determine what socioeconomic factors are related to the incidence of epilepsy. This may provide evidence to the lack of consensus in published research about the link between epilepsy and socioeconomic deprivation.

The investigation of patterns of AED prescribing showed that old AEDs, such as sodium valproate and carbamazepine, were the first-line choices in the management of epilepsy in 75% of CYP and were ever prescribed as monotherapy for 45% of CYP in this study. These two old AEDs were more frequently prescribed to CYP compared with other old AEDs and new AEDs. There was, however, an increasing trend of prescribing new AEDs, particularly lamotrigine and topiramate over the study period. The data indicate that safety warnings about the serious and irreversible visual defects of vigabatrin [350-352] influenced GP prescribing, which was reflected in the sharp decline in vigabatrin prescribing from 1997.

Employing the method of MPR, the overall and the long-term annual adherence to the prescribed AEDs showed that from 51% to 66% of CYP were issued at least 80% of their medicines over the follow-up time of each individual. Children's demographics, with the exception of age, did not significantly affect adherence to AEDs. The population mean annual adherence rate to AEDs was significantly higher (68%, p=0.03) in older children, aged 2-12 years, compared to that of infants under 2 years (65%). The fact that sociodemographic factors showed marginal association may reflect that primary care is working well to effectively monitor prescribing in all patients regardless of these factors.

Medically-attended seizures in THIN were used to investigate the clinical prognosis of epilepsy in CYP. Perhaps it was surprising to find that higher measured adherence to AEDs was associated with lower seizure control. It follows that the association between adherence to AEDs and increased seizure frequency may be due to the severity of the condition and, thus, may reflect increased children and parental motivation to adhere to medication regimens. In other words, it appears that CYP who suffered from more seizures were more likely to adhere to their prescribed medicines. However, it was not possible to distinguish CYP with possibly poor adherence who required continuous drug treatment from CYP who were truly in remission of seizures and were taken off medications.

Compared to young people, the calculated higher incidence of medically-attended seizures in infants and children less than 6 years may indicate either different severity of epilepsy subtypes in infants and young children or lower reporting of seizure events in young people. This study showed that approximately one-half of CYP can move into long-term remission of seizures for 5 years or more.

The mean direct medical costs of managing individual CYP with epilepsy were higher in the first year of diagnosis (mean £1,153, SD £1,808) than that in consecutive years (mean £458, SD £1,633) which reflect higher health care utilisation in the first year related to the diagnostic process. The estimated direct costs did not significantly vary by CYP's sociodemographic characteristics with the exception of age, where the costs were higher in infants and young children ($p=0.01$) because of more frequent hospitalisations. This may reflect that the severity and higher reported frequency of seizures in infants led to higher utilisation of hospital services which resulted in higher associated costs.

CYP who adhered to at least 80% of their prescribed medication showed lower hospital-related costs compared to CYP who adhered to less than 80%. However, the total direct costs were not significantly different among adherent and non-adherent groups ($p>0.05$) because the higher costs of drugs in the adherent group offset the higher costs of hospital care in the less adherent group.

6.2 Implications for policy

This thesis described the nature of AED prescribing in primary care and the profile of medication use in CYP with epilepsy. The choice of first-line drug treatment and the trend of prescribing AEDs for CYP may indicate that old AEDs are effective to manage childhood epilepsy syndromes. Although the prescribing of AEDs is normally initialised by specialists and followed by GPs [353], the trend of prescribing AEDs suggests that GPs were aware of the recommendations of clinical trials and consensus of specialists and experts about the management of epilepsy.

With observed increase in prevalence of epilepsy over time and regarding NICE's recommendation in 2004 that all suspected cases of epilepsy in CYP should be seen by neurologists within two weeks of first seizure attack [1], the work load impact on neurologist services should be considered. In 2008, a survey conducted by Epilepsy Action in PCTs and acute trusts across the UK revealed that only 18% of patients with epilepsy had their first neurologist's appointment within two weeks [354]. Therefore, a national plan to increase the number of paediatric neurologists should be considered in order to shorten average waiting times and improve paediatric neurology services.

Although the calculated adherence in this study does not capture the actual consumption of medicines by CYP, it reflects fair prescribing of AEDs at the population level regardless of sex, age and socioeconomic status. However, achieving long-term good adherence levels to the prescribed medicines is challenging and medication review and monitoring of adherence by GPs may assist in saving health resource. The source data enabled the thesis to capture only a small number of factors that may influence CYP's medication taking, although many other factors have been suggested [176]. The findings from this study showed that lower adherence was observed in infants and young children, then it is important to emphasise the role of parents and their responsibilities toward monitoring medication taking of their children. Self-management educational interventions have been suggested to be valuable for CYP with epilepsy and their families who feel stigmatised or excluded [355]. These

programmes should involve strategies to improve patients and parents' knowledge to understand the nature of epilepsy, treatment instructions and to reinforce the importance of adherence to medicines. Psychosocial support (e.g., improving self-efficacy) and sometimes therapeutic interventions for CYP and parents who suffer from behavioural problems such as anxiety and depression are also important for changing attitudes toward epilepsy and providing coping skills which may lead to improved seizure control. However, the long-term effects of such interventions are not known.

This study demonstrated poor recording of clinical outcomes of epilepsy in THIN. The finding that medically–attended seizures, recorded during GP consultations, were associated with higher adherence may suggest that experience of seizures potentially motivated CYP and their parents to visit their physicians and monitor their treatment. Therefore, the Department of Health should motivate GPs to regularly monitor treatment and outcomes for all patients. The current policy of Quality and Outcomes Framework (QOF) for GP incentives to improve patient care in the UK does not include CYP under 18 years in clinical indicators for epilepsy [356]. This may affect management of epilepsy and quality of care delivered to CYP.

Although limitations existed in identifying HRU, this is the first study to provide longitudinal estimates of the costs associated with treating epilepsy in CYP in the UK. This study highlighted the economic burden of epilepsy and provided new data to the scarcity of cost of illness studies in CYP with epilepsy. The study implies that the expenditure on newly diagnosed cases of epilepsy is high. However, the costs of treating epilepsy in subsequent years following diagnosis are much lower than the first year and vary slightly over the years. The cost of inpatient hospital care was the major contributor to the total direct costs of treating epilepsy which suggests that better seizure control via appropriate evidence-based prescribing and adherence to medication may reduce the costs of epilepsy. High adherence rates to prescribed medicines have been associated with lower HRU and associated costs in other chronic diseases such as asthma [357] and diabetes [358].

Using data in THIN, the total direct cost of treating children younger than 16 years was suggested to be £23,019,040 in the year 2010. The annual cost per child is (£458 SD 1,633) in this study is lower than that reported for children and adults with type 1 diabetes (£1,323 per patient) and type 2 diabetes (£1,080 per patient) in the UK for the year 2007 using THIN [359]. The NHS estimates for asthma have reported the overall direct costs of treating all people with asthma in the UK in 2004; however, it did not include cost per patient or separate data for children [360].

6.3 Implications for practice

The pattern of AED use in this study supports the current evidence from clinical trials which have recommended old AEDs for the first-line treatment of epilepsy provided that they are tolerated by CYP. This was indicated by the more frequent prescribing of old AEDs over the study period, particularly sodium valproate and carbamazepine. However, the straight rise in prescribing of new AEDs suggests that they were tried as add-on therapies and to a lesser extent as alternatives to old AEDs. The trend of combining AEDs showed that monotherapy is favoured and effective in managing epilepsy in the majority of CYP.

There was a rapid increase in prescribing of lamotrigine which may suggest that this drug shows favoured efficacy and/or tolerability as an adjunctive to old AEDs. Its use as a monotherapy was not high in this study. Two other observational studies conducted using children and adults' primary care data in the UK including one in 2012 support the current findings [118, 289].

Although GPs record data and attach notes on what they think is important for the management of their patients, GPs need to consider better recording of initial and ongoing individual-specific information such as diagnostic subtypes of epilepsy and dose instructions especially those recommended in secondary care settings. More complete recording of longitudinal data for monitoring and prognosis of epilepsy in individual children, such as seizure frequency and remission periods should also be considered in general practice. These data will also help policy makers as it will enable researchers to assess the association

between the current plan of management and the clinical outcomes and prognosis of epilepsy in CYP.

This thesis demonstrated that adherence to medications in CYP with epilepsy is suboptimal. However, being adherent or non-adherent to prescribed medication is not a phenotype, but rather a dynamic process that may deteriorate over time and potential remission of seizures must also be taken into consideration. In chronic diseases like epilepsy, the motivation toward medication is likely to decrease, particularly in asymptomatic periods, and then it is the role GPs and clinicians to assess and monitor symptoms, outcomes and medication regimens with CYP and their parents over time. In the case of CYP who demonstrate low adherence to medication, physicians need to invite CYP and their parents for medication review to assess whether they have had seizures for which they did not seek medical care, and if so, invest time to talk about the necessity of long-term therapy and address any medication-related factors that may cause low adherence. Practitioners need to be encouraged to discuss whether those CYP chose not to adhere to their medicines or they could be managed on lower doses or should be taken off medicines because their conditions are well-controlled.

6.4 Implications for pharmacists

Pharmacists represent the junction between prescribers and patients so play an important role in improving medication use processes (prescribing, dispensing and advice on administration) and thereby clinical outcomes [361]. By virtue of their expertise, pharmacists may exhibit a key role by distributing knowledge about epilepsy and the proper use of AEDs through informal contacts with CYP and their parents during dispensing of medicines [362]. There should be increased awareness among pharmacists that adherence to AEDs is an issue particularly in infants and young children under 5 years and that medication adherence was found to be negatively associated with long duration of treatment. Pharmacists may then contribute to improving medication use by checking that parents/caregivers understand prescription instructions and by counselling about the necessity of long-term and persistent use of AEDs for better outcomes.

In this study, multiple AEDs (polytherapy) were prescribed to CYP who experienced an increased level of seizure attacks. Pharmacists have an important role to play in this group of CYP. Further advice and support on medication can be provided during community based medicine management services such as the UK community pharmacy Medicine Use Review service [363] through reviewing appropriateness of AED prescribing. Pharmacists should work in collaboration with GPs to assist in preventing AED-related problems, improving CYP safety and increasing adherence to drugs [364]. A previous study investigated the association between pharmacist-managed AED therapy and the rate of hospitalisation of Medicare patients identified from 950 hospitals in the US [365]. The authors reported that death rates were 121% higher (OR=1.55, 95% CI 1.10–2.19, p=0.01) in hospitals without pharmacist managed AED therapy.

Pharmacists may choose to identity and follow-up CYP who do not present themselves at the pharmacy to collect their prescribed medications. Pharmacists may specifically target these CYP and invite them for a medication review in order to check whether they have remission of seizures. Pharmacists can also check whether these CYP are withdrawn from their medication by prescribers.

The cost of AEDs is the second largest cost contributing to the total medical costs of epilepsy after the cost of hospital care. Pharmacists can assist in saving HRU by identifying trend of prescribing of AEDs for groups of CYP with epilepsy and giving advices about the unnecessary use of medicines. Pharmacists can then report to prescribers their findings and recommending changes to AED prescribing and thus aid in lowering complexity of AED regimens and improving clinical outcomes of epilepsy.

6.5 Implications for future research

The findings of this study contribute to the validation of using the routinely collected general practice THIN database to explore the incidence and prevalence of epilepsy in CYP and the prescribing patterns of AEDs at the population level in the UK. Prescription records within THIN are considered to reflect the real-life clinical practice of managing epilepsy in primary care.

Although this study presented an estimate of the long-term medication adherence of CYP that was comparable with previous findings, the methodology for adherence depended on the frequency of issued prescriptions and not the actual consumption of medicines. The size of the effect of the examined factors within THIN on adherence of CYP was small. In fact, THIN data was not able to capture many reasons for non-adherence. Therefore, qualitative or other patient level research is needed to explain the origin of variation in adherence and to consider the possible effects of other factors on adherence such as child-physicians communication and CYP and parents' beliefs about AED treatment.

The estimated long-term seizure outcomes according to what was recorded in general practices demonstrated variable degree of seizure remission among CYP. Further research is needed to assess routine updates from physicians and parents on seizure frequency and severity and to also address the association between adherence and clinical outcomes of epilepsy.

The study estimated the direct costs associated with health resource utilisation in primary care and what was recorded in general practices as referrals to secondary care. It provides baseline data for further economic evaluations on the burden of epilepsy in CYP. Since the care of CYP with epilepsy is a collaboration between primary and secondary care settings, further research is needed to estimate epilepsy-related health resource utilisation in secondary care for CYP. This will enable a more comprehensive view of the associated costs of treating epilepsy to be available to health policy makers. The methods for estimating adherence and costs used in this thesis could also be valuable in assessing the costs of other important chronic conditions in children and adult.

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Appendices

Appendix 1: International Classification of Epilepsies and Epileptic Syndromes (1989)

1. **Localization-related (focal, local, partial) epilepsies and syndromes**
1.1. Idiopathic with age-related onset
A. Benign childhood epilepsy with centrotemporal spikes
B. Childhood epilepsy with occipital paroxysms

1.2. Symptomatic
A. Chronic progressive epilepsia partialis continua of childhood
B. Syndromes characterized by seizures with specific modes of precipitation
C. Temporal lobe epilepsies
D. Frontal lobe epilepsies
E. Parietal lobe epilepsies
F. Occipital lobe epilepsies

1.3 Cryptogenic

2. **Generalized epilepsies and syndromes**
2.1. Idiopathic, with age-related onset (listed in order of age)
A. Benign neonatal familial convulsions
B. Benign neonatal convulsions
C. Benign myoclonic epilepsy in infancy
D. Childhood absence epilepsy (pyknolepsy)
E. Juvenile absence epilepsy
F. Juvenile myoclonic epilepsy (impulsive petit mal)
G. Epilepsy with grand mal seizures on awakening
H. Other generalized idiopathic epilepsies not defined above
I. Epilepsies with seizures precipitated by specific modes of activation

2.2. Idiopathic and/or symptomatic (listed in order of age)
A. West syndrome (infantile spasms)
B. Lennox-Gastaut syndrome
C. Epilepsy with myoclonic-astatic seizures
D. Epilepsy with myoclonic absences

2.3. Symptomatic
A. Nonspecific aetiology
a. Early myoclonic encephalopathy
b. Early infantile epileptic encephalopathy with suppression burst
c. Other symptomatic generalized epilepsies not defined above
B. Specific etiology
a. Epileptic seizures may complicate many disease states

3. **Epilepsies and syndromes undetermined as to whether they are focal or generalized**
3.1. With both generalized and focal seizures
A. Neonatal seizures
B. Severe myoclonic epilepsy in infancy

C. Epilepsy with continuous spike waves during slow-wave sleep
D. Acquired epileptic aphasia (Landau-Kleffner syndrome)
E. Other undetermined epilepsies not defined above

3.2. Without unequivocal generalized or focal features
4. Special syndromes
4.1. Situation-related seizures
A. Febrile convulsions
B. Isolated, apparently unprovoked epileptic events
C. Seizures related to other identifiable situations such as stress, hormonal changes, drugs, alcohol, or sleep deprivation

Appendix 2: International Classification of Epileptic Seizures (1981)

I. Focal seizures (previously known as partial or local seizures)
  A. Simple focal seizures
    1. With motor signs
      a. Focal motor without march
      b. Focal motor with march (Jacksonian)
      c. Versive
      d. Postural
      e. Phonatory
    2. With somatosensory or special-sensory symptoms
      a. Somatosensory
      b. Visual
      c. Auditory
      d. Olfactory
      e. Gustatory
      f. Vertiginous
    3. With autonomic symptoms or signs
    4. With psychic symptoms
      a. Dysphasia
      b. Dysmnesic
      c. Cognitive
      d. Affective
      e. Illusions
      f. Structured hallucinations
  B. Complex focal seizures
    1. Simple focal seizures at onset, followed by impairment of consciousness
      a. With simple focal features
      b. With automatisms
    2. With impairment of consciousness at onset
      a. With impairment of consciousness only
      b. With automatisms
  C. Focal seizures evolving to secondarily generalized seizures
II. Generalized seizures
  A. Absence seizures
    1. Typical absence seizures
      a. Impairment of consciousness only
      b. With mild clonic components
      c. With atonic components
      d. With tonic components
      f. With autonomic components
    2. Atypical absence seizures
  B. Myoclonic seizures
  C. Clonic seizures
  D. Tonic seizures
  E. Tonic-clonic seizures
  F. Atonic seizures

Appendix 3: Epilepsies typical of childhood [7, 18]

Type	Seizures type	Age at onset	Treatment
Benign Myoclonic Epilepsy in Infancy (BMEI	Brief bursts of generalized myoclonic seizures	6 months -2 years	Easily controlled by appropriate treatment. Sodium valproate is the drug of choice
Dravet Syndrome (Severe Myoclonic Epilepsy in Infancy)	Prolonged tonic-clonic seizures. Myoclonic jerks appear secondary	first year of life	Very resistant to AEDs. Sodium valproate and the benzodiazepines are the most effective drugs
West Syndrome (Infantile Spasms)	Characteristic triad: infantile spasms, arrest of psychomotor development, and hypsarhythmia	4 -7 months	Steroids and vigabatrin are the first-line treatment. Sodium valproate, nitrazepam, pyridoxine, zonisamide, lamotrigine and topiramate are alternative treatment
Epilepsy with Myoclonic-Astatic Seizures	Generalised tonic-clonic seizures and atypical absences with clonic and tonic components	7 months - 6 years.	Sodium valproate is the drug of first choice. ethosuximide, benzodiazepines and acetazolamide are alternatives.
Lennox-Gastaut Syndrome	Multiple include: brief tonic, atonic, myoclonic and atypical absence seizures.	1 - 7 years	Resistant to therapy. Sodium valproate combined with benzodiazepine is effective. Felbamate serves as adjunctive therapy.
Childhood Absence Epilepsy (Petit mal, Pyknolepsy)	Very frequent typical absence seizures	4 -10 years	Sodium valproate is the drug of first choice. Ethosuxamide is the second choice.
Epilepsy with Myoclonic Absences	Absences seizures accompanied by severe bilateral rhythmical myoclonic jerks.	1 - 12 years	Combination of Sodium valproate and ethosuxamide at high doses

Appendix 3: Continued

Type	Seizure character	Age at onset	Treatment
Juvenile Absence Epilepsy	The absences are more severe than in pyknolepsy associated with frequent generalized tonic-clonic seizures	9-13 years	Combination of Sodium valproate, ethosuxamide and lamotrigine. Recently, levetricetam and topiramate are effective
Juvenile Myoclonic Epilepsy (Impulsive Petit Mal)	Bilateral, single or repetitive arrhythmic, irregular myoclonic jerks	Around puberty	Clonazepam is effective in combination. Lamotrigine added to sodium valproate effective in resistant cases.
Rolandic epilepsy	Mixed simple partial (motor) and complex partial seizures.	3 - 13 years	It is usually resolves by age of 14 years. Drug of first choice is carbamazepine or phenytoin.
Rasmussen Syndrome	Mainly, motor focal seizures but are often associated with other seizure types.	2 - 10 years	AEDs are not effective. Hemispheric disconnection surgery is the treatment of choice.

Appendix 4: Common side effects of antiepileptic drugs [3, 78, 271]

Drug	Side effects
Carbamazepine	Headache, ataxia, transient leukopenia, thrombocytopaenia, agranulocytosis, hyponatraemia, rare aplastic anaemia and Hepatitis
Ethosuximide	Nausea, anorexia, headache; blood dyscrasias and gingival hypertrophy
Gabapentin	Side effects less common; diarrhoea, dry mouth, dyspepsia, not associated with end-organ toxicity
Lamotrigine	Rash in 1:1000 overall, about 1:50 in children, especially with rapid titration and with valproate; headache and hepatic dysfunction.
Levetiracetam	Few idiosyncratic side effects; Nausea, vomiting and dyspepsia
Oxcarbazepine	Side effects less frequent than with carbamazepine; hyponatraemia common; no auto-induction to liver microsomal enzymes.
Phenobarbital	Sedation, paradoxical hyperactivity in children, hepatitis, possible learning difficulties and mental retardation, depression, osteomalacia, rare but serious Stevens–Johnson syndrome
Phenytoin	Gum hyperplasia, hirsutism, dose-related nystagmus and cerebellar ataxia; peripheral neuropathy, folate deficiency; rare hypersensitivity hepatitis
Primidone	Less sedating than phenobarbital in some patients; macrocytic anaemia
Sodium valproate	Rare but life-threatening idiosyncratic hepatitis and pancreatitis; tremors, weight gain, alopecia, thrombocytopenia, benign elevation of liver function tests common; transient her loss.
Tiagabine	Not associated with end-organ toxicity; may precipitate non-convulsive status in patients with generalized epilepsy
Topiramate	Cognitive impairment common above 400 mg/d; rare kidney stones (1%); rare glaucoma and cognitive side effects.
Vigabatrin	Drowsiness, fatigue, visual field defects and behavioural effects such as excitation and agitation.
Zonisamide	Kidney stones (1%); impaired sweating in children; rare rash and blood dyscrasias

Appendix 5: The 2004 NICE guidance for the choice of AEDs by seizure type [1]

Seizure type	First-line drugs	Second-line drugs	Other drugs that may be considered	Drugs to be avoided (may worsen seizures)
Generalised tonic–clonic	Carbamazepine[a] Lamotrigineb Sodium valproate Topiramate[a]	Clobazam Levetiracetam Oxcarbazepine[a]	Acetazolamide Clonazepam Phenobarbital[a] Phenytoin[a] Primidone[a],	Tiagabine Vigabatrin
Absence	Ethosuximide Lamotrigine[b] Sodium valproate	Clobazam Clonazepam Topiramate[a]	---	Carbamazepine[a] Gabapentin Oxcarbazepine[a] Tiagabine Vigabatrin
Myoclonic	Sodium valproate (Topiramate [a,d])	Clobazam Clonazepam Lamotrigine Levetiracetam Piracetam Topiramate[a]	---	Carbamazepine[a] Gabapentin Oxcarbazepine[a] Tiagabine Vigabatrin
Tonic	Tonic Lamotrigine[b] Sodium valproate	Clobazam Clonazepam Levetiracetam Topiramate[a]	Acetazolamide Phenobarbital[a] Phenytoin[a] Primidone [a,c]	Carbamazepine[a] Oxcarbazepine[a]
Atonic	Lamotrigine[b] Sodium valproate	Clobazam Clonazepam Levetiracetam Topiramatea	Acetazolamide Phenobarbital[a] Primidonea,[c]	Carbamazepine[a] Oxcarbazepine[a] Phenytoin[a]
Focal with/without secondary generalisation	Carbamazepinea Lamotrigineb Oxcarbazepinea,[b] Sodium valproate Topiramatea,[b]	Clobazam Gabapentin Levetiracetam Phenytoin[a] Tiagabine	Acetazolamide Clonazepam Phenobarbital[a] Primidone[a]	---

a: Hepatic enzyme-inducing AED.
b: Should be used as a first choice under circumstances as outlined in the NICE technology appraisal of newer AEDs[1]
c: Should rarely be initiated – if a barbiturate is required, phenobarbital is preferred.
d: In children, for severe myoclonic epilepsy of infancy

Appendix 6: The 2004 NICE guidance for the choice of AEDs by epilepsy syndrome [1]

Epilepsy syndrome	First-line drugs	Second-line drugs	Other drugs that may be considered	Drugs to be avoided (may worsen seizures)
Childhood absence epilepsy	Ethosuximide Lamotrigine[b] Sodium valproate	Levetiracetam Topiramate[a]	---	Carbamazepine[a] Oxcarbazepine[a] Phenytoin Tiagabine Vigabatrin
Juvenile absence epilepsy	Lamotrigine[b] Sodium valproate	Levetiracetam Topiramate[a]	---	Carbamazepine[a] Oxcarbazepine[a] Phenytoin[a] Tiagabine Vigabatrin
Juvenile myoclonic epilepsy	Lamotrigineb Sodium valproate	Clobazam Clonazepam Levetiracetam Topiramate[a]	Acetazolamide	Carbamazepine[a] Oxcarbazepine[a] Phenytoin[a] Tiagabine Vigabatrin
Generalised tonic–clonic seizures only	Carbamazepine[a] Lamotrigine[b] Sodium valproate Topiramate[a,b]	Levetiracetam	Acetazolamide Clobazam Clonazepam Oxcarbazepine[a] Phenobarbital[a] Phenytoin[a] Primidone[a,c]	Tiagabine Vigabatrin
Focal epilepsies: cryptogenic, symptomatic	Carbamazepine[a] Lamotrigine[b] Oxcarbazepine[a,b] Sodium valproate Topiramate[a,b]	Clobazam Gabapentin Levetiracetam Phenytoin[a] Tiagabine	Acetazolamide Clonazepam Phenobarbital[a] Primidone[a]	Carbamazepine[a] Oxcarbazepine[a] Phenytoin[a]
Infantile spasms	Steroids[c] Vigabatrin[b]	Clobazam Clonazepam Sodium valproate Topiramate[a]	Nitrazepam	Carbamazepine[a] Oxcarbazepine[a]
Benign epilepsy with centrotemporal spikes	Carbamazepine[a] Lamotrigine[b] Oxcarbazepine[a,b] Sodium valproate	Levetiracetam Topiramate[a]	Sulthiame[e]	---
Benign epilepsy with occipital paroxysms	Carbamazepine[a] Lamotrigineb Oxcarbazepine[a,b] Sodium	Levetiracetam Topiramate[a]		---

	valproate			
Severe myoclonic epilepsy of infancy	Clobazam Clonazepam Sodium valproate Topiramatea,[b]	Levetiracetam Stiripentole	Phenobarbital[a]	Carbamazepine[a] Lamotrigine Oxcarbazepine[a] Vigabatrin
Continuous spike wave of slow sleep	Clobazam Clonazepam Ethosuximide Lamotrigine[b] Sodium valproate Steroids	Levetiracetam Topiramate[a]	---	Carbamazepine[a] Oxcarbazepine[a] Vigabatrin
Lennox–Gastaut syndrome	Lamotrigine[b] Sodium valproate Topiramate[a]	Clobazam Clonazepam Ethosuximide Levetiracetam	Felbamate[e]	Carbamazepine[a] Oxcarbazepine[a]
Landau–Kleffner syndrome	Lamotrigine[b] Sodium valproate Steroids[d]	Levetiracetam Topiramate[a]	Sulthiamee	Carbamazepine[a] Oxcarbazepine[a]
Myoclonic astatic epilepsy	Clobazam Clonazepam Sodium valproate Topiramate[a,b]	Lamotrigine Levetiracetam	---	Carbamazepine[a] Oxcarbazepine[a]

a: Hepatic enzyme-inducing AED.
b: Should be used as a first choice under circumstances as outlined in the NICE technology appraisal of newer AEDs [1].
c: Should rarely be initiated – if a barbiturate is required, phenobarbital is preferred.
d: Steroids: prednisolone or ACTH (adrenocorticotrophic hormone).
e: Not licensed in the UK, but available by importation.

Appendix 7: Search methods for identification of adherence studies for CYP (EMBASE, MEDLINE and PsycINFO)

#	Key word(s)	Results
1	compliance.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id]	287094
2	patient compliance.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id]	134829
3	medication compliance.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id]	12039
4	noncompliance.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id]	169956
5	adherence.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id]	70102
6	drug adherence.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id]	674
7	patient adherence.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id]	4105
8	nonadherence.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id]	6011
9	medication adherence.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id]	11855
10	drug misuse.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id]	6052
11	drug therapy.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id]	568100
12	6 or 11 or 3 or 7 or 9 or 2 or 8 or 1 or 4 or 10 or 5	976460
13	child$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	4074746
14	pediatric.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	368699
15	girl$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	100902
16	boy$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	104158
17	young people.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	44769
18	youth$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	108755
19	adolescent$.mp. [mp=ti, ab, sh, hw, tn, ot,	2808378

	dm, mf, nm, tc, id, tw]	
20	parent.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	332022
21	parents.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	345960
22	father.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	64694
23	mother.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	249170
24	family.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	1554267
25	family therapy.mp[mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	39706
26	caregivers.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	81096
27	intervention.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	794144
28	improve.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	887712
29	treatment outcomes.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	43599
30	social support.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	146769
31	educational intervention.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	7807
32	health beliefs.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	5684
33	health care profession$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	33005
34	medication routine.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	42
35	self efficacy.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	49486
36	transition.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	363831
37	drug cost.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	53051
38	school.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	830214
39	preschool.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	1214533
40	high school.mp. [mp=ti, ab, sh, hw, tn, ot,	102926

	dm, mf, nm, tc, id, tw]	
41	students.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	726963
42	epilep$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	287852
43	seizure.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	169152
44	convulsion.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	31408
45	antiepilept$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, tc, id, tw]	40982
46	18 or 19 or 16 or 13 or 17 or 15 or 14	5708978
47	25 or 22 or 21 or 24 or 26 or 23 or 20	2208107
48	35 or 27 or 33 or 32 or 28 or 34 or 37 or 30 or 29 or 31	1883590
49	38 or 39 or 40 or 36 or 41	2765331
50	42 or 45 or 43 or 44	405190
51	46 and 12 and 48 and 47	5841
54	50 and 51	133
52	limit 51 to English language	117
53	limit 52 to humans	88

Appendix 8: Code list for diagnosis of epilepsy and epilepsy syndromes

Medical code	Medical description within the database
1473.00	H/O: epilepsy
1O30.00	Epilepsy confirmed
2126000	Epilepsy resolved
212J.00	Epilepsy resolved
667..00	Epilepsy monitoring
6671.00	Initial epilepsy assessment
6672.00	Follow-up epilepsy assessment
6674.00	Epilepsy associated problems
6677.00	Epilepsy drug side effects
6678.00	Epilepsy treatment changed
6679.00	Epilepsy treatment started
667A.00	Epilepsy treatment stopped
667B.00	Nocturnal epilepsy
667C.00	Epilepsy control good
667D.00	Epilepsy control poor
667G.00	Epilepsy restricts employment
667H.00	Epilepsy prevents employment
667J.00	Epilepsy impairs education
667K.00	Epilepsy limits activities
667L.00	Epilepsy does not limit activities
667M.00	Epilepsy management plan given
667N.00	Epilepsy severity
667W.00	Emergency epilepsy treatment since last appointment
667X.00	No epilepsy drug side effects
667Z.00	Epilepsy monitoring NOS
8BIF.00	Epilepsy medication review
9Of3.00	Epilepsy monitoring verbal invite
9Of4.00	Epilepsy monitoring telephone invite
F132100	Progressive myoclonic epilepsy
F132200	Myoclonic encephalopathy
F25..00	Epilepsy
F250.00	Generalised nonconvulsive epilepsy
F250000	Petit mal (minor) epilepsy
F250011	Epileptic absences
F250100	Pykno-epilepsy
F250200	Epileptic seizures - atonic
F250300	Epileptic seizures - akinetic
F250400	Juvenile absence epilepsy
F250500	Lennox-Gastaut syndrome
F250y00	Other specified generalised nonconvulsive epilepsy
F250z00	Generalised nonconvulsive epilepsy NOS

F251.00	Generalised convulsive epilepsy
F251000	Grand mal (major) epilepsy
F251011	Tonic-clonic epilepsy
F251100	Neonatal myoclonic epilepsy
F251111	Otohara syndrome
F251200	Epileptic seizures - clonic
F251300	Epileptic seizures - myoclonic
F251400	Epileptic seizures - tonic
F251500	Tonic-clonic epilepsy
F251y00	Other specified generalised convulsive epilepsy
F251z00	Generalised convulsive epilepsy NOS
F254.00	Partial epilepsy with impairment of consciousness
F254000	Temporal lobe epilepsy
F254100	Psychomotor epilepsy
F254200	Psychosensory epilepsy
F254300	Limbic system epilepsy
F254500	Complex partial epileptic seizure
F254z00	Partial epilepsy with impairment of consciousness NOS
F255.00	Partial epilepsy without impairment of consciousness
F255000	Jacksonian, focal or motor epilepsy
F255011	Focal epilepsy
F255012	Motor epilepsy
F255100	Sensory induced epilepsy
F255200	Somatosensory epilepsy
F255300	Visceral reflex epilepsy
F255311	Partial epilepsy with autonomic symptoms
F255400	Visual reflex epilepsy
F255500	Unilateral epilepsy
F255600	Simple partial epileptic seizure
F255y00	Partial epilepsy without impairment of consciousness OS
F255z00	Partial epilepsy without impairment of consciousness NOS
F256.00	Infantile spasms
F256.12	West syndrome
F256100	Salaam attacks
F256z00	Infantile spasms NOS
F257.00	Kojevnikov's epilepsy
F259.00	Early infant epileptic encephalopathy with suppression bursts
F259.11	Ohtahara syndrome
F25A.00	Juvenile myoclonic epilepsy
F25B.00	Alcohol-induced epilepsy
F25C.00	Drug-induced epilepsy
F25D.00	Menstrual epilepsy
F25E.00	Stress-induced epilepsy
F25F.00	Photosensitive epilepsy
F25y.00	Other forms of epilepsy
F25y000	Cursive (running) epilepsy

F25y100	Gelastic epilepsy
F25y200	Locl-rlt(foc)(part)idiop epilep&epilptic syn seiz locl onset
F25y400	Benign Rolandic epilepsy
F25y500	Panayiotopoulos syndrome
F25yz00	Other forms of epilepsy NOS
F25z.00	Epilepsy NOS
F25z.11	Fit (in known epileptic) NOS
Fyu5000	[X]Other generalized epilepsy and epileptic syndromes
Fyu5100	[X]Other epilepsy
SC20000	Traumatic epilepsy
AHD code	Description
1009200000	Epilepsy check - Fit Details
1009250000	Epilepsy check - DVLC Informed
1020000006	Placed on Epilepsy Register

Appendix 9: Code list of licensed AEDs until 2004

Multilex code	BNF code	Generic name
93530998	04.08.01.00	CARBAMAZEPINE chewable tab 100mg
93530997	04.08.01.00	CARBAMAZEPINE chewable tab 200mg
96885998	04.08.01.00	CARBAMAZEPINE liq 100mg/5ml
98360998	04.08.01.00	CARBAMAZEPINE liq 100mg/5ml
88217998	04.08.01.00	CARBAMAZEPINE mr tab 200mg
88217997	04.08.01.00	CARBAMAZEPINE mr tab 400mg
84311998	04.07.03.00	CARBAMAZEPINE oral susp 500mg/5ml
92734998	04.08.01.00	CARBAMAZEPINE supp 125mg
92734997	04.08.01.00	CARBAMAZEPINE supp 250mg
92837998	04.08.01.00	CARBAMAZEPINE tabs 100mg
92837997	04.08.01.00	CARBAMAZEPINE tabs 200mg
92837996	04.08.01.00	CARBAMAZEPINE tabs 400mg
97158992	04.08.01.00	CLOBAZAM 1 MG SUS
97159992	04.08.01.00	CLOBAZAM 2.5 MG CAP
97161992	04.08.01.00	CLOBAZAM 5 MG CAP
96160992	04.08.01.00	CLOBAZAM 5 MG TAB
97160992	04.08.01.00	CLOBAZAM 7.5 MG CAP
96648998	04.08.01.00	CLOBAZAM caps 10mg
82714998	04.08.01.15	CLOBAZAM oral susp 25mg/5ml
93529990	04.08.01.00	CLOBAZAM tabs 10mg
96634996	04.08.02.00	CLONAZEPAM conc soln inj 1mg/1ml
88422998	04.08.01.15	CLONAZEPAM oral drops 2.5mg/ml
85559998	04.08.01.15	CLONAZEPAM oral soln 250micrograms/5ml
88423996	04.08.01.00	CLONAZEPAM sf oral soln 2mg/5ml
86604998	04.08.01.00	CLONAZEPAM sf soln 500micrograms/5ml
88423997	04.08.01.00	CLONAZEPAM susp 500micrograms/5ml
92356990	04.08.01.00	CLONAZEPAM tabs 2mg
92357990	04.08.01.00	CLONAZEPAM tabs 500 micrograms
97292992	04.08.02.00	DIAZEPAM RECTAL 2 MG/ML SOL
97291992	04.08.02.00	DIAZEPAM RECTAL 4 MG SOL
89501998	04.08.02.00	DIAZEPAM rectal tubes 10mg
96407996	04.08.02.00	DIAZEPAM rectal tubes 2.5mg
91354998	04.08.02.00	DIAZEPAM rectal tubes 20mg
94665990	04.08.02.00	DIAZEPAM rectal tubes 5mg
92901998	04.01.02.00	DIAZEPAM supp 10mg
96408998	04.01.02.00	DIAZEPAM supp 5mg
86109998	04.08.01.00	ETHOSUXIMIDE caps 250mg
85954998	04.08.01.00	ETHOSUXIMIDE syrp 250mg/5ml
89991998	04.08.01.00	FOSPHENYTOIN SODIUM conc soln inf 750mg/10ml
90424998	04.08.01.00	GABAPENTIN caps & tabs 300mg + 600mg

92872990	04.08.01.00	GABAPENTIN caps 100mg
92871990	04.08.01.00	GABAPENTIN caps 300mg
92870990	04.08.01.00	GABAPENTIN caps 400mg
93743990	04.08.01.03	GABAPENTIN oral soln 250mg/5ml
90426998	04.08.01.00	GABAPENTIN tabs 600mg
90426997	04.08.01.00	GABAPENTIN tabs 800mg
85379998	04.08.01.05	LAMOTRIGINE (IPU) disp tab 200mg
92700996	04.08.01.00	LAMOTRIGINE disp tab 100mg
92700997	04.08.01.00	LAMOTRIGINE disp tab 25mg
91465997	04.08.01.00	LAMOTRIGINE disp tab 2mg
86019998	04.08.01.00	LAMOTRIGINE disp tab 50mg
92700998	04.08.01.00	LAMOTRIGINE disp tab 5mg
84903998	04.08.01.05	LAMOTRIGINE oral liq
93491990	04.08.01.00	LAMOTRIGINE tabs 100mg
91465998	04.08.01.00	LAMOTRIGINE tabs 200mg
93493990	04.08.01.00	LAMOTRIGINE tabs 25mg
93492990	04.08.01.00	LAMOTRIGINE tabs 50mg
85968998	04.08.01.00	LEVETIRACETAM conc soln inf 500mg/5ml
84953998	04.08.01.00	LEVETIRACETAM oral liq
87195998	04.08.01.00	LEVETIRACETAM oral soln 100mg/ml
89210996	04.08.01.00	LEVETIRACETAM tabs 1000mg
89210998	04.08.01.00	LEVETIRACETAM tabs 250mg
89210997	04.08.01.00	LEVETIRACETAM tabs 500mg
87194998	04.08.01.00	LEVETIRACETAM tabs 750mg
83946998	04.08.01.00	OXCARBAZEPINE oral liq
91218998	04.08.01.00	OXCARBAZEPINE sf oral susp 60mg/ml
91625998	04.08.01.00	OXCARBAZEPINE tabs 150mg
91625997	04.08.01.00	OXCARBAZEPINE tabs 300mg
89231998	04.08.01.00	OXCARBAZEPINE tabs 600mg
97081998	04.08.02.00	PARALDEHYDE IM inj
98091998	04.08.02.00	PARALDEHYDE IV inj
98091997	04.08.02.00	PARALDEHYDE rectal soln
93454998	04.08.01.00	PHENOBARBITAL SODIUM inj 15mg/1ml
95553998	04.08.01.00	PHENOBARBITAL SODIUM inj 200mg/1ml
93454997	04.08.01.00	PHENOBARBITAL SODIUM inj 30mg/1ml
93454996	04.08.01.00	PHENOBARBITAL SODIUM inj 60mg/1ml
97080998	04.08.01.00	PHENOBARBITAL SODIUM tabs 30mg
97080997	04.08.01.00	PHENOBARBITAL SODIUM tabs 60mg
98087998	04.08.01.00	PHENOBARBITAL elixir 15mg/5ml
98087997	04.08.01.07	PHENOBARBITAL oral soln 50mg/5ml
82052998	04.08.01.07	PHENOBARBITAL oral soln 75mg/5ml
96866990	04.08.01.00	PHENOBARBITAL tabs 100mg
97103990	04.08.01.00	PHENOBARBITAL tabs 15mg
97203997	04.08.01.00	PHENOBARBITAL tabs 30mg

97203996	04.08.01.00	PHENOBARBITAL tabs 60mg
93404992	04.08.01.00	PHENOBARBITONE 10 MG TAB
94282992	04.08.01.00	PHENOBARBITONE 15 MG CAP
95418992	04.08.01.00	PHENOBARBITONE 20 MG TAB
94279992	04.08.01.00	PHENOBARBITONE 22.5 MG TAB
94521992	04.08.01.00	PHENOBARBITONE 30 MG CAP
94285992	04.08.01.00	PHENOBARBITONE 50 MG CAP
95421992	04.08.01.00	PHENOBARBITONE 50 MG TAB
94284992	04.08.01.00	PHENOBARBITONE 7.5 MG TAB
94520992	04.08.01.00	PHENOBARBITONE 75 MG SUP
94278992	04.08.01.00	PHENOBARBITONE S/R 100 MG CAP
90904998	04.08.01.07	PHENYTOIN + PHENOBARBITAL caps 100mg + 50mg
99694998	04.08.01.07	PHENYTOIN + PHENOBARBITAL caps 100mg + 50mg
94288992	04.08.01.00	PHENYTOIN 150 MG SUS
94525992	04.08.01.00	PHENYTOIN 25 MG SYR
97897992	04.08.01.00	PHENYTOIN 30 MG TAB
90780996	04.08.01.00	PHENYTOIN SODIUM caps 100mg
90780998	04.08.01.00	PHENYTOIN SODIUM caps 25mg
90776998	04.08.01.00	PHENYTOIN SODIUM caps 300mg
90780997	04.08.01.00	PHENYTOIN SODIUM caps 50mg
92701990	04.08.02.00	PHENYTOIN SODIUM inj 250mg/5ml
92614990	04.08.01.00	PHENYTOIN SODIUM tabs 100mg
97140990	04.08.01.00	PHENYTOIN SODIUM tabs 50mg
97896992	04.08.01.00	PHENYTOIN SODIUM/ PHENOBARBITONE CAP
95838992	04.08.01.00	PHENYTOIN SODIUM/ PHENOBARBITONE SODIUM TAB
95532998	04.08.01.00	PHENYTOIN caps 100mg
95533997	04.08.01.00	PHENYTOIN caps 25mg
95532996	04.08.01.00	PHENYTOIN caps 300mg
95533996	04.08.01.00	PHENYTOIN caps 50mg
95533998	04.08.01.00	PHENYTOIN paed tab 50mg
92812998	04.08.01.00	PHENYTOIN sf susp 90mg/5ml
95532997	04.08.01.00	PHENYTOIN susp 30mg/5ml
87398998	04.08.01.00	PREGABALIN caps 100mg
87397998	04.08.01.00	PREGABALIN caps 150mg
87396998	04.08.01.00	PREGABALIN caps 200mg
84233998	04.08.01.00	PREGABALIN caps 225mg
87401998	04.08.01.00	PREGABALIN caps 25mg
87395998	04.08.01.00	PREGABALIN caps 300mg
87400998	04.08.01.00	PREGABALIN caps 50mg
87399998	04.08.01.00	PREGABALIN caps 75mg
97949992	04.08.01.00	PRIMIDONE 200 MG TAB
85534998	04.08.01.07	PRIMIDONE caps
95403997	04.08.01.00	PRIMIDONE oral susp 250mg/5ml
87106998	04.08.01.00	PRIMIDONE tabs 250mg

83790998	04.08.01.00	SODIUM VALPROATE + VALPROIC ACID MR granules 1000mg
83793998	04.08.01.00	SODIUM VALPROATE + VALPROIC ACID MR granules 250mg
83792998	04.08.01.12	SODIUM VALPROATE + VALPROIC ACID MR granules 500mg
83791998	04.08.01.00	SODIUM VALPROATE + VALPROIC ACID MR granules 750mg
92917998	04.08.01.00	SODIUM VALPROATE + VALPROIC ACID mr tab 200mg
92917997	04.08.01.00	SODIUM VALPROATE + VALPROIC ACID mr tab 300mg
92917996	04.08.01.00	SODIUM VALPROATE + VALPROIC ACID mr tab 500mg
82857998	04.08.01.00	SODIUM VALPROATE MR granules 1000mg
81956998	04.08.01.00	SODIUM VALPROATE MR granules 100mg
81955998	04.08.01.00	SODIUM VALPROATE MR granules 250mg
83705998	04.08.01.00	SODIUM VALPROATE MR granules 500mg
81957998	04.08.01.00	SODIUM VALPROATE MR granules 50mg
81954998	04.08.01.00	SODIUM VALPROATE MR granules 750mg
94409996	04.08.01.00	SODIUM VALPROATE crushable tab 100mg
83480998	04.08.01.00	SODIUM VALPROATE ec tab 200mg
83479998	04.08.01.00	SODIUM VALPROATE ec tab 500mg
84088998	04.08.01.00	SODIUM VALPROATE inj 1000mg/10ml
85029998	04.08.01.00	SODIUM VALPROATE inj 300mg/3ml
84667998	04.08.01.00	SODIUM VALPROATE mr cap 150mg
84666998	04.08.01.00	SODIUM VALPROATE mr cap 300mg
83321998	04.08.01.00	SODIUM VALPROATE mr tab 200mg
88177998	04.08.01.00	SODIUM VALPROATE mr tab 300mg
88178998	04.08.01.00	SODIUM VALPROATE mr tab 500mg
93148998	04.08.01.00	SODIUM VALPROATE pwdr/inj.soln 400mg
92802996	04.08.01.00	SODIUM VALPROATE sf liq 200mg/5ml
89408997	04.08.01.00	TIAGABINE tabs 10mg
89408996	04.08.01.00	TIAGABINE tabs 15mg
89408998	04.08.01.00	TIAGABINE tabs 5mg
88868998	04.08.01.00	TOPIRAMATE caps 15mg
88868997	04.08.01.00	TOPIRAMATE caps 25mg
88396998	04.08.01.00	TOPIRAMATE caps 50mg
91050997	04.08.01.00	TOPIRAMATE tabs 100mg
91050996	04.08.01.00	TOPIRAMATE tabs 200mg
91044998	04.08.01.00	TOPIRAMATE tabs 25mg
91050998	04.08.01.00	TOPIRAMATE tabs 50mg
94068998	04.08.01.00	VALPROIC ACID (AS SEMISODIUM SALT) ec tab 250mg
94068997	04.08.01.00	VALPROIC ACID (AS SEMISODIUM SALT) ec tab 500mg
93015998	04.08.01.00	VALPROIC ACID ec soft gelatin ca 150mg
93015997	04.08.01.00	VALPROIC ACID ec soft gelatin ca 300mg
93015996	04.08.01.00	VALPROIC ACID ec soft gelatin ca 500mg
93770996	04.08.01.13	VIGABATRIN caps 125mg
93769997	04.08.01.00	VIGABATRIN sf pwdr 500mg
93769998	04.08.01.00	VIGABATRIN tabs 500mg

Appendix 10: The International Statistical Classification of Diseases and Related Health Problems-10th Revision-2007

Chapter VI: Diseases of the nervous system (G00-G99)

Episodic and paroxysmal disorders (G40-G47)

G40	**Epilepsy**
	Excludes: Landau-Kleffner syndrome (F80.3) seizure (convulsive) NOS (R56.8) status epilepticus (G41.-) Todd's paralysis (G83.8)
G40.0	**Localization-related (focal)(partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset**
	Benign childhood epilepsy with centrotemporal EEG spikes Childhood epilepsy with occipital EEG paroxysms
G40.1	**Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures**
	Attacks without alteration of consciousness Simple partial seizures developing into secondarily generalized seizures
G40.2	**Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures**
	Attacks with alteration of consciousness, often with automatisms Complex partial seizures developing into secondarily generalized seizures
G40.3	**Generalized idiopathic epilepsy and epileptic syndromes**
	Benign: · myoclonic epilepsy in infancy · neonatal convulsions (familial) Childhood absence epilepsy [pyknolepsy] Epilepsy with grand mal seizures on awakening Juvenile: · absence epilepsy · myoclonic epilepsy [impulsive petit mal] Nonspecific epileptic seizures: · atonic · clonic · myoclonic · tonic · tonic-clonic
G40.4	**Other generalized epilepsy and epileptic syndromes**
	Epilepsy with: · myoclonic absences · myoclonic-astatic seizures Infantile spasms Lennox-Gastaut syndrome Salaam attacks Symptomatic early myoclonic encephalopathy West's syndrome
G40.5	**Special epileptic syndromes**
	Epilepsia partialis continua [Kozhevnikof]

	Epileptic seizures related to: · alcohol · drugs · hormonal changes · sleep deprivation · stress
G40.6	**Grand mal seizures, unspecified (with or without petit mal)**
G40.7	**Petit mal, unspecified, without grand mal seizures**
G40.8	**Other epilepsy** Epilepsies and epileptic syndromes undetermined as to whether they are focal or generalized
G40.9	**Epilepsy, unspecified** Epileptic: · convulsions NOS · fits NOS · seizures NOS
G41	Status epilepticus
G41.0	Grand mal status epilepticus
	Tonic-clonic status epilepticus
	Excludes: epilepsia partialis continua [Kozhevnikof] (G40.5)
G41.1	**Petit mal status epilepticus** Epileptic absence status
G41.2	**Complex partial status epilepticus**
G41.8	**Other status epilepticus**
G41.9	**Status epilepticus, unspecified**

Appendix 11: Code list of seizures and epilepsy symptoms

Medical codes	Description
1B63.11	Fit - had one, symptom
1B64.00	Had a convulsion
1B64.11	Convulsion - symptom
282..00	O/E - fit/convulsion
282..11	O/E - a convulsion
282..12	O/E - a fit
282..13	O/E - a seizure
2822.00	O/E - grand mal fit
2823.00	O/E - petit mal fit
2824.00	O/E - focal (Jacksonian) fit
2824.11	O/E - Jacksonian fit
2824.12	O/E - focal fit
2825.00	O/E - psychomotor fit
2828.00	Absence seizure
282Z.00	O/E - fit/convulsion NOS
6676.00	Last fit
667Q.00	Had a fit
667R.00	Had a fit
667T.00	Daily seizures
F132z12	Myoclonic seizure
F250200	Epileptic seizures - atonic
F250300	Epileptic seizures - akinetic
F251200	Epileptic seizures - clonic
F251300	Epileptic seizures - myoclonic
F251400	Epileptic seizures - tonic
F251600	Grand mal seizure
F252.00	Petit mal status
F253.00	Grand mal status
F253.11	Status epilepticus
F254500	Complex partial epileptic seizure
F255600	Simple partial epileptic seizure
F256.00	Infantile spasms
F256z00	Infantile spasms NOS
F25X.00	Status epilepticus, unspecified
F25z.11	Fit (in known epileptic) NOS
Q480.00	Convulsions in newborn
Q480.11	Fits in newborn
Q480.12	Seizures in newborn
R003.00	[D]Convulsions
R003100	[D]Convulsions, infantile
R003200	[D]Fit
R003400	[D]Nocturnal seizure
R003y00	[D]Other specified convulsion
R003z00	[D]Convulsion NOS
R003z11	[D]Seizure NOS

Appendix 12: Diagnostic terms of epilepsy and epilepsy subtypes

Read codes of the database	Assigned epilepsy subtype
Benign Rolandic epilepsy	Benign Rolandic epilepsy
Complex partial epileptic seizure	Complex focal epilepsy
Early infant epileptic encephalopathy	Early infant epileptic encephalopathy
Epilepsy	Epilepsy (unspecified)
Epilepsy NOS	Epilepsy (unspecified)
Epilepsy associated problems	Epilepsy (unspecified)
Epilepsy check - Fit Details	Epilepsy (unspecified)
Epilepsy confirmed	Epilepsy (unspecified)
Epilepsy control good	Epilepsy (unspecified)
Epilepsy control poor	Epilepsy (unspecified)
Epilepsy drug side effects	Epilepsy (unspecified)
Epilepsy medication review	Epilepsy (unspecified)
Epilepsy monitoring	Epilepsy (unspecified)
Epilepsy monitoring NOS	Epilepsy (unspecified)
Epilepsy resolved	Epilepsy (unspecified)
Epilepsy treatment changed	Epilepsy (unspecified)
Epilepsy treatment started	Epilepsy (unspecified)
Epileptic absences	Generalised epilepsy -absence seizures
Epileptic seizures - akinetic	Generalised epilepsy -atonic seizures
Epileptic seizures - atonic	Generalised epilepsy -atonic seizures
Epileptic seizures - clonic	Generalised epilepsy -clonic seizures
Epileptic seizures - myoclonic	Generalised epilepsy -myclonic seizures
Epileptic seizures - tonic	Generalised epilepsy -tonic seizures
Fit (in known epileptic) NOS	Epilepsy (unspecified)
Focal epilepsy	Focal epilepsy
Follow-up epilepsy assessment	Epilepsy (unspecified)
Generalised convulsive epilepsy	Generalised epilepsy
Generalised nonconvulsive epilepsy	Generalised epilepsy -absence seizures
Generalised nonconvulsive epilepsy NOS	Epileptic absences
Grand mal (major) epilepsy	Generalised epilepsy-tonic-clonic seizures
H/O: epilepsy	Epilepsy (unspecified)
Infantile spasms	West syndrome
Infantile spasms NOS	West syndrome
Initial epilepsy assessment	Epilepsy (unspecified)
Jacksonian, focal or motor epilepsy	Focal epilepsy
Juvenile absence epilepsy	Juvenile absence epilepsy
Juvenile myoclonic epilepsy	Juvenile myoclonic epilepsy
Locl-rlt(foc)(part)idiop epilep&epilptic	Focal epilepsy
Myoclonic encephalopathy	Myoclonic encephalopathy
Neonatal myoclonic epilepsy	Neonatal myoclonic epilepsy
Nocturnal epilepsy	Epilepsy (unspecified)

Other forms of epilepsy	Epilepsy (unspecified)
Other forms of epilepsy NOS	Epilepsy (unspecified)
Otohara syndrome	Early infant epileptic encephalopathy
Partial epilepsy with impairment of consciousness	Complex focal epilepsy
Partial epilepsy without impairment of consciousness	Focal epilepsy
Petit mal (minor) epilepsy	Generalised epilepsy -absence seizures
Progressive myoclonic epilepsy	Progressive myoclonic epilepsy
Salaam attacks	West syndrome
Temporal lobe epilepsy	Focal epilepsy
Tonic-clonic epilepsy	Generalised epilepsy-tonic-clonic seizures
Traumatic epilepsy	Epilepsy (unspecified)
Unilateral epilepsy	Focal epilepsy

Appendix 13: Read code list of common disorders treated with AEDs

Read code	Description	Disease/disorder
Eu41.00	[X]Other anxiety disorders	Anxiety disorder
Eu41100	[X]Generalized anxiety disorder	Anxiety disorder
Eu41111	[X]Anxiety neurosis	Anxiety disorder
Eu41112	[X]Anxiety reaction	Anxiety disorder
Eu41113	[X]Anxiety state	Anxiety disorder
Eu41200	[X]Mixed anxiety and depressive disorder	Anxiety disorder
Eu41211	[X]Mild anxiety depression	Anxiety disorder
Eu41300	[X]Other mixed anxiety disorders	Anxiety disorder
Eu41y00	[X]Other specified anxiety disorders	Anxiety disorder
Eu41y11	[X]Anxiety hysteria	Anxiety disorder
Eu41z00	[X]Anxiety disorder, unspecified	Anxiety disorder
Eu41z11	[X]Anxiety NOS	Anxiety disorder
Eu43012	[X]Acute reaction to stress	Anxiety disorder
E200.00	Anxiety states	Anxiety disorders
E200000	Anxiety state unspecified	Anxiety disorders
E200100	Panic disorder	Anxiety disorders
E200111	Panic attack	Anxiety disorders
E200200	Generalised anxiety disorder	Anxiety disorders
E200300	Anxiety with depression	Anxiety disorders
E200400	Chronic anxiety	Anxiety disorders
E200500	Recurrent anxiety	Anxiety disorders
E200z00	Anxiety state NOS	Anxiety disorders
Eu40.00	[X]Phobic anxiety disorders	Anxiety/phobic disorders
Eu40000	[X]Agoraphobia	Anxiety/phobic disorders
Eu40011	[X]Agoraphobia without history of panic disorder	Anxiety/phobic disorders
Eu40012	[X]Panic disorder with agoraphobia	Anxiety/phobic disorders
Eu40100	[X]Social phobias	Anxiety/phobic disorders
Eu40111	[X]Anthropophobia	Anxiety/phobic disorders
Eu40112	[X]Social neurosis	Anxiety/phobic disorders
Eu40200	[X]Specific (isolated) phobias	Anxiety/phobic disorders
Eu40211	[X]Acrophobia	Anxiety/phobic disorders
Eu40212	[X]Animal phobias	Anxiety/phobic disorders
Eu40213	[X]Claustrophobia	Anxiety/phobic disorders
Eu40214	[X]Simple phobia	Anxiety/phobic disorders
Eu40300	[X]Needle phobia	Anxiety/phobic disorders
Eu40y00	[X]Other phobic anxiety disorders	Anxiety/phobic disorders
Eu40z00	[X]Phobic anxiety disorder, unspecified	Anxiety/phobic disorders
Eu40z11	[X]Phobia NOS	Anxiety/phobic disorders
Eu40z12	[X]Phobic state NOS	Anxiety/phobic disorders
E202.00	Phobic disorders	Anxiety/phobic disorders

E202.11	Social phobic disorders	Anxiety/phobic disorders
E202.12	Phobic anxiety	Anxiety/phobic disorders
E202000	Phobia unspecified	Anxiety/phobic disorders
E202100	Agoraphobia with panic attacks	Anxiety/phobic disorders
E202200	Agoraphobia without mention of panic attc	Anxiety/phobic disorders
E202300	Social phobia, fear of eating in public	Anxiety/phobic disorders
E202400	Social phobia, fear of public speaking	Anxiety/phobic disorders
E202500	Social phobia, fear of public washing	Anxiety/phobic disorders
E28z.11	Examination fear	Anxiety/phobic disorders
E28z.12	Flying phobia	Anxiety/phobic disorders
E28z.13	Stage fright	Anxiety/phobic disorders
Eu9..00	[X]Behavioural/emotional disords onset childhood/adolescence	Behavioural &emotional disorders of childhood onset
Eu93000	[X]Separation anxiety disorder of childhood	Behavioural &emotional disorders of childhood onset
Eu93100	[X]Phobic anxiety disorder of childhood	Behavioural &emotional disorders of childhood onset
Eu93200	[X]Social anxiety disorder of childhood	Behavioural &emotional disorders of childhood onset
Eu93211	[X]Avoidant disorder childhood	Behavioural &emotional disorders of childhood onset
Eu93300	[X]Sibling rivalry disorder	Behavioural &emotional disorders of childhood onset
Eu93311	[X]Sibling jealousy	Behavioural &emotional disorders of childhood onset
Eu93y00	[X]Other childhood emotional disorders	Behavioural &emotional disorders of childhood onset
Eu93y11	[X]Childhood identity disorder	Behavioural &emotional disorders of childhood onset
Eu93y12	[X]Childhood overanxious disorder	Behavioural &emotional disorders of childhood onset
Eu93z00	[X]Childhood emotional disorder, unspecified	Behavioural &emotional disorders of childhood onset
Eu94.00	[X]Disorder social funct onset specific childhood/adolesc	Behavioural &emotional disorders of childhood onset
Eu94000	[X]Elective mutism	Behavioural &emotional disorders of childhood onset
Eu94011	[X]Selective mutism	Behavioural &emotional disorders of childhood onset
Eu94100	[X]Reactive attachment disorder of childhood	Behavioural &emotional disorders of childhood onset
Eu94200	[X]Disinhibited attachment disorder of childhood	Behavioural &emotional disorders of childhood onset
Eu94211	[X]Affectionless psychopathy	Behavioural &emotional disorders of childhood onset
Eu94212	[X]Institutional syndrome	Behavioural &emotional disorders of childhood onset
Eu94y00	[X]Other childhood disorders of social functioning	Behavioural &emotional disorders of childhood onset
Eu94z00	[X]Childhood disorder of social functioning, unspecified	Behavioural &emotional disorders of childhood onset
E270.00	Stammering or stuttering	Behavioural &emotional disorders of childhood onset
E270.11	Stammering	Behavioural &emotional disorders of childhood onset
E270.12	Stuttering	Behavioural &emotional disorders of childhood onset
E272.00	Tics	Behavioural &emotional disorders of childhood onset
E272000	Tic disorder unspecified	Behavioural &emotional disorders of childhood onset
E272100	Transient childhood tic	Behavioural &emotional disorders of childhood onset
E272200	Chronic motor tic disorder	Behavioural &emotional disorders of childhood onset
E272300	Gilles de la Tourette's disorder	Behavioural &emotional disorders of childhood onset
E272z00	Tic NOS	Behavioural &emotional disorders of childhood onset
E273.00	Stereotyped repetitive movements	Behavioural &emotional disorders of childhood onset
E273000	Body-rocking	Behavioural &emotional disorders of childhood onset

E273100	Head-banging	Behavioural &emotional disorders of childhood onset
E273200	Spasmus nutans - nodding spasm	Behavioural &emotional disorders of childhood onset
E273z00	Stereotyped repetitive movements NOS	Behavioural &emotional disorders of childhood onset
E27z000	Hair plucking	Behavioural &emotional disorders of childhood onset
E27z400	Nail-biting	Behavioural &emotional disorders of childhood onset
E27z500	Thumb-sucking	Behavioural &emotional disorders of childhood onset
E292000	Separation anxiety disorder	Behavioural &emotional disorders of childhood onset
E292100	Adolescent emancipation disorder	Behavioural &emotional disorders of childhood onset
E292300	Specific academic or work inhibition	Behavioural &emotional disorders of childhood onset
E292311	Specific academic or work inhibition	Behavioural &emotional disorders of childhood onset
E292312	Specific work inhibition	Behavioural &emotional disorders of childhood onset
Eu5..00	[X]Behav synd assoc with physiolgcl disturb + physical fctrs	Behavioural syndromes associated with physiological disturbances
Eu50.00	[X]Eating disorders	Behavioural syndromes associated with physiological disturbances
Eu50000	[X]Anorexia nervosa	Behavioural syndromes associated with physiological disturbances
Eu50100	[X]Atypical anorexia nervosa	Behavioural syndromes associated with physiological disturbances
Eu50200	[X]Bulimia nervosa	Behavioural syndromes associated with physiological disturbances
Eu50211	[X]Bulimia NOS	Behavioural syndromes associated with physiological disturbances
Eu50212	[X]Hyperorexia nervosa	Behavioural syndromes associated with physiological disturbances
Eu50300	[X]Atypical bulimia nervosa	Behavioural syndromes associated with physiological disturbances
Eu50400	[X]Overeating associated with other psychological disturbncs	Behavioural syndromes associated with physiological disturbances
Eu50411	[X]Psychogenic overeating	Behavioural syndromes associated with physiological disturbances
Eu50500	[X]Vomiting associated with other psychological disturbances	Behavioural syndromes associated with physiological disturbances
Eu50511	[X]Psychogenic vomiting	Behavioural syndromes associated with physiological disturbances
Eu50y00	[X]Other eating disorders	Behavioural syndromes associated with physiological disturbances
Eu50y12	[X]Psychogenic loss of appetite	Behavioural syndromes associated with physiological disturbances
Eu50z00	[X]Eating disorder, unspecified	Behavioural syndromes associated with physiological disturbances
Eu52z00	[X]Unspec sex dysfunction not caused by organic disordr/dis	Behavioural syndromes associated with physiological disturbances
Eu53.00	[X]Mental and behav disorders assoc with the puerperium NEC	Behavioural syndromes associated with physiological disturbances
Eu53000	[X]Mild mental/behav disorder assoc with the puerperium NEC	Behavioural syndromes associated with physiological disturbances
Eu53011	[X]Postnatal depression NOS	Behavioural syndromes associated with physiological disturbances
Eu53012	[X]Postpartum depression NOS	Behavioural syndromes associated with physiological disturbances
Eu53100	[X]Severe mental and behav disorder assoc wth puerperium NEC	Behavioural syndromes associated with physiological disturbances
Eu53111	[X]Puerperal psychosis NOS	Behavioural syndromes associated with physiological disturbances
Eu53y00	[X]Oth mental and behav disorders assoc with puerperium NEC	Behavioural syndromes associated with physiological disturbances
Eu53z00	[X]Puerperal mental disorder, unspecified	Behavioural syndromes associated with physiological

		disturbances
Eu54.00	[X]Psychological/behav factor assoc with disorder or dis EC	Behavioural syndromes associated with physiological disturbances
Eu5z.00	[X]Unsp behav synd assoc with physiol disturb physical facts	Behavioural syndromes associated with physiological disturbances
Eu5z.11	[X]Psychogenic physiological dysfunction NOS	Behavioural syndromes associated with physiological disturbances
E27..00	Psychogenic syndromes NEC	Behavioural syndromes associated with physiological disturbances
E271.00	Anorexia nervosa	Behavioural syndromes associated with physiological disturbances
E275.00	Other and unspecified non-organic eating disorders	Behavioural syndromes associated with physiological disturbances
E275000	Unspecified non-organic eating disorder	Behavioural syndromes associated with physiological disturbances
E275100	Bulimia (non-organic overeating)	Behavioural syndromes associated with physiological disturbances
E275111	Compulsive eating disorder	Behavioural syndromes associated with physiological disturbances
E275200	Pica	Behavioural syndromes associated with physiological disturbances
E275300	Psychogenic rumination	Behavioural syndromes associated with physiological disturbances
E275400	Psychogenic vomiting NOS	Behavioural syndromes associated with physiological disturbances
E275500	Non-organic infant feeding disturbance	Behavioural syndromes associated with physiological disturbances
E275600	Non-organic loss of appetite	Behavioural syndromes associated with physiological disturbances
E275700	Psychogenic polydipsia	Behavioural syndromes associated with physiological disturbances
E275711	Compulsive water drinking	Behavioural syndromes associated with physiological disturbances
E275800	Specific food craving	Behavioural syndromes associated with physiological disturbances
E275y00	Other specified non-organic eating disorder	Behavioural syndromes associated with physiological disturbances
E275z00	Non-organic eating disorder NOS	Behavioural syndromes associated with physiological disturbances
E27z300	Masturbation	Behavioural syndromes associated with physiological disturbances
E27zz00	Psychogenic syndromes NOS	Behavioural syndromes associated with physiological disturbances
E204.11	Postnatal depression	Behavioural syndromes associated with physiological disturbances
E114.00	Bipolar affective disorder, currently manic	Bipolar affective disorder
E114.11	Manic-depressive - now manic	Bipolar affective disorder
E114000	Bipolar affective disorder, currently manic, unspecified	Bipolar affective disorder
E114100	Bipolar affective disorder, currently manic, mild	Bipolar affective disorder
E114200	Bipolar affective disorder, currently manic, moderate	Bipolar affective disorder
E114300	Bipolar affect disord, currently manic, severe, no psychosis	Bipolar affective disorder
E114400	Bipolar affect disord, currently manic,severe with psychosis	Bipolar affective disorder
E114500	Bipolar affect disord,currently manic, part/unspec remission	Bipolar affective disorder
E114600	Bipolar affective disorder, currently manic, full remission	Bipolar affective disorder

E114z00	Bipolar affective disorder, currently manic, NOS	Bipolar affective disorder
E115.00	Bipolar affective disorder, currently depressed	Bipolar affective disorder
E115.11	Manic-depressive - now depressed	Bipolar affective disorder
E115000	Bipolar affective disorder, currently depressed, unspecified	Bipolar affective disorder
E115100	Bipolar affective disorder, currently depressed, mild	Bipolar affective disorder
E115200	Bipolar affective disorder, currently depressed, moderate	Bipolar affective disorder
E115300	Bipolar affect disord, now depressed, severe, no psychosis	Bipolar affective disorder
E115400	Bipolar affect disord, now depressed, severe with psychosis	Bipolar affective disorder
E115500	Bipolar affect disord, now depressed, part/unspec remission	Bipolar affective disorder
E115600	Bipolar affective disorder, now depressed, in full remission	Bipolar affective disorder
E115z00	Bipolar affective disorder, currently depressed, NOS	Bipolar affective disorder
E116.00	Mixed bipolar affective disorder	Bipolar affective disorder
E116000	Mixed bipolar affective disorder, unspecified	Bipolar affective disorder
E116100	Mixed bipolar affective disorder, mild	Bipolar affective disorder
E116200	Mixed bipolar affective disorder, moderate	Bipolar affective disorder
E116300	Mixed bipolar affective disorder, severe, without psychosis	Bipolar affective disorder
E116400	Mixed bipolar affective disorder, severe, with psychosis	Bipolar affective disorder
E116500	Mixed bipolar affective disorder, partial/unspec remission	Bipolar affective disorder
E116600	Mixed bipolar affective disorder, in full remission	Bipolar affective disorder
E116z00	Mixed bipolar affective disorder, NOS	Bipolar affective disorder
E117.00	Unspecified bipolar affective disorder	Bipolar affective disorder
E117000	Unspecified bipolar affective disorder, unspecified	Bipolar affective disorder
E117100	Unspecified bipolar affective disorder, mild	Bipolar affective disorder
E117200	Unspecified bipolar affective disorder, moderate	Bipolar affective disorder
E117300	Unspecified bipolar affective disorder, severe, no psychosis	Bipolar affective disorder
E117400	Unspecified bipolar affective disorder,severe with psychosis	Bipolar affective disorder
E117500	Unspecified bipolar affect disord, partial/unspec remission	Bipolar affective disorder
E117600	Unspecified bipolar affective disorder, in full remission	Bipolar affective disorder
E117z00	Unspecified bipolar affective disorder, NOS	Bipolar affective disorder
E118.00	Seasonal affective disorder	Bipolar affective disorder
E11y.00	Other and unspecified manic-depressive psychoses	Bipolar affective disorder
E11y000	Unspecified manic-depressive psychoses	Bipolar affective disorder
E11y300	Other mixed manic-depressive psychoses	Bipolar affective disorder
E11yz00	Other and unspecified manic-depressive psychoses NOS	Bipolar affective disorder
Eu31.00	[X]Bipolar affective disorder	Bipolar affective disorder

Eu31.11	[X]Manic-depressive illness	Bipolar affective disorder
Eu31.12	[X]Manic-depressive psychosis	Bipolar affective disorder
Eu31.13	[X]Manic-depressive reaction	Bipolar affective disorder
Eu31000	[X]Bipolar affective disorder, current episode hypomanic	Bipolar affective disorder
Eu31100	[X]Bipolar affect disorder cur epi manic wout psychotic symp	Bipolar affective disorder
Eu31200	[X]Bipolar affect disorder cur epi manic with psychotic symp	Bipolar affective disorder
Eu31300	[X]Bipolar affect disorder cur epi mild or moderate depressn	Bipolar affective disorder
Eu31400	[X]Bipol aff disord, curr epis sev depress, no psychot symp	Bipolar affective disorder
Eu31500	[X]Bipolar affect dis cur epi severe depres with psyc symp	Bipolar affective disorder
Eu31600	[X]Bipolar affective disorder, current episode mixed	Bipolar affective disorder
Eu31700	[X]Bipolar affective disorder, currently in remission	Bipolar affective disorder
Eu31y00	[X]Other bipolar affective disorders	Bipolar affective disorder
Eu31y11	[X]Bipolar II disorder	Bipolar affective disorder
Eu31y12	[X]Recurrent manic episodes	Bipolar affective disorder
Eu31z00	[X]Bipolar affective disorder, unspecified	Bipolar affective disorder
E2C..00	Disturbance of conduct NEC	Conduct disorder
E2C..11	Behaviour disorder	Conduct disorder
E2C0.00	Aggressive unsocial conduct disorder	Conduct disorder
E2C0000	Aggressive outburst	Conduct disorder
E2C0100	Anger reaction	Conduct disorder
E2C0z00	Aggressive unsocial conduct disorder NOS	Conduct disorder
E2C1.00	Nonaggressive unsocial conduct disorder	Conduct disorder
E2C1000	Unsocial childhood truancy	Conduct disorder
E2C1011	School refusal	Conduct disorder
E2C1100	Solitary stealing	Conduct disorder
E2C1z00	Nonaggressive unsocial conduct disorder NOS	Conduct disorder
E2C2.00	Socialised conduct disorder	Conduct disorder
E2C2000	Socialised childhood truancy	Conduct disorder
E2C2300	Group delinquency	Conduct disorder
E2C2z00	Socialised conduct disorder NOS	Conduct disorder
E2C3.00	Impulse control disorder NEC	Conduct disorder
E2C3000	Impulse control disorder, unspecified	Conduct disorder
E2Cy.00	Other conduct disturbances	Conduct disorder
E2Cyz00	Other conduct disturbances NOS	Conduct disorder
E2Cz.00	Unspecified disturbance of conduct	Conduct disorder
E2Cz000	Juvenile delinquency unspecified	Conduct disorder
E2Czz00	Disturbance of conduct NOS	Conduct disorder
Eu91.00	[X]Conduct disorders	Conduct disorder
Eu91000	[X]Conduct disorder confined to the family context	Conduct disorder
Eu91100	[X]Unsocialized conduct disorder	Conduct disorder
Eu91111	[X]Conduct disorder, solitary aggressive type	Conduct disorder

Eu91112	[X]Unsocialised aggressive disorder	Conduct disorder
Eu91200	[X]Socialized conduct disorder	Conduct disorder
Eu91211	[X]Conduct disorder, group type	Conduct disorder
Eu91212	[X]Group delinquency	Conduct disorder
Eu91213	[X]Offences in the context of gang membership	Conduct disorder
Eu91214	[X]Stealing in company of others	Conduct disorder
Eu91215	[X]Truancy from school	Conduct disorder
Eu91300	[X]Oppositional defiant disorder	Conduct disorder
Eu91y00	[X]Other conduct disorders	Conduct disorder
Eu91z00	[X]Conduct disorder, unspecified	Conduct disorder
Eu91z11	[X]Childhood behavioural disorder NOS	Conduct disorder
Eu91z12	[X]Childhood conduct disorder NOS	Conduct disorder
E2C1200	Tantrums	Conduct disorder
Eu44.00	[X]Dissociative [conversion] disorders	Dissociative [conversion] disorders
Eu44.11	[X]Conversion hysteria	Dissociative [conversion] disorders
Eu44.12	[X]Conversion reaction	Dissociative [conversion] disorders
Eu44.13	[X]Hysteria	Dissociative [conversion] disorders
Eu44.14	[X]Hysterical psychosis	Dissociative [conversion] disorders
Eu44000	[X]Dissociative amnesia	Dissociative [conversion] disorders
Eu44100	[X]Dissociative fugue	Dissociative [conversion] disorders
Eu44200	[X]Dissociative stupor	Dissociative [conversion] disorders
Eu44300	[X]Trance and possession disorders	Dissociative [conversion] disorders
Eu44400	[X]Dissociative motor disorders	Dissociative [conversion] disorders
Eu44411	[X]Psychogenic aphonia	Dissociative [conversion] disorders
Eu44412	[X]Psychogenic dysphonia	Dissociative [conversion] disorders
Eu44500	[X]Dissociative convulsions	Dissociative [conversion] disorders
Eu44511	[X]Pseudoseizures	Dissociative [conversion] disorders
Eu44600	[X]Dissociative anaesthesia and sensory loss	Dissociative [conversion] disorders
Eu44611	[X]Psychogenic deafness	Dissociative [conversion] disorders
Eu44700	[X]Mixed dissociative [conversion] disorders	Dissociative [conversion] disorders
Eu44y00	[X]Other dissociative [conversion] disorders	Dissociative [conversion] disorders
Eu44y11	[X]Ganser's syndrome	Dissociative [conversion] disorders
Eu44y12	[X]Multiple personality	Dissociative [conversion] disorders
Eu44y13	[X]Psychogenic confusion	Dissociative [conversion] disorders
Eu44y14	[X]Psychogenic twilight state	Dissociative [conversion] disorders
Eu44z00	[X]Dissociative [conversion] disorder, unspecified	Dissociative [conversion] disorders
E201.00	Hysteria	Dissociative [conversion] disorders
E201000	Hysteria unspecified	Dissociative [conversion] disorders
E201100	Hysterical blindness	Dissociative [conversion] disorders
E201200	Hysterical deafness	Dissociative [conversion] disorders
E201300	Hysterical tremor	Dissociative [conversion] disorders
E201400	Hysterical paralysis	Dissociative [conversion] disorders
E201500	Hysterical seizures	Dissociative [conversion] disorders
E201511	Fit - hysterical	Dissociative [conversion] disorders

E201600	Other conversion disorder	Dissociative [conversion] disorders
E201611	Astasia - abasia, hysterical	Dissociative [conversion] disorders
E201700	Hysterical amnesia	Dissociative [conversion] disorders
E201800	Hysterical fugue	Dissociative [conversion] disorders
E201900	Multiple personality	Dissociative [conversion] disorders
E201A00	Dissociative reaction unspecified	Dissociative [conversion] disorders
E201C00	Phantom pregnancy	Dissociative [conversion] disorders
E201z00	Hysteria NOS	Dissociative [conversion] disorders
E201z11	Aphonia - hysterical	Dissociative [conversion] disorders
E201z12	Ataxia - hysterical	Dissociative [conversion] disorders
E201z13	Ganser's syndrome - hysterical	Dissociative [conversion] disorders
1474.00	H/O: migraine	Migraine
1967.00	Abdominal migraine - symptom	Migraine
8B6N.00	Migraine prophylaxis	Migraine
F26..00	Migraine	Migraine
F260.00	Classical migraine	Migraine
F261.00	Common migraine	Migraine
F261000	Atypical migraine	Migraine
F261100	Sick headache	Migraine
F261z00	Common migraine NOS	Migraine
F262.00	Migraine variants	Migraine
F262200	Abdominal migraine	Migraine
F262300	Basilar migraine	Migraine
F262400	Ophthalmic migraine	Migraine
F262500	Periodic migrainous neuralgia	Migraine
F262z00	Migraine variant NOS	Migraine
F26y.00	Other forms of migraine	Migraine
F26y000	Hemiplegic migraine	Migraine
F26y100	Ophthalmoplegic migraine	Migraine
F26y111	Moebius' ophthalmoplegic migraine	Migraine
F26y200	Status migrainosus	Migraine
F26y300	Complicated migraine	Migraine
F26yz00	Other forms of migraine NOS	Migraine
F26z.00	Migraine NOS	Migraine
Fyu5300	[X]Other migraine	Migraine
K584.11	Migraine - menstrual	Migraine
R090D00	[D]Abdominal migraine	Migraine
E2C4.00	Mixed disturbance of conduct and emotion	Mixed disorders of conduct and emotions
E2C4z00	Mixed disturbance of conduct and emotion NOS	Mixed disorders of conduct and emotions
Eu92.00	[X]Mixed disorders of conduct and emotions	Mixed disorders of conduct and emotions
Eu92.11	[X]Emotional behavioural problems	Mixed disorders of conduct and emotions
Eu92000	[X]Depressive conduct disorder	Mixed disorders of conduct and emotions
Eu92y00	[X]Other mixed disorders of conduct and emotions	Mixed disorders of conduct and emotions
Eu92y11	[X]Conduct disorder associated with emotional disorder	Mixed disorders of conduct and emotions

Eu92y12	[X]Conduct disorder associated with neurotic disorder	Mixed disorders of conduct and emotions
Eu93.00	[X]Emotional disorders with onset specific to childhood	Mixed disorders of conduct and emotions
1475.00	H/O: trigeminal neuralgia	Neuropathic pain
A531.11	Post-herpetic neuralgia	Neuropathic pain
A531200	Postherpetic trigeminal neuralgia	Neuropathic pain
A531500	Postzoster neuralgia	Neuropathic pain
A531511	Postherpetic neuralgia	Neuropathic pain
C327413	Anderson-Fabry disease	Neuropathic pain
F262100	Horton's (histamine) neuralgia	Neuropathic pain
F300.00	Post-herpetic trigeminal neuralgia	Neuropathic pain
F301.00	Other specified trigeminal neuralgia	Neuropathic pain
F321.00	Glossopharyngeal neuralgia	Neuropathic pain
F356100	Morton's neuralgia	Neuropathic pain
F36..00	Hereditary and idiopathic peripheral neuropathy	Neuropathic pain
F360.00	Hereditary peripheral neuropathy	Neuropathic pain
F362.00	Hereditary sensory neuropathy	Neuropathic pain
F367.00	Peripheral neuropathy	Neuropathic pain
F372.12	Diabetic neuropathy	Neuropathic pain
F372000	Acute painful diabetic neuropathy	Neuropathic pain
F372100	Chronic painful diabetic neuropathy	Neuropathic pain
F372200	Asymptomatic diabetic neuropathy	Neuropathic pain
M271100	Neuropathic diabetic ulcer - foot	Neuropathic pain
N11y200	Neuropathic spondylopathy	Neuropathic pain
N242.00	Neuralgia, neuritis and radiculitis unspecified	Neuropathic pain
N242000	Neuralgia unspecified	Neuropathic pain
N242100	Neuritis unspecified	Neuropathic pain
N242300	Neuropathic pain	Neuropathic pain
N242z00	Neuralgia, neuritis or radiculitis NOS	Neuropathic pain
Eu45.00	[X]Somatoform disorders	Neurotic, stress - related and somoform disorders
Eu45000	[X]Somatization disorder	Neurotic, stress - related and somoform disorders
Eu45011	[X]Multiple psychosomatic disorder	Neurotic, stress - related and somoform disorders
Eu45012	[X]Briquet's syndrome	Neurotic, stress - related and somoform disorders
Eu45013	[X]Briquet's disorder	Neurotic, stress - related and somoform disorders
Eu45100	[X]Undifferentiated somatoform disorder	Neurotic, stress - related and somoform disorders
Eu45111	[X]Undifferentiated psychosomatic disorder	Neurotic, stress - related and somoform disorders
Eu45200	[X]Hypochondriacal disorder	Neurotic, stress - related and somoform disorders
Eu45211	[X]Body dysmorphic disorder	Neurotic, stress - related and somoform disorders
Eu45212	[X]Dysmorphophobia nondelusional	Neurotic, stress - related and somoform disorders
Eu45213	[X]Hypochondriacal neurosis	Neurotic, stress - related and somoform disorders
Eu45214	[X]Hypochondriasis	Neurotic, stress - related and somoform disorders
Eu45215	[X]Nosophobia	Neurotic, stress - related and somoform disorders
Eu45300	[X]Somatoform autonomic dysfunction	Neurotic, stress - related and somoform disorders
Eu45311	[X]Cardiac neurosis	Neurotic, stress - related and somoform disorders
Eu45312	[X]Da Costa's syndrome	Neurotic, stress - related and somoform disorders

Eu45313	[X]Gastric neurosis	Neurotic, stress - related and somoform disorders
Eu45314	[X]Neurocirculatory asthenia	Neurotic, stress - related and somoform disorders
Eu45y12	[X]Globus hystericus	Neurotic, stress - related and somoform disorders
Eu45y13	[X]Psychogenic pruritis	Neurotic, stress - related and somoform disorders
Eu45y14	[X]Psychogenic torticollis	Neurotic, stress - related and somoform disorders
Eu45y15	[X]Teeth-grinding	Neurotic, stress - related and somoform disorders
Eu45z00	[X]Somatoform disorder, unspecified	Neurotic, stress - related and somoform disorders
Eu45z11	[X]Psychosomatic disorder NOS	Neurotic, stress - related and somoform disorders
Eu46.00	[X]Other neurotic disorders	Neurotic, stress - related and somoform disorders
Eu46000	[X]Neurasthenia	Neurotic, stress - related and somoform disorders
Eu46011	[X]Fatigue syndrome	Neurotic, stress - related and somoform disorders
Eu46100	[X]Depersonalization - derealization syndrome	Neurotic, stress - related and somoform disorders
Eu46y00	[X]Other specified neurotic disorders	Neurotic, stress - related and somoform disorders
Eu46y11	[X]Briquet's disorder	Neurotic, stress - related and somoform disorders
Eu46y12	[X]Dhat syndrome	Neurotic, stress - related and somoform disorders
Eu46y13	[X]Occupational neurosis, including writer's cramp	Neurotic, stress - related and somoform disorders
Eu46y14	[X]Psychasthenia	Neurotic, stress - related and somoform disorders
Eu46y15	[X]Psychasthenia neurosis	Neurotic, stress - related and somoform disorders
Eu46y16	[X]Psychogenic syncope	Neurotic, stress - related and somoform disorders
Eu46z00	[X]Neurotic disorder, unspecified	Neurotic, stress - related and somoform disorders
Eu46z11	[X]Neurosis NOS	Neurotic, stress - related and somoform disorders
E204.00	Neurotic depression reactive type	Neurotic, stress - related and somoform disorders
E205.00	Neurasthenia - nervous debility	Neurotic, stress - related and somoform disorders
E205.11	Nervous exhaustion	Neurotic, stress - related and somoform disorders
E205.12	Tired all the time	Neurotic, stress - related and somoform disorders
E206.00	Depersonalisation syndrome	Neurotic, stress - related and somoform disorders
E207.00	Hypochondriasis	Neurotic, stress - related and somoform disorders
E20y.00	Other neurotic disorders	Neurotic, stress - related and somoform disorders
E20y000	Somatization disorder	Neurotic, stress - related and somoform disorders
E20y011	Briquet's disorder	Neurotic, stress - related and somoform disorders
E20y100	Writer's cramp neurosis	Neurotic, stress - related and somoform disorders
E20y200	Other occupational neurosis	Neurotic, stress - related and somoform disorders
E20y300	Psychasthenic neurosis	Neurotic, stress - related and somoform disorders
E20yz00	Other neurotic disorder NOS	Neurotic, stress - related and somoform disorders
E20z.00	Neurotic disorder NOS	Neurotic, stress - related and somoform disorders
E20z.11	Nervous breakdown	Neurotic, stress - related and somoform disorders
E2...00	Neurotic, personality and other nonpsychotic disorders	Neurotic, stress - related and somoform disorders
E20..00	Neurotic disorders	Neurotic, stress - related and somoform disorders
E201612	Globus hystericus	Neurotic, stress - related and somoform disorders
Eu4..00	[X]Neurotic, stress - related and somoform disorders	Neurotic, stress - related and somoform disorders
Eu43.00	[X]Reaction to severe stress, and adjustment disorders	Neurotic, stress - related and somoform disorders
Eu43000	[X]Acute stress reaction	Neurotic, stress - related and somoform disorders
Eu43011	[X]Acute crisis reaction	Neurotic, stress - related and somoform disorders
Eu43012	[X]Acute reaction to stress	Neurotic, stress - related and somoform disorders

Eu43013	[X]Combat fatigue	Neurotic, stress - related and somoform disorders
Eu43014	[X]Crisis state	Neurotic, stress - related and somoform disorders
Eu43015	[X]Psychic shock	Neurotic, stress - related and somoform disorders
Eu43100	[X]Post - traumatic stress disorder	Neurotic, stress - related and somoform disorders
Eu43111	[X]Traumatic neurosis	Neurotic, stress - related and somoform disorders
Eu43200	[X]Adjustment disorders	Neurotic, stress - related and somoform disorders
Eu43211	[X]Culture shock	Neurotic, stress - related and somoform disorders
Eu43212	[X]Grief reaction	Neurotic, stress - related and somoform disorders
Eu43213	[X]Hospitalism in children	Neurotic, stress - related and somoform disorders
Eu43y00	[X]Other reactions to severe stress	Neurotic, stress - related and somoform disorders
Eu43z00	[X]Reaction to severe stress, unspecified	Neurotic, stress - related and somoform disorders
13H4.12	Marital stress	Neurotic, stress - related and somoform disorders
13HT100	Stress at home	Neurotic, stress - related and somoform disorders
13HT111	Domestic stress	Neurotic, stress - related and somoform disorders
13JM.13	Stress at work	Neurotic, stress - related and somoform disorders
1B1L.00	Stress related problem	Neurotic, stress - related and somoform disorders
7P0H400	Stress echocardiography	Neurotic, stress - related and somoform disorders
9ON..00	Stress monitoring admin.	Neurotic, stress - related and somoform disorders
9ON..11	Stress clinic administration	Neurotic, stress - related and somoform disorders
9ON3.00	Stress monitoring default	Neurotic, stress - related and somoform disorders
9ON7.00	Stress monitoring verbal inv.	Neurotic, stress - related and somoform disorders
E28..00	Acute reaction to stress	Neurotic, stress - related and somoform disorders
E28..11	Combat fatigue	Neurotic, stress - related and somoform disorders
E280.00	Acute panic state due to acute stress reaction	Neurotic, stress - related and somoform disorders
E281.00	Acute fugue state due to acute stress reaction	Neurotic, stress - related and somoform disorders
E282.00	Acute stupor state due to acute stress reaction	Neurotic, stress - related and somoform disorders
E283.00	Other acute stress reactions	Neurotic, stress - related and somoform disorders
E283000	Acute situational disturbance	Neurotic, stress - related and somoform disorders
E283100	Acute posttrauma stress state	Neurotic, stress - related and somoform disorders
E283z00	Other acute stress reaction NOS	Neurotic, stress - related and somoform disorders
E284.00	Stress reaction causing mixed disturbance of emotion/conduct	Neurotic, stress - related and somoform disorders
E28z.00	Acute stress reaction NOS	Neurotic, stress - related and somoform disorders
E29..00	Adjustment reaction	Neurotic, stress - related and somoform disorders
E290.00	Brief depressive reaction	Neurotic, stress - related and somoform disorders
E290000	Grief reaction	Neurotic, stress - related and somoform disorders
E290011	Bereavement reaction	Neurotic, stress - related and somoform disorders
E290z00	Brief depressive reaction NOS	Neurotic, stress - related and somoform disorders
E291.00	Prolonged depressive reaction	Neurotic, stress - related and somoform disorders
E292.00	Adjustment reaction, predominant disturbance other emotions	Neurotic, stress - related and somoform disorders
E292400	Adjustment reaction with anxious mood	Neurotic, stress - related and somoform disorders
E292500	Culture shock	Neurotic, stress - related and somoform disorders
E292y00	Adjustment reaction with mixed disturbance of emotion	Neurotic, stress - related and somoform disorders
E292z00	Adjustment reaction with disturbance of other emotion NOS	Neurotic, stress - related and somoform disorders

E293.00	Adjustment reaction with predominant disturbance of conduct	Neurotic, stress - related and somoform disorders
E293000	Adjustment reaction with aggression	Neurotic, stress - related and somoform disorders
E293100	Adjustment reaction with antisocial behaviour	Neurotic, stress - related and somoform disorders
E293200	Adjustment reaction with destructiveness	Neurotic, stress - related and somoform disorders
E293z00	Adjustment reaction with predominant disturbance conduct NOS	Neurotic, stress - related and somoform disorders
E294.00	Adjustment reaction with disturbance emotion and conduct	Neurotic, stress - related and somoform disorders
E29y.00	Other adjustment reactions	Neurotic, stress - related and somoform disorders
E29y000	Concentration camp syndrome	Neurotic, stress - related and somoform disorders
E29y100	Other post-traumatic stress disorder	Neurotic, stress - related and somoform disorders
E29y200	Adjustment reaction with physical symptoms	Neurotic, stress - related and somoform disorders
E29y300	Elective mutism due to an adjustment reaction	Neurotic, stress - related and somoform disorders
E29y400	Adjustment reaction due to hospitalisation	Neurotic, stress - related and somoform disorders
E29y500	Other adjustment reaction with withdrawal	Neurotic, stress - related and somoform disorders
E29yz00	Other adjustment reactions NOS	Neurotic, stress - related and somoform disorders
E29z.00	Adjustment reaction NOS	Neurotic, stress - related and somoform disorders
Eu41000	[X]Panic disorder [episodic paroxysmal anxiety]	Neurotic, stress - related and somoform disorders
Eu41011	[X]Panic attack	Neurotic, stress - related and somoform disorders
Eu41012	[X]Panic state	Neurotic, stress - related and somoform disorders
Eu41012	[X]Acute reaction to stress	Neurotic, stress - related and somoform disorders
Eu43y00	[X]Other reactions to severe stress	Neurotic, stress - related and somoform disorders
F25E.00	Stress-induced epilepsy	Neurotic, stress - related and somoform disorders
Eu51.00	[X]Nonorganic sleep disorders	Nonorganic sleep disorders
Eu51000	[X]Nonorganic insomnia	Nonorganic sleep disorders
Eu51100	[X]Nonorganic hypersomnia	Nonorganic sleep disorders
Eu51200	[X]Nonorganic disorder of the sleep-wake schedule	Nonorganic sleep disorders
Eu51211	[X]Psychogenic inversion of circadian rhythm	Nonorganic sleep disorders
Eu51212	[X]Psychogenic inversion of nyctohemeral rhythm	Nonorganic sleep disorders
Eu51213	[X]Psychogenic inversion of sleep rhythm	Nonorganic sleep disorders
Eu51300	[X]Sleepwalking	Nonorganic sleep disorders
Eu51400	[X]Sleep terrors	Nonorganic sleep disorders
Eu51500	[X]Nightmares	Nonorganic sleep disorders
Eu51511	[X]Dream anxiety disorder	Nonorganic sleep disorders
Eu51y00	[X]Other nonorganic sleep disorders	Nonorganic sleep disorders
Eu51z00	[X]Nonorganic sleep disorder, unspecified	Nonorganic sleep disorders
Eu51z11	[X]Emotional sleep disorder NOS	Nonorganic sleep disorders
1B1B.00	Cannot sleep - insomnia	Nonorganic sleep disorders
1B1B.11	C/O - insomnia	Nonorganic sleep disorders
1B1B000	Initial insomnia	Nonorganic sleep disorders
1B1B100	Middle insomnia	Nonorganic sleep disorders
1B1B200	Late insomnia	Nonorganic sleep disorders
E274.00	Non-organic sleep disorders	Nonorganic sleep disorders

E274.11	Hypersomnia of non-organic origin	Nonorganic sleep disorders
E274.12	Insomnia due to nonorganic sleep disorder	Nonorganic sleep disorders
E274000	Unspecified non-organic sleep disorder	Nonorganic sleep disorders
E274100	Transient insomnia	Nonorganic sleep disorders
E274111	Insomnia NOS	Nonorganic sleep disorders
E274200	Persistent insomnia	Nonorganic sleep disorders
E274300	Transient hypersomnia	Nonorganic sleep disorders
E274311	Hypersomnia NOS	Nonorganic sleep disorders
E274400	Persistent hypersomnia	Nonorganic sleep disorders
E274500	Jet lag syndrome	Nonorganic sleep disorders
E274600	Shifting sleep-work schedule	Nonorganic sleep disorders
E274700	Somnambulism - sleep walking	Nonorganic sleep disorders
E274800	Night terrors	Nonorganic sleep disorders
E274900	Nightmares	Nonorganic sleep disorders
E274A00	Sleep drunkenness	Nonorganic sleep disorders
E274B00	Repeated rapid eye movement sleep interruptions	Nonorganic sleep disorders
E274C00	Other sleep stage or arousal dysfunction	Nonorganic sleep disorders
E274D00	Repetitive intrusions of sleep	Nonorganic sleep disorders
E274D11	Restless sleep	Nonorganic sleep disorders
E274E00	"Short-sleeper"	Nonorganic sleep disorders
E274F00	Inversion of sleep rhythm	Nonorganic sleep disorders
E274y00	Other non-organic sleep disorder	Nonorganic sleep disorders
E274y11	Dreams	Nonorganic sleep disorders
E274z00	Non-organic sleep disorder NOS	Nonorganic sleep disorders
Eu42.00	[X]Obsessive - compulsive disorder	Obsessive-compulsive disorder
Eu42.11	[X]Anankastic neurosis	Obsessive-compulsive disorder
Eu42.12	[X]Obsessive-compulsive neurosis	Obsessive-compulsive disorder
Eu42000	[X]Predominantly obsessional thoughts or ruminations	Obsessive-compulsive disorder
Eu42100	[X]Predominantly compulsive acts [obsessional rituals]	Obsessive-compulsive disorder
Eu42200	[X]Mixed obsessional thoughts and acts	Obsessive-compulsive disorder
Eu42y00	[X]Other obsessive-compulsive disorders	Obsessive-compulsive disorder
Eu42z00	[X]Obsessive-compulsive disorder, unspecified	Obsessive-compulsive disorder
Eu3y.00	[X]Other mood affective disorders	Other mood affective disorders
Eu3y000	[X]Other single mood affective disorders	Other mood affective disorders
Eu3y011	[X]Mixed affective episode	Other mood affective disorders
Eu3y100	[X]Other recurrent mood affective disorders	Other mood affective disorders
Eu3y111	[X]Recurrent brief depressive episodes	Other mood affective disorders
Eu3yy00	[X]Other specified mood affective disorders	Other mood affective disorders
Eu3z.00	[X]Unspecified mood affective disorder	Other mood affective disorders
Eu34.00	[X]Persistent mood affective disorders	Other mood affective disorders
Eu3..00	[X]Mood - affective disorders	Other mood affective disorders
E11zz00	Other affective psychosis NOS	Other mood affective disorders
146H.00	H/O: psychosis	Psychoses

212T.00	Psychosis, schizophrenia + bipolar affective disord resolved	Psychoses
212X.00	Psychosis resolved	Psychoses
E02..00	Drug psychoses	Psychoses
E02y.00	Other drug psychoses	Psychoses
E03..00	Transient organic psychoses	Psychoses
E03y.00	Other transient organic psychoses	Psychoses
E03y300	Unspecified puerperal psychosis	Psychoses
E04..00	Other chronic organic psychoses	Psychoses
E040.11	Korsakoff's non-alcoholic psychosis	Psychoses
E04y.00	Other specified chronic organic psychoses	Psychoses
E0y..00	Other specified organic psychoses	Psychoses
E1...00	Non-organic psychoses	Psychoses
E11..00	Affective psychoses	Psychoses
E11..11	Bipolar psychoses	Psychoses
E11..12	Depressive psychoses	Psychoses
E11..13	Manic psychoses	Psychoses
E110.11	Hypomanic psychoses	Psychoses
E110400	Single manic episode, severe, with psychosis	Psychoses
E111400	Recurrent manic episodes, severe, with psychosis	Psychoses
E112400	Single major depressive episode, severe, with psychosis	Psychoses
E113400	Recurrent major depressive episodes, severe, with psychosis	Psychoses
E11z.00	Other and unspecified affective psychoses	Psychoses
E11z000	Unspecified affective psychoses NOS	Psychosis
E12..00	Paranoid states	Psychoses
E120.00	Simple paranoid state	Psychoses
E121.00	Chronic paranoid psychosis	Psychoses
E121.11	Sander's disease	Psychoses
E123.00	Shared paranoid disorder	Psychoses
E123.11	Folie a deux	Psychoses
E12y.00	Other paranoid states	Psychoses
E12y000	Paranoia querulans	Psychoses
E12yz00	Other paranoid states NOS	Psychoses
E12z.00	Paranoid psychosis NOS	Psychoses
E13..00	Other nonorganic psychoses	Psychoses
E13..11	Reactive psychoses	Psychoses
E130.00	Reactive depressive psychosis	Psychoses
E131.00	Acute hysterical psychosis	Psychoses
E132.00	Reactive confusion	Psychoses
E133.00	Acute paranoid reaction	Psychoses
E133.11	Bouffee delirante	Psychoses
E134.00	Psychogenic paranoid psychosis	Psychoses
E13y.00	Other reactive psychoses	Psychoses
E13y000	Psychogenic stupor	Psychoses
E13y100	Brief reactive psychosis	Psychoses

E13yz00	Other reactive psychoses NOS	Psychoses
E13z.00	Nonorganic psychosis NOS	Psychoses
E13z.11	Psychotic episode NOS	Psychoses
E14..00	Psychoses with origin in childhood	Psychoses
E141.00	Disintegrative psychosis	Psychoses
E141000	Active disintegrative psychoses	Psychoses
E141100	Residual disintegrative psychoses	Psychoses
E14y.00	Other childhood psychoses	Psychoses
E14y000	Atypical childhood psychoses	Psychoses
E14y100	Borderline psychosis of childhood	Psychoses
E14yz00	Other childhood psychoses NOS	Psychoses
E14z.00	Child psychosis NOS	Psychoses
E14z.11	Childhood schizophrenia NOS	Psychoses
E1y..00	Other specified non-organic psychoses	Psychoses
Eu04.13	[X]Acute / subacute infective psychosis	Psychoses
Eu05y11	[X]Epileptic psychosis NOS	Psychoses
Eu0z.11	[X]Organic psychosis NOS	Psychoses
Eu0z.12	[X]Symptomatic psychosis NOS	Psychoses
Eu22.00	[X]Persistent delusional disorders	Psychoses
Eu22000	[X]Delusional disorder	Psychoses
Eu22011	[X]Paranoid psychosis	Psychoses
Eu22012	[X]Paranoid state	Psychoses
Eu22013	[X]Paraphrenia - late	Psychoses
Eu22014	[X]Sensitiver Beziehungswahn	Psychoses
Eu22015	[X]Paranoia	Psychoses
Eu22100	[X]Delusional misidentification syndrome	Psychoses
Eu22111	[X]Capgras syndrome	Psychoses
Eu22200	[X]Cotard syndrome	Psychoses
Eu22y00	[X]Other persistent delusional disorders	Psychoses
Eu22y11	[X]Delusional dysmorphophobia	Psychoses
Eu22y12	[X]Involutional paranoid state	Psychoses
Eu22y13	[X]Paranoia querulans	Psychoses
Eu22z00	[X]Persistent delusional disorder, unspecified	Psychoses
Eu23.00	[X]Acute and transient psychotic disorders	Psychoses
Eu23000	[X]Acute polymorphic psychot disord without symp of schizoph	Psychoses
Eu23011	[X]Bouffee delirante	Psychoses
Eu23012	[X]Cycloid psychosis	Psychoses
Eu23100	[X]Acute polymorphic psychot disord with symp of schizophren	Psychoses
Eu23111	[X]Bouffee delirante with symptoms of schizophrenia	Psychoses
Eu23112	[X]Cycloid psychosis with symptoms of schizophrenia	Psychoses
Eu23200	[X]Acute schizophrenia-like psychotic disorder	Psychoses
Eu23211	[X]Brief schizophreniform disorder	Psychoses
Eu23212	[X]Brief schizophrenifrm psych	Psychoses

Eu23213	[X]Oneirophrenia	Psychoses
Eu23214	[X]Schizophrenic reaction	Psychoses
Eu23300	[X]Other acute predominantly delusional psychotic disorders	Psychoses
Eu23312	[X]Psychogenic paranoid psychosis	Psychoses
Eu23y00	[X]Other acute and transient psychotic disorders	Psychoses
Eu23z00	[X]Acute and transient psychotic disorder, unspecified	Psychoses
Eu23z11	[X]Brief reactive psychosis NOS	Psychoses
Eu23z12	[X]Reactive psychosis	Psychoses
Eu24.00	[X]Induced delusional disorder	Psychoses
Eu24.11	[X]Folie a deux	Psychoses
Eu24.12	[X]Induced paranoid disorder	Psychoses
Eu24.13	[X]Induced psychotic disorder	Psychoses
Eu25.00	[X]Schizoaffective disorders	Psychoses
Eu25000	[X]Schizoaffective disorder, manic type	Psychoses
Eu25011	[X]Schizoaffective psychosis, manic type	Psychoses
Eu25012	[X]Schizophreniform psychosis, manic type	Psychoses
Eu25100	[X]Schizoaffective disorder, depressive type	Psychoses
Eu25111	[X]Schizoaffective psychosis, depressive type	Psychoses
Eu25112	[X]Schizophreniform psychosis, depressive type	Psychoses
Eu25200	[X]Schizoaffective disorder, mixed type	Psychoses
Eu25211	[X]Cyclic schizophrenia	Psychoses
Eu25212	[X]Mixed schizophrenic and affective psychosis	Psychoses
Eu25y00	[X]Other schizoaffective disorders	Psychoses
Eu25z00	[X]Schizoaffective disorder, unspecified	Psychoses
Eu25z11	[X]Schizoaffective psychosis NOS	Psychoses
Eu2y.00	[X]Other nonorganic psychotic disorders	Psychoses
Eu2y.11	[X]Chronic hallucinatory psychosis	Psychoses
Eu2z.00	[X]Unspecified nonorganic psychosis	Psychoses
Eu2z.11	[X]Psychosis NOS	Psychoses
Eu32312	[X]Single episode of psychogenic depressive psychosis	Psychoses
Eu32314	[X]Single episode of reactive depressive psychosis	Psychoses
Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis	Psychoses
Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis	Psychoses
Eu3z.11	[X]Affective psychosis NOS	Psychoses
Eu44.14	[X]Hysterical psychosis	Psychoses
Eu84013	[X]Infantile psychosis	Psychoses
Eu84111	[X]Atypical childhood psychosis	Psychoses
Eu84312	[X]Disintegrative psychosis	Psychoses
Eu84314	[X]Symbiotic psychosis	Psychoses
R20..00	[D]Senility, without mention of psychosis	Psychoses
ZV11111	[V]Personal history of manic-depressive psychosis	Psychoses

Appendix 14: The Read code list of possible comorbid diseases

Read code	Description	Disease/disorder
14B4.00	H/O: asthma	Asthma
1O2..00	Asthma confirmed	Asthma
663..11	Asthma monitoring	Asthma
663e.00	Asthma restricts exercise	Asthma
663e000	Asthma sometimes restricts exercise	Asthma
663e100	Asthma severely restricts exercise	Asthma
663f.00	Asthma never restricts exercise	Asthma
663h.00	Asthma - currently dormant	Asthma
663j.00	Asthma - currently active	Asthma
663N.00	Asthma disturbing sleep	Asthma
663n.00	Asthma treatment compliance satisfactory	Asthma
663N000	Asthma causing night waking	Asthma
663N100	Asthma disturbs sleep weekly	Asthma
663N200	Asthma disturbs sleep frequently	Asthma
663O.00	Asthma not disturbing sleep	Asthma
663O000	Asthma never disturbs sleep	Asthma
663P.00	Asthma limiting activities	Asthma
663p.00	Asthma treatment compliance unsatisfactory	Asthma
663q.00	Asthma daytime symptoms	Asthma
663Q.00	Asthma not limiting activities	Asthma
663r.00	Asthma causes night symptoms 1 to 2 times per month	Asthma
663s.00	Asthma never causes daytime symptoms	Asthma
663t.00	Asthma causes daytime symptoms 1 to 2 times per month	Asthma
663u.00	Asthma causes daytime symptoms 1 to 2 times per week	Asthma
663U.00	Asthma management plan given	Asthma
663v.00	Asthma causes daytime symptoms most days	Asthma
663V.00	Asthma severity	Asthma
663V000	Occasional asthma	Asthma
663V100	Mild asthma	Asthma
663V200	Moderate asthma	Asthma
663V300	Severe asthma	Asthma
663w.00	Asthma limits walking up hills or stairs	Asthma
663x.00	Asthma limits walking on the flat	Asthma
663y.00	Number of asthma exacerbations in past year	Asthma
66Y5.00	Change in asthma management plan	Asthma
66Y9.00	Step up change in asthma management plan	Asthma
66YA.00	Step down change in asthma management plan	Asthma
66YC.00	Absent from work or school due to asthma	Asthma
66YE.00	Asthma monitoring due	Asthma
66YK.00	Asthma follow-up	Asthma
66YP.00	Asthma night-time symptoms	Asthma

66YQ.00	Asthma monitoring by nurse	Asthma
66YR.00	Asthma monitoring by doctor	Asthma
8793.00	Asthma control step 0	Asthma
8794.00	Asthma control step 1	Asthma
8795.00	Asthma control step 2	Asthma
8796.00	Asthma control step 3	Asthma
8797.00	Asthma control step 4	Asthma
8798.00	Asthma control step 5	Asthma
8B3j.00	Asthma medication review	Asthma
8CR0.00	Asthma clinical management plan	Asthma
9OJ..00	Asthma monitoring admin.	Asthma
9OJ..11	Asthma clinic administration	Asthma
9OJ1.00	Attends asthma monitoring	Asthma
9OJ4.00	Asthma monitor 1st letter	Asthma
9OJ5.00	Asthma monitor 2nd letter	Asthma
9OJ6.00	Asthma monitor 3rd letter	Asthma
9OJ7.00	Asthma monitor verbal invite	Asthma
9OJ8.00	Asthma monitor phone invite	Asthma
9OJA.00	Asthma monitoring check done	Asthma
9OJA.11	Asthma monitored	Asthma
9OJZ.00	Asthma monitoring admin.NOS	Asthma
H33..00	Asthma	Asthma
H33..11	Bronchial asthma	Asthma
H330.00	Extrinsic (atopic) asthma	Asthma
H330.11	Allergic asthma	Asthma
H330.12	Childhood asthma	Asthma
H330.13	Hay fever with asthma	Asthma
H330.14	Pollen asthma	Asthma
H330000	Extrinsic asthma without status asthmaticus	Asthma
H330011	Hay fever with asthma	Asthma
H330100	Extrinsic asthma with status asthmaticus	Asthma
H330111	Extrinsic asthma with asthma attack	Asthma
H330z00	Extrinsic asthma NOS	Asthma
H331.00	Intrinsic asthma	Asthma
H331.11	Late onset asthma	Asthma
H331000	Intrinsic asthma without status asthmaticus	Asthma
H331100	Intrinsic asthma with status asthmaticus	Asthma
H331111	Intrinsic asthma with asthma attack	Asthma
H331z00	Intrinsic asthma NOS	Asthma
H332.00	Mixed asthma	Asthma
H334.00	Brittle asthma	Asthma
H33z.00	Asthma unspecified	Asthma
H33z011	Severe asthma attack	Asthma
H33z100	Asthma attack	Asthma
H33z111	Asthma attack NOS	Asthma
H33z200	Late-onset asthma	Asthma

H33zz00	Asthma NOS	Asthma
H33zz11	Exercise induced asthma	Asthma
H33zz12	Allergic asthma NEC	Asthma
H35y600	Sequoiosis (red-cedar asthma)	Asthma
H35y700	Wood asthma	Asthma
H47y000	Detergent asthma	Asthma
TJF7.00	Adverse reaction to antiasthmatics	Asthma
TJF7300	Adverse reaction to theophylline (asthma)	Asthma
TJF7z00	Adverse reaction to antiasthmatic NOS	Asthma
U60F600	[X]Antiasthmats caus adverse effects in therapeut use, NEC	Asthma
U60F611	[X] Adverse reaction to antiasthmatics	Asthma
U60F615	[X] Adverse reaction to theophylline - asthma	Asthma
U60F61A	[X] Adverse reaction to antiasthmatic NOS	Asthma
14A..00	H/O: cardiovascular disease	Cardiovascular diseases
66f..00	Cardiovascular disease monitoring	Cardiovascular diseases
G....00	Circulatory system diseases	Cardiovascular diseases
G....11	Cardiovascular system diseases	Cardiovascular diseases
G....12	Cardiac diseases	Cardiovascular diseases
G....13	Heart diseases	Cardiovascular diseases
G0...00	Acute rheumatic fever	Cardiovascular diseases
G00..00	Rheumatic fever without heart involvement	Cardiovascular diseases
G01..00	Rheumatic fever with heart involvement	Cardiovascular diseases
G010.00	Acute rheumatic pericarditis	Cardiovascular diseases
G011.00	Acute rheumatic endocarditis	Cardiovascular diseases
G012.00	Acute rheumatic myocarditis	Cardiovascular diseases
G01y.00	Other acute rheumatic heart disease	Cardiovascular diseases
G01y000	Acute rheumatic pancarditis	Cardiovascular diseases
G01yz00	Other acute rheumatic heart disease NOS	Cardiovascular diseases
G01z.00	Acute rheumatic heart disease NOS	Cardiovascular diseases
G02..00	Rheumatic chorea	Cardiovascular diseases
G02..11	Sydenham's chorea	Cardiovascular diseases
G020.00	Rheumatic chorea with heart involvement	Cardiovascular diseases
G021.00	Rheumatic chorea without mention of heart involvement	Cardiovascular diseases
G02z.00	Rheumatic chorea NOS	Cardiovascular diseases
G0y..00	Other specified acute rheumatic fever	Cardiovascular diseases
G0z..00	Acute rheumatic fever NOS	Cardiovascular diseases
G1...00	Chronic rheumatic heart disease	Cardiovascular diseases
G10..00	Chronic rheumatic pericarditis	Cardiovascular diseases
G100.00	Adherent rheumatic pericardium	Cardiovascular diseases
G101.00	Chronic rheumatic mediastinopericarditis	Cardiovascular diseases
G102.00	Chronic rheumatic myopericarditis	Cardiovascular diseases
G10z.00	Chronic rheumatic pericarditis NOS	Cardiovascular diseases
G11..00	Mitral valve diseases	Cardiovascular diseases
G11..11	Rheumatic mitral valve disease	Cardiovascular diseases
G110.00	Mitral stenosis	Cardiovascular diseases

G110.11	Rheumatic mitral stenosis	Cardiovascular diseases
G111.00	Rheumatic mitral insufficiency	Cardiovascular diseases
G111.11	Mitral incompetence - rheumatic	Cardiovascular diseases
G111.12	Mitral regurgitation - rheumatic	Cardiovascular diseases
G112.00	Mitral stenosis with insufficiency	Cardiovascular diseases
G112.12	Mitral stenosis with incompetence	Cardiovascular diseases
G112.13	Mitral stenosis with regurgitation	Cardiovascular diseases
G113.00	Nonrheumatic mitral valve stenosis	Cardiovascular diseases
G114.00	Ruptured mitral valve cusp	Cardiovascular diseases
G11z.00	Mitral valve disease NOS	Cardiovascular diseases
G12..00	Rheumatic aortic valve disease	Cardiovascular diseases
G120.00	Rheumatic aortic stenosis	Cardiovascular diseases
G121.00	Rheumatic aortic insufficiency	Cardiovascular diseases
G121.11	Aortic incompetence - rheumatic	Cardiovascular diseases
G121.12	Aortic regurgitation - rheumatic	Cardiovascular diseases
G122.00	Rheumatic aortic stenosis with insufficiency	Cardiovascular diseases
G12z.00	Rheumatic aortic valve disease NOS	Cardiovascular diseases
G13..00	Diseases of mitral and aortic valves	Cardiovascular diseases
G130.00	Mitral and aortic stenosis	Cardiovascular diseases
G131.00	Mitral stenosis and aortic insufficiency	Cardiovascular diseases
G131.13	Mitral stenosis and aortic incompetence	Cardiovascular diseases
G131.14	Mitral stenosis and aortic regurgitation	Cardiovascular diseases
G132.00	Mitral insufficiency and aortic stenosis	Cardiovascular diseases
G132.12	Mitral incompetence and aortic stenosis	Cardiovascular diseases
G132.13	Mitral regurgitation and aortic stenosis	Cardiovascular diseases
G133.00	Mitral and aortic incompetence	Cardiovascular diseases
G133.11	Mitral and aortic insufficiency	Cardiovascular diseases
G133.12	Mitral and aortic regurgitation	Cardiovascular diseases
G13y.00	Multiple mitral and aortic valve involvement	Cardiovascular diseases
G13z.00	Mitral and aortic valve disease NOS	Cardiovascular diseases
G14..00	Other chronic rheumatic endocardial disease	Cardiovascular diseases
G140.00	Tricuspid valve disease NEC	Cardiovascular diseases
G140000	Rheumatic tricuspid stenosis	Cardiovascular diseases
G140100	Rheumatic tricuspid insufficiency	Cardiovascular diseases
G140111	Tricuspid regurgitation - rheumatic	Cardiovascular diseases
G140112	Tricuspid incompetence - rheumatic	Cardiovascular diseases
G140200	Rheumatic tricuspid stenosis and insufficiency	Cardiovascular diseases
G14021X	Rheumatic tricuspid stenosis and regurgitation	Cardiovascular diseases
G14021Y	Rheumatic tricuspid stenosis and incompetence	Cardiovascular diseases
G140300	Tricuspid stenosis, cause unspecified	Cardiovascular diseases
G140400	Tricuspid insufficiency, cause unspecified	Cardiovascular diseases
G140412	Tricuspid incompetence, cause unspecified	Cardiovascular diseases
G140413	Tricuspid regurgitation, cause unspecified	Cardiovascular diseases
G140500	Tricuspid stenosis and insufficiency, cause unspecified	Cardiovascular diseases
G140511	Tricuspid stenosis and incompetence, cause unspecified	Cardiovascular diseases

G140514	Tricuspid stenosis and regurgitation, cause unspecified	Cardiovascular diseases
G140z00	Rheumatic tricuspid valve disease NOS	Cardiovascular diseases
G141.00	Rheumatic pulmonary valve disease	Cardiovascular diseases
G141000	Rheumatic pulmonary stenosis	Cardiovascular diseases
G141100	Rheumatic pulmonary insufficiency	Cardiovascular diseases
G141200	Rheumatic pulmonary stenosis and insufficiency	Cardiovascular diseases
G141z00	Rheumatic pulmonary valve disease NOS	Cardiovascular diseases
G14z.00	Rheumatic endocarditis NOS	Cardiovascular diseases
G14z.11	Rheumatic valvulitis, chronic NOS	Cardiovascular diseases
G1y..00	Other specified chronic rheumatic heart disease	Cardiovascular diseases
G1y0.00	Rheumatic myocarditis	Cardiovascular diseases
G1yz.00	Other and unspecified rheumatic heart disease	Cardiovascular diseases
G1yz000	Rheumatic heart disease unspecified	Cardiovascular diseases
G1yz100	Rheumatic left ventricular failure	Cardiovascular diseases
G1yzz00	Other rheumatic heart disease NOS	Cardiovascular diseases
G1z..00	Chronic rheumatic heart disease NOS	Cardiovascular diseases
G3...00	Ischaemic heart disease	Cardiovascular diseases
G3...11	Arteriosclerotic heart disease	Cardiovascular diseases
G3...12	Atherosclerotic heart disease	Cardiovascular diseases
G3...13	IHD - Ischaemic heart disease	Cardiovascular diseases
G30..00	Acute myocardial infarction	Cardiovascular diseases
G30..11	Attack - heart	Cardiovascular diseases
G30..12	Coronary thrombosis	Cardiovascular diseases
G30..13	Cardiac rupture following myocardial infarction (MI)	Cardiovascular diseases
G30..14	Heart attack	Cardiovascular diseases
G30..15	MI - acute myocardial infarction	Cardiovascular diseases
G30..16	Thrombosis - coronary	Cardiovascular diseases
G30..17	Silent myocardial infarction	Cardiovascular diseases
G300.00	Acute anterolateral infarction	Cardiovascular diseases
G301.00	Other specified anterior myocardial infarction	Cardiovascular diseases
G301000	Acute anteroapical infarction	Cardiovascular diseases
G301100	Acute anteroseptal infarction	Cardiovascular diseases
G301z00	Anterior myocardial infarction NOS	Cardiovascular diseases
G302.00	Acute inferolateral infarction	Cardiovascular diseases
G303.00	Acute inferoposterior infarction	Cardiovascular diseases
G304.00	Posterior myocardial infarction NOS	Cardiovascular diseases
G305.00	Lateral myocardial infarction NOS	Cardiovascular diseases
G306.00	True posterior myocardial infarction	Cardiovascular diseases
G307.00	Acute subendocardial infarction	Cardiovascular diseases
G307000	Acute non-Q wave infarction	Cardiovascular diseases
G307100	Acute non-ST segment elevation myocardial infarction	Cardiovascular diseases
G308.00	Inferior myocardial infarction NOS	Cardiovascular diseases
G309.00	Acute Q-wave infarct	Cardiovascular diseases
G30A.00	Mural thrombosis	Cardiovascular diseases
G30B.00	Acute posterolateral myocardial infarction	Cardiovascular diseases
G30X.00	Acute transmural myocardial infarction of unspecif site	Cardiovascular diseases

G30X000	Acute ST segment elevation myocardial infarction	Cardiovascular diseases
G30y.00	Other acute myocardial infarction	Cardiovascular diseases
G30y000	Acute atrial infarction	Cardiovascular diseases
G30y100	Acute papillary muscle infarction	Cardiovascular diseases
G30y200	Acute septal infarction	Cardiovascular diseases
G30yz00	Other acute myocardial infarction NOS	Cardiovascular diseases
G30z.00	Acute myocardial infarction NOS	Cardiovascular diseases
G31..00	Other acute and subacute ischaemic heart disease	Cardiovascular diseases
G310.00	Postmyocardial infarction syndrome	Cardiovascular diseases
G310.11	Dressler's syndrome	Cardiovascular diseases
G311.00	Preinfarction syndrome	Cardiovascular diseases
G311.11	Crescendo angina	Cardiovascular diseases
G311.12	Impending infarction	Cardiovascular diseases
G311.13	Unstable angina	Cardiovascular diseases
G311.14	Angina at rest	Cardiovascular diseases
G311000	Myocardial infarction aborted	Cardiovascular diseases
G311011	MI - myocardial infarction aborted	Cardiovascular diseases
G311100	Unstable angina	Cardiovascular diseases
G311200	Angina at rest	Cardiovascular diseases
G311300	Refractory angina	Cardiovascular diseases
G311400	Worsening angina	Cardiovascular diseases
G311500	Acute coronary syndrome	Cardiovascular diseases
G311z00	Preinfarction syndrome NOS	Cardiovascular diseases
G312.00	Coronary thrombosis not resulting in myocardial infarction	Cardiovascular diseases
G31y.00	Other acute and subacute ischaemic heart disease	Cardiovascular diseases
G31y000	Acute coronary insufficiency	Cardiovascular diseases
G31y100	Microinfarction of heart	Cardiovascular diseases
G31y200	Subendocardial ischaemia	Cardiovascular diseases
G31y300	Transient myocardial ischaemia	Cardiovascular diseases
G31yz00	Other acute and subacute ischaemic heart disease NOS	Cardiovascular diseases
G32..00	Old myocardial infarction	Cardiovascular diseases
G32..11	Healed myocardial infarction	Cardiovascular diseases
G32..12	Personal history of myocardial infarction	Cardiovascular diseases
G33..00	Angina pectoris	Cardiovascular diseases
G330.00	Angina decubitus	Cardiovascular diseases
G330000	Nocturnal angina	Cardiovascular diseases
G330z00	Angina decubitus NOS	Cardiovascular diseases
G331.00	Prinzmetal's angina	Cardiovascular diseases
G331.11	Variant angina pectoris	Cardiovascular diseases
G332.00	Coronary artery spasm	Cardiovascular diseases
G33z.00	Angina pectoris NOS	Cardiovascular diseases
G33z000	Status anginosus	Cardiovascular diseases
G33z100	Stenocardia	Cardiovascular diseases
G33z200	Syncope anginosa	Cardiovascular diseases
G33z300	Angina on effort	Cardiovascular diseases
G33z400	Ischaemic chest pain	Cardiovascular diseases

G33z500	Post infarct angina	Cardiovascular diseases
G33z600	New onset angina	Cardiovascular diseases
G33z700	Stable angina	Cardiovascular diseases
G33zz00	Angina pectoris NOS	Cardiovascular diseases
G34..00	Other chronic ischaemic heart disease	Cardiovascular diseases
G340.00	Coronary atherosclerosis	Cardiovascular diseases
G340.11	Triple vessel disease of the heart	Cardiovascular diseases
G340.12	Coronary artery disease	Cardiovascular diseases
G340000	Single coronary vessel disease	Cardiovascular diseases
G340100	Double coronary vessel disease	Cardiovascular diseases
G341.00	Aneurysm of heart	Cardiovascular diseases
G341.11	Cardiac aneurysm	Cardiovascular diseases
G341000	Ventricular cardiac aneurysm	Cardiovascular diseases
G341100	Other cardiac wall aneurysm	Cardiovascular diseases
G341111	Mural cardiac aneurysm	Cardiovascular diseases
G341200	Aneurysm of coronary vessels	Cardiovascular diseases
G341300	Acquired atrioventricular fistula of heart	Cardiovascular diseases
G341z00	Aneurysm of heart NOS	Cardiovascular diseases
G342.00	Atherosclerotic cardiovascular disease	Cardiovascular diseases
G343.00	Ischaemic cardiomyopathy	Cardiovascular diseases
G344.00	Silent myocardial ischaemia	Cardiovascular diseases
G34y.00	Other specified chronic ischaemic heart disease	Cardiovascular diseases
G34y000	Chronic coronary insufficiency	Cardiovascular diseases
G34y100	Chronic myocardial ischaemia	Cardiovascular diseases
G34yz00	Other specified chronic ischaemic heart disease NOS	Cardiovascular diseases
G34z.00	Other chronic ischaemic heart disease NOS	Cardiovascular diseases
G34z000	Asymptomatic coronary heart disease	Cardiovascular diseases
G35..00	Subsequent myocardial infarction	Cardiovascular diseases
G350.00	Subsequent myocardial infarction of anterior wall	Cardiovascular diseases
G351.00	Subsequent myocardial infarction of inferior wall	Cardiovascular diseases
G353.00	Subsequent myocardial infarction of other sites	Cardiovascular diseases
G35X.00	Subsequent myocardial infarction of unspecified site	Cardiovascular diseases
G36..00	Certain current complication follow acute myocardial infarct	Cardiovascular diseases
G360.00	Haemopericardium/current comp folow acut myocard infarct	Cardiovascular diseases
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct	Cardiovascular diseases
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn	Cardiovascular diseases
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI	Cardiovascular diseases
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct	Cardiovascular diseases
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct	Cardiovascular diseases
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI	Cardiovascular diseases
G37..00	Cardiac syndrome X	Cardiovascular diseases
G38..00	Postoperative myocardial infarction	Cardiovascular diseases

G380.00	Postoperative transmural myocardial infarction anterior wall	Cardiovascular diseases
G381.00	Postoperative transmural myocardial infarction inferior wall	Cardiovascular diseases
G382.00	Postoperative transmural myocardial infarction other sites	Cardiovascular diseases
G383.00	Postoperative transmural myocardial infarction unspec site	Cardiovascular diseases
G384.00	Postoperative subendocardial myocardial infarction	Cardiovascular diseases
G38z.00	Postoperative myocardial infarction, unspecified	Cardiovascular diseases
G3y..00	Other specified ischaemic heart disease	Cardiovascular diseases
G3z..00	Ischaemic heart disease NOS	Cardiovascular diseases
G54..00	Other diseases of endocardium	Cardiovascular diseases
G54..11	Heart valve disorders - non rheumatic	Cardiovascular diseases
G540.00	Mitral valve incompetence	Cardiovascular diseases
G540.12	Mitral valve insufficiency	Cardiovascular diseases
G540.14	Mitral valve regurgitation	Cardiovascular diseases
G540.15	Mitral valve prolapse	Cardiovascular diseases
G540.16	Mitral regurgitation	Cardiovascular diseases
G540000	Mitral incompetence, non-rheumatic	Cardiovascular diseases
G540100	Mitral incompetence, cause unspecified	Cardiovascular diseases
G540200	Mitral valve prolapse	Cardiovascular diseases
G540300	Mitral valve leaf prolapse	Cardiovascular diseases
G540z00	Mitral valve disorders NOS	Cardiovascular diseases
G541.00	Aortic valve disorders	Cardiovascular diseases
G541000	Aortic incompetence, non-rheumatic	Cardiovascular diseases
G541011	Aortic insufficiency, non-rheumatic	Cardiovascular diseases
G541012	Aortic regurgitation, non-rheumatic	Cardiovascular diseases
G541100	Aortic stenosis, non-rheumatic	Cardiovascular diseases
G541200	Aortic incompetence alone, cause unspecified	Cardiovascular diseases
G541211	Aortic insufficiency alone, cause unspecified	Cardiovascular diseases
G541212	Aortic regurgitation alone, cause unspecified	Cardiovascular diseases
G541300	Aortic stenosis alone, cause unspecified	Cardiovascular diseases
G541400	Aortic valve stenosis with insufficiency	Cardiovascular diseases
G541500	Aortic stenosis	Cardiovascular diseases
G541600	Aortic valve sclerosis	Cardiovascular diseases
G541700	Aortic valve calcification	Cardiovascular diseases
G541z00	Aortic valve disorders NOS	Cardiovascular diseases
G542.00	Tricuspid valve disorders, non-rheumatic	Cardiovascular diseases
G542000	Tricuspid incompetence, non-rheumatic	Cardiovascular diseases
G542011	Tricuspid insufficiency, non-rheumatic	Cardiovascular diseases
G542012	Tricuspid regurgitation, non-rheumatic	Cardiovascular diseases
G542100	Tricuspid stenosis, non-rheumatic	Cardiovascular diseases
G542200	Nonrheumatic tricuspid valve stenosis with insufficiency	Cardiovascular diseases
G542X00	Nonrheumatic tricuspid valve disorder, unspecified	Cardiovascular diseases
G542z00	Tricuspid valve disorders NOS	Cardiovascular diseases
G543.00	Pulmonary valve disorders	Cardiovascular diseases
G543000	Pulmonary incompetence, non-rheumatic	Cardiovascular diseases

G543011	Pulmonary insufficiency, non-rheumatic	Cardiovascular diseases
G543012	Pulmonary regurgitation, non-rheumatic	Cardiovascular diseases
G543100	Pulmonary stenosis, non-rheumatic	Cardiovascular diseases
G543200	Pulmonary incompetence, cause unspecified	Cardiovascular diseases
G543213	Pulmonary insufficiency, cause unspecified	Cardiovascular diseases
G543215	Pulmonary regurgitation, cause unspecified	Cardiovascular diseases
G543300	Pulmonary stenosis, cause unspecified	Cardiovascular diseases
G543311	Pulmonary stenosis, cause unspecified	Cardiovascular diseases
G543400	Pulmonary valve stenosis with insufficiency	Cardiovascular diseases
G543z00	Pulmonary valve disorders NOS	Cardiovascular diseases
G544.00	Multiple valve diseases	Cardiovascular diseases
G544000	Disorders of both aortic and tricuspid valves	Cardiovascular diseases
G544100	Disorders of both mitral and tricuspid valves	Cardiovascular diseases
G544200	Combined disorders of mitral, aortic and tricuspid valves	Cardiovascular diseases
G544X00	Multiple valve disease, unspecified	Cardiovascular diseases
G54z.00	Endocarditis, valve unspecified	Cardiovascular diseases
G54z000	Incompetence of unspecified heart valve	Cardiovascular diseases
G54z013	Regurgitation of unspecified heart valve	Cardiovascular diseases
G54z014	Insufficiency of unspecified heart valve	Cardiovascular diseases
G54z100	Stenosis of unspecified heart valve	Cardiovascular diseases
G54z200	Chronic cardiac valvulitis NOS	Cardiovascular diseases
G54z300	Endocarditis, valve unspecified, OS	Cardiovascular diseases
G54z400	Endocarditis in disease EC	Cardiovascular diseases
G54z500	Valvular heart disease	Cardiovascular diseases
G54zz00	Endocarditis, valve unspecified, NOS	Cardiovascular diseases
G58..00	Heart failure	Cardiovascular diseases
G58..11	Cardiac failure	Cardiovascular diseases
G580.00	Congestive heart failure	Cardiovascular diseases
G580.11	Congestive cardiac failure	Cardiovascular diseases
G580.12	Right heart failure	Cardiovascular diseases
G580.13	Right ventricular failure	Cardiovascular diseases
G580.14	Biventricular failure	Cardiovascular diseases
G580000	Acute congestive heart failure	Cardiovascular diseases
G580100	Chronic congestive heart failure	Cardiovascular diseases
G580200	Decompensated cardiac failure	Cardiovascular diseases
G580300	Compensated cardiac failure	Cardiovascular diseases
G580400	Congestive heart failure due to valvular disease	Cardiovascular diseases
G581.00	Left ventricular failure	Cardiovascular diseases
G581.11	Asthma - cardiac	Cardiovascular diseases
G581.12	Pulmonary oedema - acute	Cardiovascular diseases
G581.13	Impaired left ventricular function	Cardiovascular diseases
G581000	Acute left ventricular failure	Cardiovascular diseases
G582.00	Acute heart failure	Cardiovascular diseases
G58z.00	Heart failure NOS	Cardiovascular diseases
G58z.11	Weak heart	Cardiovascular diseases

G58z.12	Cardiac failure NOS	Cardiovascular diseases
G5y..00	Other specified heart disease	Cardiovascular diseases
G5y0.00	Myocarditis NOS	Cardiovascular diseases
G5y1.00	Myocardial degeneration	Cardiovascular diseases
G5y2.00	Cardiovascular arteriosclerosis unspecified	Cardiovascular diseases
G5yX.00	Cardiovascular disease, unspecified	Cardiovascular diseases
G5yy500	Hyperkinetic heart disease	Cardiovascular diseases
G5yy600	Atrial thrombosis	Cardiovascular diseases
G5yy700	Left ventricular thrombosis	Cardiovascular diseases
G5yy800	Right ventricular thrombosis	Cardiovascular diseases
G5yy900	Left ventricular systolic dysfunction	Cardiovascular diseases
G5yyA00	Left ventricular diastolic dysfunction	Cardiovascular diseases
G5yyz00	Other ill-defined heart disease NOS	Cardiovascular diseases
G5yz.00	Other heart disease NOS	Cardiovascular diseases
G5z..00	Heart disease NOS	Cardiovascular diseases
Gyu5g00	[X]Cardiovascular disease, unspecified	Cardiovascular diseases
Eu81100	[X]Specific spelling disorder	Cognitive dsiorder
Eu81111	[X]Specific spelling retardation without reading disorder	Cognitive dsiorder
Eu81200	[X]Specific disorder of arithmetical skills	Cognitive dsiorder
Eu81211	[X]Developmental acalculia	Cognitive dsiorder
Eu81212	[X]Developmental arithmetical disorder	Cognitive dsiorder
Eu81213	[X]Developmental Gerstmann's syndrome	Cognitive dsiorder
Eu81300	[X]Mixed disorder of scholastic skills	Cognitive dsiorder
Eu81y00	[X]Other developmental disorders of scholastic skills	Cognitive dsiorder
Eu81y11	[X]Developmental expressive writing disorder	Cognitive dsiorder
Eu81z00	[X]Developmental disorder of scholastic skills, unspecified	Cognitive dsiorder
Eu81z11	[X]Learning disability NOS	Cognitive dsiorder
Eu81z12	[X]Learning disorder NOS	Cognitive dsiorder
Eu81z13	[X]Learn acquisition disab NOS	Cognitive dsiorder
Eu05700	[X]Mild cognitive disorder	Cognitive dsiorder
28E..00	Cognitive decline	Cognitive dsiorder
7L1a.00	Cognitive behavioural therapy	Cognitive dsiorder
7L1a000	Cognitive behavioural therapy by unidisciplinary team	Cognitive dsiorder
7L1a100	Cognitive behavioural therapy by multidisciplinary team	Cognitive dsiorder
7L1az00	Cognitive behavioural therapy NOS	Cognitive dsiorder
8G13.00	Cognitive-behaviour therapy	Cognitive dsiorder
8G14.00	Cognitive analytic therapy	Cognitive dsiorder
3AE1.00	GDS level 2 - very mild cognitive decline	Cognitive dsiorder
3AE2.00	GDS level 3 - mild cognitive decline	Cognitive dsiorder
3AE3.00	GDS level 4 - moderate cognitive decline	Cognitive dsiorder
3AE4.00	GDS level 5 - moderately severe cognitive decline	Cognitive dsiorder
3AE5.00	GDS level 6 - severe cognitive decline	Cognitive dsiorder
3AE6.00	GDS level 7 - very severe cognitive decline	Cognitive dsiorder
7L1ay00	Other specified cognitive behavioural therapy	Cognitive dsiorder

8G11.00	Psychotherapy - cognitive	Cognitive dsiorder
8G15.00	Computerised cognitive behavioural therapy	Cognitive dsiorder
Z46..00	Cognitively-based interventions to modify behaviour	Cognitive dsiorder
Z52..00	Cognitive and behavioural therapy	Cognitive dsiorder
Z521.00	Cognitive - behaviour therapy	Cognitive dsiorder
Z521.11	CBT - Cognitive - behaviour therapy	Cognitive dsiorder
Z521.12	Cognitive-behavioural therapy approach	Cognitive dsiorder
Z521.13	Cognitive-behaviour therapy	Cognitive dsiorder
Z521100	Generic cognitive behavioural therapy	Cognitive dsiorder
Z522.00	Behavioural psychotherapy	Cognitive dsiorder
Z522.11	Behaviour therapy	Cognitive dsiorder
Z522.13	Cognitive therapy approach	Cognitive dsiorder
Z522.14	Cognitive approach	Cognitive dsiorder
Z523.00	Cognitive therapy	Cognitive dsiorder
Z523.11	Cognitive therapy approach	Cognitive dsiorder
Z523.12	Cognitive approach	Cognitive dsiorder
Z523100	Beck's cognitive therapy	Cognitive dsiorder
Z523300	Cognitive restructuring	Cognitive dsiorder
Z582100	Cognitive analytic therapy	Cognitive dsiorder
Z73..00	Cognitive intervention strategies	Cognitive dsiorder
Z7A1.00	Cognitive skills training	Cognitive dsiorder
Z7A2100	Strategy training for cognitive skills	Cognitive dsiorder
Z7C..00	Cognitive function observations	Cognitive dsiorder
ZD15.00	Cognitive neuropsychological language therapy	Cognitive dsiorder
ZD38200	Cognitive behavioural language therapy	Cognitive dsiorder
1B1A.00	Memory loss - amnesia	Cognitive dsiorder
1B1a.00	Poor auditory sequential memory	Cognitive dsiorder
1B1A.11	Amnesia symptom	Cognitive dsiorder
1B1A.12	Memory loss symptom	Cognitive dsiorder
1B1A.13	Memory disturbance	Cognitive dsiorder
Z7CE.00	Memory observations	Cognitive dsiorder
Z7CE.11	Observations relating to memory	Cognitive dsiorder
Z7CE.12	Observations relating to retention of information	Cognitive dsiorder
Z7CE111	Average memory	Cognitive dsiorder
Z7CE300	Recovery of memory	Cognitive dsiorder
Z7CE400	Memory disturbance (& amnesia (& symptom))	Cognitive dsiorder
Z7CE411	Amnesia symptom	Cognitive dsiorder
Z7CE412	Memory loss symptom	Cognitive dsiorder
Z7CE413	Memory loss - amnesia	Cognitive dsiorder
Z7CE414	Memory disturbance	Cognitive dsiorder
Z7CE415	Loss of memory	Cognitive dsiorder
Z7CE500	Forgetful	Cognitive dsiorder
Z7CE600	Amnesia	Cognitive dsiorder
Z7CE611	Memory loss	Cognitive dsiorder
Z7CE612	Memory gone	Cognitive dsiorder
Z7CE613	Dysmnesia	Cognitive dsiorder

Z7CE614	Memory loss - amnesia	Cognitive dsiorder
Z7CE615	Loss of memory	Cognitive dsiorder
Z7CE616	LOM - Loss of memory	Cognitive dsiorder
Z7CE800	Anterograde amnesia	Cognitive dsiorder
Z7CE811	Antegrade amnesia	Cognitive dsiorder
Z7CE900	Retrograde amnesia	Cognitive dsiorder
Z7CE911	RA - Retrograde amnesia	Cognitive dsiorder
Z7CEA00	Impairment of registration	Cognitive dsiorder
Z7CEA11	Impairment of working memory	Cognitive dsiorder
Z7CEA12	Impairment of immediate recall	Cognitive dsiorder
Z7CEA13	Impairment of primary memory	Cognitive dsiorder
Z7CEB00	Amnesia for remote events	Cognitive dsiorder
Z7CEB11	Loss of memory for remote events	Cognitive dsiorder
Z7CEB12	Poor memory for remote events	Cognitive dsiorder
Z7CEC00	Amnesia for recent events	Cognitive dsiorder
Z7CEC11	Loss of memory for recent events	Cognitive dsiorder
Z7CEC12	No memory for recent events	Cognitive dsiorder
Z7CED00	Amnesia for day to day facts	Cognitive dsiorder
Z7CEE00	Amnesia for important personal information	Cognitive dsiorder
Z7CEG00	Transient memory loss	Cognitive dsiorder
Z7CEH00	Memory impairment	Cognitive dsiorder
Z7CEH11	Memory dysfunction	Cognitive dsiorder
Z7CEH12	Memory deficit	Cognitive dsiorder
Z7CEH13	Bad memory	Cognitive dsiorder
Z7CEH14	Memory problem	Cognitive dsiorder
Z7CEH15	Poor memory	Cognitive dsiorder
Z7CEI00	Mixes past with present	Cognitive dsiorder
Z7CEJ00	Memory lapses	Cognitive dsiorder
Z7CEK00	Minor memory lapses	Cognitive dsiorder
Z7CEL00	Mild memory disturbance	Cognitive dsiorder
Z7CEM00	Distortion of memory	Cognitive dsiorder
Z7CEN00	Confabulation	Cognitive dsiorder
Z7CEN11	Invents experiences to compensate for loss of memory	Cognitive dsiorder
Z7CEO00	Momentary confabulation	Cognitive dsiorder
Z7CEP00	Fantastical confabulation	Cognitive dsiorder
1B1W.00	Transient epileptic amnesia	Cognitive dsiorder
E201700	Hysterical amnesia	Cognitive dsiorder
G655.00	Transient global amnesia	Cognitive dsiorder
R00z500	[D]Anterograde amnesia	Cognitive dsiorder
Ryu5000	[X]Other amnesia	Cognitive dsiorder
C370.00	Cystic fibrosis	Cystic fibrosis
C370.11	Fibrocystic disease	Cystic fibrosis
C370.12	Mucoviscidosis	Cystic fibrosis
C370000	Cystic fibrosis with no meconium ileus	Cystic fibrosis

C370100	Cystic fibrosis with meconium ileus	Cystic fibrosis
C370111	Meconium ileus in cystic fibrosis	Cystic fibrosis
C370200	Cystic fibrosis with pulmonary manifestations	Cystic fibrosis
C370300	Cystic fibrosis with intestinal manifestations	Cystic fibrosis
C370y00	Cystic fibrosis with other manifestations	Cystic fibrosis
C370y11	Cystic fibrosis with combined manifestations	Cystic fibrosis
C370z00	Cystic fibrosis NOS	Cystic fibrosis
1465.00	H/O: depression	Depression
212S.00	Depression resolved	Depression
32E4.00	ECG: S-T depression	Depression
8CAa.00	Patient given advice about management of depression	Depression
8HHq.00	Referral for guided self-help for depression	Depression
9H90.00	Depression annual review	Depression
9H91.00	Depression medication review	Depression
9kQ..11	On full dose long term treatment for depression	Depression
9Ov..00	Depression monitoring administration	Depression
9Ov0.00	Depression monitoring first letter	Depression
9Ov1.00	Depression monitoring second letter	Depression
9Ov2.00	Depression monitoring third letter	Depression
9Ov3.00	Depression monitoring verbal invite	Depression
9Ov4.00	Depression monitoring telephone invite	Depression
E112.00	Single major depressive episode	Depression
E112.11	Agitated depression	Depression
E112.12	Endogenous depression first episode	Depression
E112.13	Endogenous depression first episode	Depression
E112.14	Endogenous depression	Depression
E112000	Single major depressive episode, unspecified	Depression
E112100	Single major depressive episode, mild	Depression
E112200	Single major depressive episode, moderate	Depression
E112300	Single major depressive episode, severe, without psychosis	Depression
E112400	Single major depressive episode, severe, with psychosis	Depression
E112500	Single major depressive episode, partial or unspec remission	Depression
E112600	Single major depressive episode, in full remission	Depression
E112z00	Single major depressive episode NOS	Depression
E113.00	Recurrent major depressive episode	Depression
E113.11	Endogenous depression - recurrent	Depression
E113000	Recurrent major depressive episodes, unspecified	Depression
E113100	Recurrent major depressive episodes, mild	Depression
E113200	Recurrent major depressive episodes, moderate	Depression
E113300	Recurrent major depressive episodes, severe, no psychosis	Depression
E113400	Recurrent major depressive episodes, severe, with psychosis	Depression
E113500	Recurrent major depressive episodes,partial/unspec remission	Depression
E113600	Recurrent major depressive episodes, in full remission	Depression

E113700	Recurrent depression	Depression
E113z00	Recurrent major depressive episode NOS	Depression
E11z200	Masked depression	Depression
E130.11	Psychotic reactive depression	Depression
E135.00	Agitated depression	Depression
E2B1.00	Chronic depression	Depression
Eu32.00	[X]Depressive episode	Depression
Eu32.11	[X]Single episode of depressive reaction	Depression
Eu32.12	[X]Single episode of psychogenic depression	Depression
Eu32.13	[X]Single episode of reactive depression	Depression
Eu32000	[X]Mild depressive episode	Depression
Eu32100	[X]Moderate depressive episode	Depression
Eu32200	[X]Severe depressive episode without psychotic symptoms	Depression
Eu32211	[X]Single episode agitated depressn w'out psychotic symptoms	Depression
Eu32212	[X]Single episode major depression w'out psychotic symptoms	Depression
Eu32213	[X]Single episode vital depression w'out psychotic symptoms	Depression
Eu32300	[X]Severe depressive episode with psychotic symptoms	Depression
Eu32311	[X]Single episode of major depression and psychotic symptoms	Depression
Eu32312	[X]Single episode of psychogenic depressive psychosis	Depression
Eu32313	[X]Single episode of psychotic depression	Depression
Eu32314	[X]Single episode of reactive depressive psychosis	Depression
Eu32400	[X]Mild depression	Depression
Eu32y00	[X]Other depressive episodes	Depression
Eu32y11	[X]Atypical depression	Depression
Eu32y12	[X]Single episode of masked depression NOS	Depression
Eu32z00	[X]Depressive episode, unspecified	Depression
Eu32z11	[X]Depression NOS	Depression
Eu32z12	[X]Depressive disorder NOS	Depression
Eu32z13	[X]Prolonged single episode of reactive depression	Depression
Eu32z14	[X] Reactive depression NOS	Depression
Eu33.00	[X]Recurrent depressive disorder	Depression
Eu33.11	[X]Recurrent episodes of depressive reaction	Depression
Eu33.12	[X]Recurrent episodes of psychogenic depression	Depression
Eu33.13	[X]Recurrent episodes of reactive depression	Depression
Eu33.14	[X]Seasonal depressive disorder	Depression
Eu33000	[X]Recurrent depressive disorder, current episode mild	Depression
Eu33100	[X]Recurrent depressive disorder, current episode moderate	Depression
Eu33200	[X]Recurr depress disorder cur epi severe without psyc sympt	Depression
Eu33211	[X]Endogenous depression without psychotic symptoms	Depression
Eu33212	[X]Major depression, recurrent without psychotic symptoms	Depression
Eu33213	[X]Manic-depress psychosis,depressd,no psychotic symptoms	Depression

Eu33214	[X]Vital depression, recurrent without psychotic symptoms	Depression
Eu33300	[X]Recurrent depress disorder cur epi severe with psyc symp	Depression
Eu33311	[X]Endogenous depression with psychotic symptoms	Depression
Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms	Depression
Eu33313	[X]Recurr severe episodes/major depression+psychotic symptom	Depression
Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis	Depression
Eu33315	[X]Recurrent severe episodes of psychotic depression	Depression
Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis	Depression
Eu33400	[X]Recurrent depressive disorder, currently in remission	Depression
Eu33y00	[X]Other recurrent depressive disorders	Depression
Eu33z00	[X]Recurrent depressive disorder, unspecified	Depression
Eu33z11	[X]Monopolar depression NOS	Depression
E2B..00	Depressive disorder NEC	Depression
Eu8..00	[X]Disorders of psychological development	Developmental disorders of speech and language
Eu80.00	[X]Specific developmental disorders of speech and language	Developmental disorders of speech and language
Eu80000	[X]Specific speech articulation disorder	Developmental disorders of speech and language
Eu80011	[X]Developmental phonological disorder	Developmental disorders of speech and language
Eu80012	[X]Developmental speech articulation disorder	Developmental disorders of speech and language
Eu80013	[X]Dyslalia	Developmental disorders of speech and language
Eu80014	[X]Functional speech articulation disorder	Developmental disorders of speech and language
Eu80015	[X]Lalling	Developmental disorders of speech and language
Eu80100	[X]Expressive language disorder	Developmental disorders of speech and language
Eu80111	[X]Developmental dysphasia, expressive type	Developmental disorders of speech and language
Eu80112	[X]Developmental aphasia, expressive type	Developmental disorders of speech and language
Eu80200	[X]Receptive language disorder	Developmental disorders of speech and language
Eu80211	[X]Congenital auditory imperception	Developmental disorders of speech and language
Eu80212	[X]Developmental dysphasia, receptive type	Developmental disorders of speech and language
Eu80213	[X]Developmental Wernicke's aphasia	Developmental disorders of speech and language
Eu80214	[X]Word deafness	Developmental disorders of speech and language
Eu80215	[X]Developmental aphasia, receptive type	Developmental disorders of speech and language
Eu80300	[X]Acquired aphasia with epilepsy [Landau - Kleffner]	Developmental disorders of speech and language
Eu80400	[X]Cocktail party syndrome	Developmental disorders of speech and language
Eu80500	[X]Semantic-pragmatic disorder	Developmental disorders of speech and language

Eu80y00	[X]Other developmental disorders of speech and language	Developmental disorders of speech and language
Eu80y11	[X]Lisping	Developmental disorders of speech and language
Eu80z00	[X]Developmental disorder of speech and language unspecified	Developmental disorders of speech and language
Eu80z11	[X]Language development disorder NOS	Developmental disorders of speech and language
Eu81.00	[X]Specific developmental disorders of scholastic skills	Developmental disorders of speech and language
Eu81000	[X]Specific reading disorder	Developmental disorders of speech and language
Eu81011	[X]Backward reading	Developmental disorders of speech and language
Eu81012	[X]Developmental dyslexia	Developmental disorders of speech and language
Eu81013	[X]Specific reading retardation	Developmental disorders of speech and language
1434.00	H/O: diabetes mellitus	Diabetes mellitus
42c..00	HbA1 - diabetic control	Diabetes mellitus
42W..00	Hb. A1C - diabetic control	Diabetes mellitus
42WZ.00	Hb. A1C - diabetic control NOS	Diabetes mellitus
66A..00	Diabetic monitoring	Diabetes mellitus
66A4.00	Diabetic on oral treatment	Diabetes mellitus
66A5.00	Diabetic on insulin	Diabetes mellitus
66A8.00	Has seen dietician - diabetes	Diabetes mellitus
66A9.00	Understands diet - diabetes	Diabetes mellitus
66Aa.00	Diabetic diet - poor compliance	Diabetes mellitus
66AA.11	Injection sites - diabetic	Diabetes mellitus
66AG.00	Diabetic drug side effects	Diabetes mellitus
66AH.00	Diabetic treatment changed	Diabetes mellitus
66AI.00	Diabetic - good control	Diabetes mellitus
66Ai.00	Diabetic 6 month review	Diabetes mellitus
66AJ.00	Diabetic - poor control	Diabetes mellitus
66AJ.11	Unstable diabetes	Diabetes mellitus
66AJ100	Brittle diabetes	Diabetes mellitus
66AJz00	Diabetic - poor control NOS	Diabetes mellitus
66AK.00	Diabetic - cooperative patient	Diabetes mellitus
66Ak.00	Diabetic monitoring - lower risk albumin excretion	Diabetes mellitus
66Al.00	Diabetic monitoring - higher risk albumin excretion	Diabetes mellitus
66AL.00	Diabetic-uncooperative patient	Diabetes mellitus
66AM.00	Diabetic - follow-up default	Diabetes mellitus
66AN.00	Date diabetic treatment start	Diabetes mellitus
66An.00	Diabetes type 1 review	Diabetes mellitus
66AO.00	Date diabetic treatment stopp.	Diabetes mellitus
66Ao.00	Diabetes type 2 review	Diabetes mellitus
66AP.00	Diabetes: practice programme	Diabetes mellitus
66AQ.00	Diabetes: shared care programme	Diabetes mellitus
66AU.00	Diabetes care by hospital only	Diabetes mellitus
66AV.00	Diabetic on insulin and oral treatment	Diabetes mellitus

66AW.00	Diabetic foot risk assessment	Diabetes mellitus
66AY.00	Diabetic diet - good compliance	Diabetes mellitus
66AZ.00	Diabetic monitoring NOS	Diabetes mellitus
8A12.00	Diabetic crisis monitoring	Diabetes mellitus
8B3l.00	Diabetes medication review	Diabetes mellitus
8BL2.00	Patient on maximal tolerated therapy for diabetes	Diabetes mellitus
8CA4100	Pt advised re diabetic diet	Diabetes mellitus
8CS0.00	Diabetes care plan agreed	Diabetes mellitus
8H2J.00	Admit diabetic emergency	Diabetes mellitus
8H3O.00	Non-urgent diabetic admission	Diabetes mellitus
8HBG.00	Diabetic retinopathy 12 month review	Diabetes mellitus
8HBH.00	Diabetic retinopathy 6 month review	Diabetes mellitus
9NN8.00	Under care of diabetologist	Diabetes mellitus
9NN9.00	Under care of diabetes specialist nurse	Diabetes mellitus
9OL..00	Diabetes monitoring admin.	Diabetes mellitus
9OL..11	Diabetes clinic administration	Diabetes mellitus
9OL1.00	Attends diabetes monitoring	Diabetes mellitus
9OL3.00	Diabetes monitoring default	Diabetes mellitus
9OL4.00	Diabetes monitoring 1st letter	Diabetes mellitus
9OL5.00	Diabetes monitoring 2nd letter	Diabetes mellitus
9OL6.00	Diabetes monitoring 3rd letter	Diabetes mellitus
9OL7.00	Diabetes monitor.verbal invite	Diabetes mellitus
9OL8.00	Diabetes monitor.phone invite	Diabetes mellitus
9OLA.00	Diabetes monitor. check done	Diabetes mellitus
9OLA.11	Diabetes monitored	Diabetes mellitus
9OLD.00	Diabetic patient unsuitable for digital retinal photography	Diabetes mellitus
9OLZ.00	Diabetes monitoring admin.NOS	Diabetes mellitus
C10..00	Diabetes mellitus	Diabetes mellitus
C100.00	Diabetes mellitus with no mention of complication	Diabetes mellitus
C100000	Diabetes mellitus, juvenile type, no mention of complication	Diabetes mellitus
C100011	Insulin dependent diabetes mellitus	Diabetes mellitus
C100111	Maturity onset diabetes	Diabetes mellitus
C100112	Non-insulin dependent diabetes mellitus	Diabetes mellitus
C100z00	Diabetes mellitus NOS with no mention of complication	Diabetes mellitus
C101.00	Diabetes mellitus with ketoacidosis	Diabetes mellitus
C101000	Diabetes mellitus, juvenile type, with ketoacidosis	Diabetes mellitus
C101y00	Other specified diabetes mellitus with ketoacidosis	Diabetes mellitus
C101z00	Diabetes mellitus NOS with ketoacidosis	Diabetes mellitus
C102.00	Diabetes mellitus with hyperosmolar coma	Diabetes mellitus
C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma	Diabetes mellitus
C102z00	Diabetes mellitus NOS with hyperosmolar coma	Diabetes mellitus
C103.00	Diabetes mellitus with ketoacidotic coma	Diabetes mellitus
C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma	Diabetes mellitus

C103y00	Other specified diabetes mellitus with coma	Diabetes mellitus
C103z00	Diabetes mellitus NOS with ketoacidotic coma	Diabetes mellitus
C104.00	Diabetes mellitus with renal manifestation	Diabetes mellitus
C104.11	Diabetic nephropathy	Diabetes mellitus
C104000	Diabetes mellitus, juvenile type, with renal manifestation	Diabetes mellitus
C104y00	Other specified diabetes mellitus with renal complications	Diabetes mellitus
C104z00	Diabetes mellitis with nephropathy NOS	Diabetes mellitus
C105.00	Diabetes mellitus with ophthalmic manifestation	Diabetes mellitus
C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation	Diabetes mellitus
C105y00	Other specified diabetes mellitus with ophthalmic complicatn	Diabetes mellitus
C105z00	Diabetes mellitus NOS with ophthalmic manifestation	Diabetes mellitus
C106.00	Diabetes mellitus with neurological manifestation	Diabetes mellitus
C106.11	Diabetic amyotrophy	Diabetes mellitus
C106.12	Diabetes mellitus with neuropathy	Diabetes mellitus
C106.13	Diabetes mellitus with polyneuropathy	Diabetes mellitus
C106000	Diabetes mellitus, juvenile, + neurological manifestation	Diabetes mellitus
C106y00	Other specified diabetes mellitus with neurological comps	Diabetes mellitus
C106z00	Diabetes mellitus NOS with neurological manifestation	Diabetes mellitus
C107.00	Diabetes mellitus with peripheral circulatory disorder	Diabetes mellitus
C107.11	Diabetes mellitus with gangrene	Diabetes mellitus
C107.12	Diabetes with gangrene	Diabetes mellitus
C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder	Diabetes mellitus
C107y00	Other specified diabetes mellitus with periph circ comps	Diabetes mellitus
C107z00	Diabetes mellitus NOS with peripheral circulatory disorder	Diabetes mellitus
C108.00	Insulin dependent diabetes mellitus	Diabetes mellitus
C108.11	IDDM-Insulin dependent diabetes mellitus	Diabetes mellitus
C108.12	Type 1 diabetes mellitus	Diabetes mellitus
C108.13	Type I diabetes mellitus	Diabetes mellitus
C108000	Insulin-dependent diabetes mellitus with renal complications	Diabetes mellitus
C108011	Type I diabetes mellitus with renal complications	Diabetes mellitus
C108012	Type 1 diabetes mellitus with renal complications	Diabetes mellitus
C108100	Insulin-dependent diabetes mellitus with ophthalmic comps	Diabetes mellitus
C108111	Type I diabetes mellitus with ophthalmic complications	Diabetes mellitus
C108112	Type 1 diabetes mellitus with ophthalmic complications	Diabetes mellitus
C108200	Insulin-dependent diabetes mellitus with neurological comps	Diabetes mellitus
C108211	Type I diabetes mellitus with neurological complications	Diabetes mellitus
C108212	Type 1 diabetes mellitus with neurological complications	Diabetes mellitus
C108300	Insulin dependent diabetes mellitus with multiple complicatn	Diabetes mellitus

C108311	Type I diabetes mellitus with multiple complications	Diabetes mellitus
C108312	Type 1 diabetes mellitus with multiple complications	Diabetes mellitus
C108400	Unstable insulin dependent diabetes mellitus	Diabetes mellitus
C108411	Unstable type I diabetes mellitus	Diabetes mellitus
C108412	Unstable type 1 diabetes mellitus	Diabetes mellitus
C108500	Insulin dependent diabetes mellitus with ulcer	Diabetes mellitus
C108511	Type I diabetes mellitus with ulcer	Diabetes mellitus
C108512	Type 1 diabetes mellitus with ulcer	Diabetes mellitus
C108600	Insulin dependent diabetes mellitus with gangrene	Diabetes mellitus
C108611	Type I diabetes mellitus with gangrene	Diabetes mellitus
C108612	Type 1 diabetes mellitus with gangrene	Diabetes mellitus
C108700	Insulin dependent diabetes mellitus with retinopathy	Diabetes mellitus
C108711	Type I diabetes mellitus with retinopathy	Diabetes mellitus
C108712	Type 1 diabetes mellitus with retinopathy	Diabetes mellitus
C108800	Insulin dependent diabetes mellitus - poor control	Diabetes mellitus
C108811	Type I diabetes mellitus - poor control	Diabetes mellitus
C108812	Type 1 diabetes mellitus - poor control	Diabetes mellitus
C108900	Insulin dependent diabetes maturity onset	Diabetes mellitus
C108911	Type I diabetes mellitus maturity onset	Diabetes mellitus
C108912	Type 1 diabetes mellitus maturity onset	Diabetes mellitus
C108A00	Insulin-dependent diabetes without complication	Diabetes mellitus
C108A11	Type I diabetes mellitus without complication	Diabetes mellitus
C108A12	Type 1 diabetes mellitus without complication	Diabetes mellitus
C108B00	Insulin dependent diabetes mellitus with mononeuropathy	Diabetes mellitus
C108B11	Type I diabetes mellitus with mononeuropathy	Diabetes mellitus
C108B12	Type 1 diabetes mellitus with mononeuropathy	Diabetes mellitus
C108C00	Insulin dependent diabetes mellitus with polyneuropathy	Diabetes mellitus
C108C11	Type I diabetes mellitus with polyneuropathy	Diabetes mellitus
C108C12	Type 1 diabetes mellitus with polyneuropathy	Diabetes mellitus
C108D00	Insulin dependent diabetes mellitus with nephropathy	Diabetes mellitus
C108D11	Type I diabetes mellitus with nephropathy	Diabetes mellitus
C108D12	Type 1 diabetes mellitus with nephropathy	Diabetes mellitus
C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma	Diabetes mellitus
C108E11	Type I diabetes mellitus with hypoglycaemic coma	Diabetes mellitus
C108E12	Type 1 diabetes mellitus with hypoglycaemic coma	Diabetes mellitus
C108F00	Insulin dependent diabetes mellitus with diabetic cataract	Diabetes mellitus
C108F11	Type I diabetes mellitus with diabetic cataract	Diabetes mellitus
C108F12	Type 1 diabetes mellitus with diabetic cataract	Diabetes mellitus
C108G11	Type I diabetes mellitus with peripheral angiopathy	Diabetes mellitus
C108G12	Type 1 diabetes mellitus with peripheral angiopathy	Diabetes mellitus
C108H00	Insulin dependent diabetes mellitus with arthropathy	Diabetes mellitus
C108H11	Type I diabetes mellitus with arthropathy	Diabetes mellitus
C108H12	Type 1 diabetes mellitus with arthropathy	Diabetes mellitus

C108J11	Type I diabetes mellitus with neuropathic arthropathy	Diabetes mellitus
C108J12	Type 1 diabetes mellitus with neuropathic arthropathy	Diabetes mellitus
C108y00	Other specified diabetes mellitus with multiple comps	Diabetes mellitus
C108z00	Unspecified diabetes mellitus with multiple complications	Diabetes mellitus
C109.00	Non-insulin dependent diabetes mellitus	Diabetes mellitus
C109.11	NIDDM - Non-insulin dependent diabetes mellitus	Diabetes mellitus
C109.12	Type 2 diabetes mellitus	Diabetes mellitus
C109.13	Type II diabetes mellitus	Diabetes mellitus
C109000	Non-insulin-dependent diabetes mellitus with renal comps	Diabetes mellitus
C109011	Type II diabetes mellitus with renal complications	Diabetes mellitus
C109012	Type 2 diabetes mellitus with renal complications	Diabetes mellitus
C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps	Diabetes mellitus
C109111	Type II diabetes mellitus with ophthalmic complications	Diabetes mellitus
C109112	Type 2 diabetes mellitus with ophthalmic complications	Diabetes mellitus
C109200	Non-insulin-dependent diabetes mellitus with neuro comps	Diabetes mellitus
C109211	Type II diabetes mellitus with neurological complications	Diabetes mellitus
C109212	Type 2 diabetes mellitus with neurological complications	Diabetes mellitus
C109300	Non-insulin-dependent diabetes mellitus with multiple comps	Diabetes mellitus
C109311	Type II diabetes mellitus with multiple complications	Diabetes mellitus
C109312	Type 2 diabetes mellitus with multiple complications	Diabetes mellitus
C109400	Non-insulin dependent diabetes mellitus with ulcer	Diabetes mellitus
C109411	Type II diabetes mellitus with ulcer	Diabetes mellitus
C109412	Type 2 diabetes mellitus with ulcer	Diabetes mellitus
C109500	Non-insulin dependent diabetes mellitus with gangrene	Diabetes mellitus
C109511	Type II diabetes mellitus with gangrene	Diabetes mellitus
C109512	Type 2 diabetes mellitus with gangrene	Diabetes mellitus
C109600	Non-insulin-dependent diabetes mellitus with retinopathy	Diabetes mellitus
C109611	Type II diabetes mellitus with retinopathy	Diabetes mellitus
C109612	Type 2 diabetes mellitus with retinopathy	Diabetes mellitus
C109700	Non-insulin dependent diabetes mellitus - poor control	Diabetes mellitus
C109711	Type II diabetes mellitus - poor control	Diabetes mellitus
C109712	Type 2 diabetes mellitus - poor control	Diabetes mellitus
C109900	Non-insulin-dependent diabetes mellitus without complication	Diabetes mellitus
C109911	Type II diabetes mellitus without complication	Diabetes mellitus
C109912	Type 2 diabetes mellitus without complication	Diabetes mellitus
C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy	Diabetes mellitus
C109A11	Type II diabetes mellitus with mononeuropathy	Diabetes mellitus
C109A12	Type 2 diabetes mellitus with mononeuropathy	Diabetes mellitus
C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy	Diabetes mellitus
C109B11	Type II diabetes mellitus with polyneuropathy	Diabetes mellitus
C109B12	Type 2 diabetes mellitus with polyneuropathy	Diabetes mellitus

C109C00	Non-insulin dependent diabetes mellitus with nephropathy	Diabetes mellitus
C109C11	Type II diabetes mellitus with nephropathy	Diabetes mellitus
C109C12	Type 2 diabetes mellitus with nephropathy	Diabetes mellitus
C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma	Diabetes mellitus
C109D11	Type II diabetes mellitus with hypoglycaemic coma	Diabetes mellitus
C109D12	Type 2 diabetes mellitus with hypoglycaemic coma	Diabetes mellitus
C109E00	Non-insulin depend diabetes mellitus with diabetic cataract	Diabetes mellitus
C109E11	Type II diabetes mellitus with diabetic cataract	Diabetes mellitus
C109E12	Type 2 diabetes mellitus with diabetic cataract	Diabetes mellitus
C109F11	Type II diabetes mellitus with peripheral angiopathy	Diabetes mellitus
C109F12	Type 2 diabetes mellitus with peripheral angiopathy	Diabetes mellitus
C109G00	Non-insulin dependent diabetes mellitus with arthropathy	Diabetes mellitus
C109G11	Type II diabetes mellitus with arthropathy	Diabetes mellitus
C109G12	Type 2 diabetes mellitus with arthropathy	Diabetes mellitus
C109H11	Type II diabetes mellitus with neuropathic arthropathy	Diabetes mellitus
C109H12	Type 2 diabetes mellitus with neuropathic arthropathy	Diabetes mellitus
C109J00	Insulin treated Type 2 diabetes mellitus	Diabetes mellitus
C109J11	Insulin treated non-insulin dependent diabetes mellitus	Diabetes mellitus
C109J12	Insulin treated Type II diabetes mellitus	Diabetes mellitus
C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus	Diabetes mellitus
C10A.00	Malnutrition-related diabetes mellitus	Diabetes mellitus
C10A000	Malnutrition-related diabetes mellitus with coma	Diabetes mellitus
C10A100	Malnutrition-related diabetes mellitus with ketoacidosis	Diabetes mellitus
C10A200	Malnutrition-related diabetes mellitus with renal complicatn	Diabetes mellitus
C10A300	Malnutrit-related diabetes mellitus wth ophthalmic complicat	Diabetes mellitus
C10A400	Malnutrition-related diabetes mellitus wth neuro complicatns	Diabetes mellitus
C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn	Diabetes mellitus
C10A600	Malnutrition-related diabetes mellitus with multiple comps	Diabetes mellitus
C10A700	Malnutrition-related diabetes mellitus without complications	Diabetes mellitus
C10AW00	Malnutrit-related diabetes mellitus with unspec complics	Diabetes mellitus
C10AX00	Malnutrit-relat diabetes mellitus with other spec comps	Diabetes mellitus
C10B.00	Diabetes mellitus induced by steroids	Diabetes mellitus
C10B000	Steroid induced diabetes mellitus without complication	Diabetes mellitus
C10C.00	Diabetes mellitus autosomal dominant	Diabetes mellitus
C10C.11	Maturity onset diabetes in youth	Diabetes mellitus
C10C.12	Maturity onset diabetes in youth type 1	Diabetes mellitus
C10D.00	Diabetes mellitus autosomal dominant type 2	Diabetes mellitus
C10D.11	Maturity onset diabetes in youth type 2	Diabetes mellitus
C10E.00	Type 1 diabetes mellitus	Diabetes mellitus
C10E.11	Type I diabetes mellitus	Diabetes mellitus

C10E.12	Insulin dependent diabetes mellitus	Diabetes mellitus
C10E000	Type 1 diabetes mellitus with renal complications	Diabetes mellitus
C10E011	Type I diabetes mellitus with renal complications	Diabetes mellitus
C10E012	Insulin-dependent diabetes mellitus with renal complications	Diabetes mellitus
C10E100	Type 1 diabetes mellitus with ophthalmic complications	Diabetes mellitus
C10E111	Type I diabetes mellitus with ophthalmic complications	Diabetes mellitus
C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps	Diabetes mellitus
C10E200	Type 1 diabetes mellitus with neurological complications	Diabetes mellitus
C10E211	Type I diabetes mellitus with neurological complications	Diabetes mellitus
C10E212	Insulin-dependent diabetes mellitus with neurological comps	Diabetes mellitus
C10E300	Type 1 diabetes mellitus with multiple complications	Diabetes mellitus
C10E311	Type I diabetes mellitus with multiple complications	Diabetes mellitus
C10E312	Insulin dependent diabetes mellitus with multiple complicat	Diabetes mellitus
C10E400	Unstable type 1 diabetes mellitus	Diabetes mellitus
C10E411	Unstable type I diabetes mellitus	Diabetes mellitus
C10E412	Unstable insulin dependent diabetes mellitus	Diabetes mellitus
C10E500	Type 1 diabetes mellitus with ulcer	Diabetes mellitus
C10E511	Type I diabetes mellitus with ulcer	Diabetes mellitus
C10E512	Insulin dependent diabetes mellitus with ulcer	Diabetes mellitus
C10E600	Type 1 diabetes mellitus with gangrene	Diabetes mellitus
C10E611	Type I diabetes mellitus with gangrene	Diabetes mellitus
C10E612	Insulin dependent diabetes mellitus with gangrene	Diabetes mellitus
C10E700	Type 1 diabetes mellitus with retinopathy	Diabetes mellitus
C10E711	Type I diabetes mellitus with retinopathy	Diabetes mellitus
C10E712	Insulin dependent diabetes mellitus with retinopathy	Diabetes mellitus
C10E800	Type 1 diabetes mellitus - poor control	Diabetes mellitus
C10E811	Type I diabetes mellitus - poor control	Diabetes mellitus
C10E812	Insulin dependent diabetes mellitus - poor control	Diabetes mellitus
C10E900	Type 1 diabetes mellitus maturity onset	Diabetes mellitus
C10E911	Type I diabetes mellitus maturity onset	Diabetes mellitus
C10E912	Insulin dependent diabetes maturity onset	Diabetes mellitus
C10EA00	Type 1 diabetes mellitus without complication	Diabetes mellitus
C10EA11	Type I diabetes mellitus without complication	Diabetes mellitus
C10EA12	Insulin-dependent diabetes without complication	Diabetes mellitus
C10EB00	Type 1 diabetes mellitus with mononeuropathy	Diabetes mellitus
C10EB11	Type I diabetes mellitus with mononeuropathy	Diabetes mellitus
C10EB12	Insulin dependent diabetes mellitus with mononeuropathy	Diabetes mellitus
C10EC00	Type 1 diabetes mellitus with polyneuropathy	Diabetes mellitus
C10EC11	Type I diabetes mellitus with polyneuropathy	Diabetes mellitus
C10EC12	Insulin dependent diabetes mellitus with polyneuropathy	Diabetes mellitus
C10ED00	Type 1 diabetes mellitus with nephropathy	Diabetes mellitus
C10ED11	Type I diabetes mellitus with nephropathy	Diabetes mellitus

C10ED12	Insulin dependent diabetes mellitus with nephropathy	Diabetes mellitus
C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma	Diabetes mellitus
C10EE11	Type I diabetes mellitus with hypoglycaemic coma	Diabetes mellitus
C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma	Diabetes mellitus
C10EF00	Type 1 diabetes mellitus with diabetic cataract	Diabetes mellitus
C10EF11	Type I diabetes mellitus with diabetic cataract	Diabetes mellitus
C10EF12	Insulin dependent diabetes mellitus with diabetic cataract	Diabetes mellitus
C10EG00	Type 1 diabetes mellitus with peripheral angiopathy	Diabetes mellitus
C10EG11	Type I diabetes mellitus with peripheral angiopathy	Diabetes mellitus
C10EH00	Type 1 diabetes mellitus with arthropathy	Diabetes mellitus
C10EH11	Type I diabetes mellitus with arthropathy	Diabetes mellitus
C10EH12	Insulin dependent diabetes mellitus with arthropathy	Diabetes mellitus
C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy	Diabetes mellitus
C10EJ11	Type I diabetes mellitus with neuropathic arthropathy	Diabetes mellitus
C10EK00	Type 1 diabetes mellitus with persistent proteinuria	Diabetes mellitus
C10EK11	Type I diabetes mellitus with persistent proteinuria	Diabetes mellitus
C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria	Diabetes mellitus
C10EL11	Type I diabetes mellitus with persistent microalbuminuria	Diabetes mellitus
C10EM00	Type 1 diabetes mellitus with ketoacidosis	Diabetes mellitus
C10EM11	Type I diabetes mellitus with ketoacidosis	Diabetes mellitus
C10EN00	Type 1 diabetes mellitus with ketoacidotic coma	Diabetes mellitus
C10EN11	Type I diabetes mellitus with ketoacidotic coma	Diabetes mellitus
C10EP00	Type 1 diabetes mellitus with exudative maculopathy	Diabetes mellitus
C10EP11	Type I diabetes mellitus with exudative maculopathy	Diabetes mellitus
C10EQ00	Type 1 diabetes mellitus with gastroparesis	Diabetes mellitus
C10F.00	Type 2 diabetes mellitus	Diabetes mellitus
C10F.11	Type II diabetes mellitus	Diabetes mellitus
C10F000	Type 2 diabetes mellitus with renal complications	Diabetes mellitus
C10F011	Type II diabetes mellitus with renal complications	Diabetes mellitus
C10F100	Type 2 diabetes mellitus with ophthalmic complications	Diabetes mellitus
C10F111	Type II diabetes mellitus with ophthalmic complications	Diabetes mellitus
C10F200	Type 2 diabetes mellitus with neurological complications	Diabetes mellitus
C10F211	Type II diabetes mellitus with neurological complications	Diabetes mellitus
C10F300	Type 2 diabetes mellitus with multiple complications	Diabetes mellitus
C10F311	Type II diabetes mellitus with multiple complications	Diabetes mellitus
C10F400	Type 2 diabetes mellitus with ulcer	Diabetes mellitus
C10F411	Type II diabetes mellitus with ulcer	Diabetes mellitus
C10F500	Type 2 diabetes mellitus with gangrene	Diabetes mellitus
C10F511	Type II diabetes mellitus with gangrene	Diabetes mellitus
C10F600	Type 2 diabetes mellitus with retinopathy	Diabetes mellitus
C10F611	Type II diabetes mellitus with retinopathy	Diabetes mellitus
C10F700	Type 2 diabetes mellitus - poor control	Diabetes mellitus
C10F711	Type II diabetes mellitus - poor control	Diabetes mellitus

C10F900	Type 2 diabetes mellitus without complication	Diabetes mellitus
C10F911	Type II diabetes mellitus without complication	Diabetes mellitus
C10FA00	Type 2 diabetes mellitus with mononeuropathy	Diabetes mellitus
C10FA11	Type II diabetes mellitus with mononeuropathy	Diabetes mellitus
C10FB00	Type 2 diabetes mellitus with polyneuropathy	Diabetes mellitus
C10FB11	Type II diabetes mellitus with polyneuropathy	Diabetes mellitus
C10FC00	Type 2 diabetes mellitus with nephropathy	Diabetes mellitus
C10FC11	Type II diabetes mellitus with nephropathy	Diabetes mellitus
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma	Diabetes mellitus
C10FD11	Type II diabetes mellitus with hypoglycaemic coma	Diabetes mellitus
C10FE00	Type 2 diabetes mellitus with diabetic cataract	Diabetes mellitus
C10FE11	Type II diabetes mellitus with diabetic cataract	Diabetes mellitus
C10FF00	Type 2 diabetes mellitus with peripheral angiopathy	Diabetes mellitus
C10FF11	Type II diabetes mellitus with peripheral angiopathy	Diabetes mellitus
C10FG00	Type 2 diabetes mellitus with arthropathy	Diabetes mellitus
C10FG11	Type II diabetes mellitus with arthropathy	Diabetes mellitus
C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy	Diabetes mellitus
C10FH11	Type II diabetes mellitus with neuropathic arthropathy	Diabetes mellitus
C10FJ00	Insulin treated Type 2 diabetes mellitus	Diabetes mellitus
C10FJ11	Insulin treated Type II diabetes mellitus	Diabetes mellitus
C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus	Diabetes mellitus
C10FL00	Type 2 diabetes mellitus with persistent proteinuria	Diabetes mellitus
C10FL11	Type II diabetes mellitus with persistent proteinuria	Diabetes mellitus
C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria	Diabetes mellitus
C10FM11	Type II diabetes mellitus with persistent microalbuminuria	Diabetes mellitus
C10FN00	Type 2 diabetes mellitus with ketoacidosis	Diabetes mellitus
C10FN11	Type II diabetes mellitus with ketoacidosis	Diabetes mellitus
C10FP00	Type 2 diabetes mellitus with ketoacidotic coma	Diabetes mellitus
C10FP11	Type II diabetes mellitus with ketoacidotic coma	Diabetes mellitus
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy	Diabetes mellitus
C10FQ11	Type II diabetes mellitus with exudative maculopathy	Diabetes mellitus
C10FR00	Type 2 diabetes mellitus with gastroparesis	Diabetes mellitus
C10FS00	Maternally inherited diabetes mellitus	Diabetes mellitus
C10G.00	Secondary pancreatic diabetes mellitus	Diabetes mellitus
C10G000	Secondary pancreatic diabetes mellitus without complication	Diabetes mellitus
C10H.00	Diabetes mellitus induced by non-steroid drugs	Diabetes mellitus
C10M.00	Lipoatrophic diabetes mellitus	Diabetes mellitus
C10M000	Lipoatrophic diabetes mellitus without complication	Diabetes mellitus
C10N.00	Secondary diabetes mellitus	Diabetes mellitus
C10N000	Secondary diabetes mellitus without complication	Diabetes mellitus
C10N100	Cystic fibrosis related diabetes mellitus	Diabetes mellitus
C10y.00	Diabetes mellitus with other specified manifestation	Diabetes mellitus
C10y000	Diabetes mellitus, juvenile, + other specified manifestation	Diabetes mellitus
C10yy00	Other specified diabetes mellitus with other spec	Diabetes mellitus

	comps	
C10yz00	Diabetes mellitus NOS with other specified manifestation	Diabetes mellitus
C10z.00	Diabetes mellitus with unspecified complication	Diabetes mellitus
C10z000	Diabetes mellitus, juvenile type, + unspecified complication	Diabetes mellitus
C10zy00	Other specified diabetes mellitus with unspecified comps	Diabetes mellitus
C10zz00	Diabetes mellitus NOS with unspecified complication	Diabetes mellitus
C11y000	Steroid induced diabetes	Diabetes mellitus
Cyu2.00	[X]Diabetes mellitus	Diabetes mellitus
Cyu2000	[X]Other specified diabetes mellitus	Diabetes mellitus
Cyu2100	[X]Malnutrit-relat diabetes mellitus with other spec comps	Diabetes mellitus
Cyu2200	[X]Malnutrit-related diabetes mellitus with unspec complics	Diabetes mellitus
Cyu2300	[X]Unspecified diabetes mellitus with renal complications	Diabetes mellitus
F171100	Autonomic neuropathy due to diabetes	Diabetes mellitus
F345000	Diabetic mononeuritis multiplex	Diabetes mellitus
F35z000	Diabetic mononeuritis NOS	Diabetes mellitus
F372.00	Polyneuropathy in diabetes	Diabetes mellitus
F372.11	Diabetic polyneuropathy	Diabetes mellitus
F372.12	Diabetic neuropathy	Diabetes mellitus
F372000	Acute painful diabetic neuropathy	Diabetes mellitus
F372100	Chronic painful diabetic neuropathy	Diabetes mellitus
F372200	Asymptomatic diabetic neuropathy	Diabetes mellitus
F381300	Myasthenic syndrome due to diabetic amyotrophy	Diabetes mellitus
F381311	Diabetic amyotrophy	Diabetes mellitus
F3y0.00	Diabetic mononeuropathy	Diabetes mellitus
F420.00	Diabetic retinopathy	Diabetes mellitus
F420000	Background diabetic retinopathy	Diabetes mellitus
F420100	Proliferative diabetic retinopathy	Diabetes mellitus
F420200	Preproliferative diabetic retinopathy	Diabetes mellitus
F420300	Advanced diabetic maculopathy	Diabetes mellitus
F420400	Diabetic maculopathy	Diabetes mellitus
F420500	Advanced diabetic retinal disease	Diabetes mellitus
F420600	Non proliferative diabetic retinopathy	Diabetes mellitus
F420700	High risk proliferative diabetic retinopathy	Diabetes mellitus
F420800	High risk non proliferative diabetic retinopathy	Diabetes mellitus
F420z00	Diabetic retinopathy NOS	Diabetes mellitus
F440700	Diabetic iritis	Diabetes mellitus
F464000	Diabetic cataract	Diabetes mellitus
G73y000	Diabetic peripheral angiopathy	Diabetes mellitus
K01x100	Nephrotic syndrome in diabetes mellitus	Diabetes mellitus
Kyu0300	[X]Glomerular disorders in diabetes mellitus	Diabetes mellitus
M037200	Cellulitis in diabetic foot	Diabetes mellitus
M271000	Ischaemic ulcer diabetic foot	Diabetes mellitus
M271100	Neuropathic diabetic ulcer - foot	Diabetes mellitus

M271200	Mixed diabetic ulcer - foot	Diabetes mellitus
N030000	Diabetic cheiroarthropathy	Diabetes mellitus
N030011	Diabetic cheiropathy	Diabetes mellitus
N030100	Diabetic Charcot arthropathy	Diabetes mellitus
R054200	[D]Gangrene of toe in diabetic	Diabetes mellitus
R054300	[D]Widespread diabetic foot gangrene	Diabetes mellitus
TJ23.00	Adverse reaction to insulins and antidiabetic agents	Diabetes mellitus
TJ23z00	Adverse reaction to insulins and antidiabetic agents NOS	Diabetes mellitus
U602311	[X] Adverse reaction to insulins and antidiabetic agents	Diabetes mellitus
U60231E	[X] Adverse reaction to insulins and antidiabetic agents NOS	Diabetes mellitus
ZC2C800	Dietary advice for diabetes mellitus	Diabetes mellitus
ZC2C900	Dietary advice for type I diabetes	Diabetes mellitus
ZC2C911	Diet advice for insulin-dependent diabetes	Diabetes mellitus
ZC2CA00	Dietary advice for type II diabetes	Diabetes mellitus
ZC2CA11	Dietary advice non-insulin-dependent diabetes	Diabetes mellitus
43C3.11	HIV positive	HIV
A788.00	Acquired immune deficiency syndrome	HIV
A788.11	Human immunodeficiency virus infection	HIV
A788000	Acute human immunodeficiency virus infection	HIV
A788100	Asymptomatic human immunodeficiency virus infection	HIV
A788200	HIV infection with persistent generalised lymphadenopathy	HIV
A788300	Human immunodeficiency virus with constitutional disease	HIV
A788400	Human immunodeficiency virus with neurological disease	HIV
A788500	Human immunodeficiency virus with secondary infection	HIV
A788600	Human immunodeficiency virus with secondary cancers	HIV
A788U00	HIV disease result/haematological+immunologic abnorms,NEC	HIV
A788V00	HIV disease resulting in multiple diseases CE	HIV
A788W00	HIV disease resulting in unspecified malignant neoplasm	HIV
A788X00	HIV disease resulting/unspcf infectious+parasitic disease	HIV
A788y00	Human immunodeficiency virus with other clinical findings	HIV
A788z00	Acquired human immunodeficiency virus infection syndrome NOS	HIV
A789.00	Human immunodef virus resulting in other disease	HIV
A789000	HIV disease resulting in mycobacterial infection	HIV
A789100	HIV disease resulting in cytomegaloviral disease	HIV
A789200	HIV disease resulting in candidiasis	HIV
A789300	HIV disease resulting in Pneumocystis carinii pneumonia	HIV
A789400	HIV disease resulting in multiple infections	HIV
A789500	HIV disease resulting in Kaposi's sarcoma	HIV
A789600	HIV disease resulting in Burkitt's lymphoma	HIV
A789700	HIV dis resulting oth types of non-Hodgkin's lymphoma	HIV

A789800	HIV disease resulting in multiple malignant neoplasms	HIV
A789900	HIV disease resulting in lymphoid interstitial pneumonitis	HIV
A789A00	HIV disease resulting in wasting syndrome	HIV
A789X00	HIV dis reslt/oth mal neopl/lymph,h'matopoetc+reltd tissu	HIV
AyuC.00	[X]Human immunodeficiency virus disease	HIV
AyuC000	[X]HIV disease resulting in other bacterial infections	HIV
AyuC100	[X]HIV disease resulting in other viral infections	HIV
AyuC200	[X]HIV disease resulting in other mycoses	HIV
AyuC300	[X]HIV disease resulting in multiple infections	HIV
AyuC400	[X]HIV disease resulting/other infectious+parasitic diseases	HIV
AyuC500	[X]HIV disease resulting/unspcf infectious+parasitic disease	HIV
AyuC600	[X]HIV disease resulting in other non-Hodgkin's lymphoma	HIV
AyuC700	[X]HIV dis reslt/oth mal neopl/lymph,h'matopoetc+reltd tissu	HIV
AyuC800	[X]HIV disease resulting in other malignant neoplasms	HIV
AyuC900	[X]HIV disease resulting in unspecified malignant neoplasm	HIV
AyuCA00	[X]HIV disease resulting in multiple diseases CE	HIV
AyuCB00	[X]HIV disease result/haematological+immunologic abnorms,NEC	HIV
AyuCC00	[X]HIV disease resulting in other specified conditions	HIV
AyuCD00	[X]Unspecified human immunodeficiency virus [HIV] disease	HIV
Eu02400	[X]Dementia in human immunodef virus [HIV] disease	HIV
R109.00	[D]Laboratory evidence of human immunodefiency virus [HIV]	HIV
E2E..00	Childhood hyperkinetic syndrome	Hyperkinetic disorder
E2E..11	Overactive child syndrome	Hyperkinetic disorder
E2E0.00	Child attention deficit disorder	Hyperkinetic disorder
E2E0000	Attention deficit without hyperactivity	Hyperkinetic disorder
E2E0100	Attention deficit with hyperactivity	Hyperkinetic disorder
E2E0z00	Child attention deficit disorder NOS	Hyperkinetic disorder
E2E1.00	Hyperkinesis with developmental delay	Hyperkinetic disorder
E2E2.00	Hyperkinetic conduct disorder	Hyperkinetic disorder
E2Ey.00	Other hyperkinetic manifestation	Hyperkinetic disorder
E2Ez.00	Hyperkinetic syndrome NOS	Hyperkinetic disorder
ZS9..00	Disorders of attention and motor control	Hyperkinetic disorder
ZS91.00	Attention deficit disorder	Hyperkinetic disorder
ZS91.11	ADD - Attention deficit disorder	Hyperkinetic disorder
ZS91.12	[X]Attention deficit disorder	Hyperkinetic disorder
ZS92.00	Persistent developmental avoidance	Hyperkinetic disorder
ZS92.11	PDA - Persistent developmental avoidance	Hyperkinetic disorder
ZS93.00	Deficits in attention motor control and perception	Hyperkinetic disorder
ZS93.11	DAMP - Deficits in attention motor control and perception	Hyperkinetic disorder
ZS94.00	Minimal brain dysfunction	Hyperkinetic disorder
ZS94.11	MBD - Minimal brain dysfunction	Hyperkinetic disorder

ZS94.12	Soft neurological signs	Hyperkinetic disorder
Eu90100	[X]Hyperkinetic conduct disorder	Hyperkinetic disorder
Eu90111	[X]Hyperkinetic disorder associated with conduct disorder	Hyperkinetic disorder
E3...00	Mental retardation	Mental retardation
E30..00	Mild mental retardation, IQ in range 50-70	Mental retardation
E30..11	Educationally subnormal	Mental retardation
E30..12	Feeble-minded	Mental retardation
E30..13	Moron	Mental retardation
E31..00	Other specified mental retardation	Mental retardation
E310.00	Moderate mental retardation, IQ in range 35-49	Mental retardation
E310.11	Imbecile	Mental retardation
E311.00	Severe mental retardation, IQ in range 20-34	Mental retardation
E312.00	Profound mental retardation with IQ less than 20	Mental retardation
E312.11	Idiocy	Mental retardation
E31z.00	Other specified mental retardation NOS	Mental retardation
E3y..00	Other specified mental retardation	Mental retardation
E3z..00	Mental retardation NOS	Mental retardation
Eu7..00	[X]Mental retardation	Mental retardation
Eu70.00	[X]Mild mental retardation	Mental retardation
Eu70.11	[X]Feeble-mindedness	Mental retardation
Eu70.12	[X]Mild mental subnormality	Mental retardation
Eu70000	[X]Mld mental retard with statement no or min impairm behav	Mental retardation
Eu70100	[X]Mld mental retard sig impairment behav req attent/treatmt	Mental retardation
Eu70y00	[X]Mild mental retardation, other impairments of behaviour	Mental retardation
Eu70z00	[X]Mild mental retardation without mention impairment behav	Mental retardation
Eu71.00	[X]Moderate mental retardation	Mental retardation
Eu71.11	[X]Moderate mental subnormality	Mental retardation
Eu71000	[X]Mod mental retard with statement no or min impairm behav	Mental retardation
Eu71100	[X]Mod mental retard sig impairment behav req attent/treatmt	Mental retardation
Eu71y00	[X]Mod retard oth behav impair	Mental retardation
Eu71z00	[X]Mod mental retardation without mention impairment behav	Mental retardation
Eu72.00	[X]Severe mental retardation	Mental retardation
Eu72.11	[X]Severe mental subnormality	Mental retardation
Eu72000	[X]Sev mental retard with statement no or min impairm behav	Mental retardation
Eu72100	[X]Sev mental retard sig impairment behav req attent/treatmt	Mental retardation
Eu72y00	[X]Severe mental retardation, other impairments of behaviour	Mental retardation
Eu72z00	[X]Sev mental retardation without mention impairment behav	Mental retardation
Eu73.00	[X]Profound mental retardation	Mental retardation
Eu73.11	[X]Profound mental subnormality	Mental retardation
Eu73000	[X]Profound ment retrd wth statement no or min impairm behav	Mental retardation

Eu73100	[X]Profound ment retard sig impairmnt behav req attent/treat	Mental retardation
Eu73y00	[X]Profound mental retardation, other impairments of behavr	Mental retardation
Eu73z00	[X]Prfnd mental retardation without mention impairment behav	Mental retardation
Eu7y.00	[X]Other mental retardation	Mental retardation
Eu7y000	[X]Oth mental retard with statement no or min impairm behav	Mental retardation
Eu7y100	[X]Oth mental retard sig impairment behav req attent/treatmt	Mental retardation
Eu7yy00	[X]Other mental retardation, other impairments of behaviour	Mental retardation
Eu7yz00	[X]Other mental retardation without mention impairment behav	Mental retardation
Eu7z.00	[X]Unspecified mental retardation	Mental retardation
Eu7z.11	[X]Mental deficiency NOS	Mental retardation
Eu7z.12	[X]Mental subnormality NOS	Mental retardation
Eu7z000	[X]Unsp mental retard with statement no or min impairm behav	Mental retardation
Eu7z100	[X]Unsp mentl retard sig impairment behav req attent/treatmt	Mental retardation
Eu7zy00	[X]Unspecified mental retardatn, other impairments of behav	Mental retardation
Eu7zz00	[X]Unsp mental retardation without mention impairment behav	Mental retardation
8893.00	Renal perfusion	Renal disorder
1A52.00	Renal colic	Renal disorder
1A52.11	Renal colic, symptom	Renal disorder
1A53.00	Lumbar ache - renal	Renal disorder
44J5.00	Renal profile	Renal disorder
7B0..11	Renal operations	Renal disorder
7L1A000	Renal dialysis	Renal disorder
8L5..00	Renal/urological operation planned	Renal disorder
8L50.00	Renal transplant planned	Renal disorder
A954.11	Renal syphilis	Renal disorder
B4A..11	Renal malignant neoplasm	Renal disorder
B7D..11	Renal benign neoplasms	Renal disorder
B91z111	Renal neoplasm of uncertain behaviour	Renal disorder
C341111	Renal stone - uric acid	Renal disorder
C354711	Renal calcinosis	Renal disorder
D410400	Renal polycythaemia	Renal disorder
F421200	Renal retinopathy	Renal disorder
G701.00	Renal artery atherosclerosis	Renal disorder
K034.00	Renal cortical necrosis unspecified	Renal disorder
K035.00	Renal medullary necrosis unspecified	Renal disorder
K04..00	Acute renal failure	Renal disorder
K040.00	Acute renal tubular necrosis	Renal disorder
K041.00	Acute renal cortical necrosis	Renal disorder
K042.00	Acute renal medullary necrosis	Renal disorder
K042.11	Necrotising renal papillitis	Renal disorder
K04y.00	Other acute renal failure	Renal disorder

K04z.00	Acute renal failure NOS	Renal disorder
K05..00	Chronic renal failure	Renal disorder
K05..11	Chronic uraemia	Renal disorder
K05..12	End stage renal failure	Renal disorder
K050.00	End stage renal failure	Renal disorder
K06..00	Renal failure unspecified	Renal disorder
K06..11	Uraemia NOS	Renal disorder
K060.00	Renal impairment	Renal disorder
K060.11	Impaired renal function	Renal disorder
K07..00	Renal sclerosis unspecified	Renal disorder
K070.00	Atrophy of kidney	Renal disorder
K071.00	Renal fibrosis	Renal disorder
K072.00	Glomerulosclerosis	Renal disorder
K07z.00	Renal sclerosis NOS	Renal disorder
K08..00	Impaired renal function disorder	Renal disorder
K080.00	Renal osteodystrophy	Renal disorder
K080000	Phosphate-losing tubular disorders	Renal disorder
K080100	Renal dwarfism	Renal disorder
K080200	Renal infantilism	Renal disorder
K080300	Renal rickets	Renal disorder
K080z00	Renal osteodystrophy NOS	Renal disorder
K081.00	Nephrogenic diabetes insipidus	Renal disorder
K08y.00	Other impaired renal function disorder	Renal disorder
K08y000	Hypokalaemic nephropathy	Renal disorder
K08y100	Secondary hyperparathyroidism	Renal disorder
K08y200	Lightwood - Albright syndrome	Renal disorder
K08y211	Albright's renal tubular acidosis	Renal disorder
K08y300	Renal function impairment with growth failure	Renal disorder
K08y400	Renal tubular acidosis	Renal disorder
K08y412	Renal tubular acidaemia	Renal disorder
K08y500	Acute interstitial nephritis	Renal disorder
K08yz00	Other impaired renal function disorder NOS	Renal disorder
K08yz11	Renal acidaemia	Renal disorder
K08yz12	Renotubular acidaemia	Renal disorder
K08z.00	Impaired renal function disorder NOS	Renal disorder
K0B..00	Renal tubulo-interstitial disorders in diseases EC	Renal disorder
K0B1.00	Renal tubulo-interstitial disorder/ neoplastic diseases	Renal disorder
K0B3.00	Renal tubulo-interstitial disorders in metabolic diseases	Renal disorder
K0B4000	Renal tubulo-interstitial disorder in SLE	Renal disorder
K0B5.00	Renal tubulo-interstitial disordrs in transplant rejectn	Renal disorder
K10..00	Infections of kidney	Renal disorder
K10..11	Renal infections	Renal disorder
K100.00	Chronic pyelonephritis	Renal disorder
K100000	Chronic pyelonephritis without medullary necrosis	Renal disorder
K100100	Chronic pyelonephritis with medullary necrosis	Renal disorder
K100200	Chronic pyelitis	Renal disorder

K100300	Chronic pyonephrosis	Renal disorder
K100400	Nonobstructive reflux-associated chronic pyelonephritis	Renal disorder
K100500	Chronic obstructive pyelonephritis	Renal disorder
K100600	Calculous pyelonephritis	Renal disorder
K100z00	Chronic pyelonephritis NOS	Renal disorder
K101.00	Acute pyelonephritis	Renal disorder
K101000	Acute pyelonephritis without medullary necrosis	Renal disorder
K101100	Acute pyelonephritis with medullary necrosis	Renal disorder
K101200	Acute pyelitis	Renal disorder
K101300	Acute pyonephrosis	Renal disorder
K101z00	Acute pyelonephritis NOS	Renal disorder
K102.00	Renal and perinephric abscess	Renal disorder
K102000	Renal abscess	Renal disorder
K102100	Perinephric abscess	Renal disorder
K102200	Renal carbuncle	Renal disorder
K102z00	Renal and perinephric abscess NOS	Renal disorder
K103.00	Pyeloureteritis cystica	Renal disorder
K103.11	Ureteritis cystica	Renal disorder
K103.12	Infestation of renal pelvis with ureter	Renal disorder
K104.00	Xanthogranulomatous pyelonephritis	Renal disorder
K10y.00	Pyelonephritis and pyonephrosis unspecified	Renal disorder
K10y000	Pyelonephritis unspecified	Renal disorder
K10y100	Pyelitis unspecified	Renal disorder
K10y200	Pyonephrosis unspecified	Renal disorder
K10y300	Pyelonephritis in diseases EC	Renal disorder
K10y400	Pyelitis in diseases EC	Renal disorder
K10yz00	Unspecified pyelonephritis NOS	Renal disorder
K10z.00	Infection of kidney NOS	Renal disorder
K120.12	Renal calculus	Renal disorder
K120.13	Renal stone	Renal disorder
K120z00	Renal calculus NOS	Renal disorder
K138.11	Renal vascular disorders	Renal disorder
K138000	Renal artery embolism	Renal disorder
K138011	Renal artery embolus	Renal disorder
K138100	Renal artery haemorrhage	Renal disorder
K138200	Renal artery thrombosis	Renal disorder
K138z00	Renal vascular disorders NOS	Renal disorder
K138z11	Renal infarction	Renal disorder
L093.00	Renal failure following abortive pregnancy	Renal disorder
L093200	Renal shutdown following abortive pregnancy	Renal disorder
L093300	Renal tubular necrosis following abortive pregnancy	Renal disorder
L093z00	Renal failure NOS following abortive pregnancy	Renal disorder
L121.00	Renal hypertension in pregnancy/childbirth/puerperium	Renal disorder
L121000	Renal hypertension in pregnancy/childbirth/puerp unspecified	Renal disorder
L121100	Renal hypertension in pregnancy/childbirth/puerp -	Renal disorder

	delivered	
L121200	Renal hypertension in preg/childb/puerp -deliv with p/n comp	Renal disorder
L121300	Renal hypertension in preg/childbirth/puerp - not delivered	Renal disorder
L121400	Renal hypertension in preg/childb/puerp + p/n complication	Renal disorder
L121z00	Renal hypertension in pregnancy/childbirth/puerperium NOS	Renal disorder
P769000	Renal artery stenosis	Renal disorder
PD0..00	Renal agenesis and dysgenesis	Renal disorder
PD00.00	Renal agenesis, unspecified	Renal disorder
PD00z00	Renal agenesis, unspecified NOS	Renal disorder
PD0z.00	Renal agenesis or dysgenesis NOS	Renal disorder
PD2..00	Renal pelvis and ureter obstructive defects	Renal disorder
PD30.12	Renal duplication NEC	Renal disorder
Q20yz13	Renal injury due to birth trauma	Renal disorder
S760111	Renal haematoma without mention of open wound into cavity	Renal disorder
S761111	Renal haematoma with open wound into cavity	Renal disorder
SB24.00	Renal blood vessel injury	Renal disorder
SB24000	Renal blood vessel injury, unspecified	Renal disorder
SB24100	Renal artery injury	Renal disorder
SB24200	Renal vein injury	Renal disorder
SB24z00	Renal blood vessel injury NOS	Renal disorder
SK05.00	Renal failure following crush syndrome	Renal disorder
SK05.11	Renal failure after crushing	Renal disorder
SP15400	Renal failure as a complication of care	Renal disorder
TB00111	Renal transplant with complication, without blame	Renal disorder
TB11.11	Renal dialysis with complication, without blame	Renal disorder
14G1.00	H/O: rheumatoid arthritis	Rheumatoid arthritis
F371200	Polyneuropathy in rheumatoid arthritis	Rheumatoid arthritis
F396400	Myopathy due to rheumatoid arthritis	Rheumatoid arthritis
N04..00	Rheumatoid arthritis and other inflammatory polyarthropathy	Rheumatoid arthritis
N040200	Rheumatoid arthritis of shoulder	Rheumatoid arthritis
N040300	Rheumatoid arthritis of sternoclavicular joint	Rheumatoid arthritis
N040400	Rheumatoid arthritis of acromioclavicular joint	Rheumatoid arthritis
N040500	Rheumatoid arthritis of elbow	Rheumatoid arthritis
N040600	Rheumatoid arthritis of distal radio-ulnar joint	Rheumatoid arthritis
N040700	Rheumatoid arthritis of wrist	Rheumatoid arthritis
N040800	Rheumatoid arthritis of MCP joint	Rheumatoid arthritis
N040900	Rheumatoid arthritis of PIP joint of finger	Rheumatoid arthritis
N040A00	Rheumatoid arthritis of DIP joint of finger	Rheumatoid arthritis
N040B00	Rheumatoid arthritis of hip	Rheumatoid arthritis
N040C00	Rheumatoid arthritis of sacro-iliac joint	Rheumatoid arthritis
N040D00	Rheumatoid arthritis of knee	Rheumatoid arthritis
N040E00	Rheumatoid arthritis of tibio-fibular joint	Rheumatoid arthritis
N040F00	Rheumatoid arthritis of ankle	Rheumatoid arthritis

N040G00	Rheumatoid arthritis of subtalar joint	Rheumatoid arthritis
N040H00	Rheumatoid arthritis of talonavicular joint	Rheumatoid arthritis
N040J00	Rheumatoid arthritis of other tarsal joint	Rheumatoid arthritis
N040K00	Rheumatoid arthritis of 1st MTP joint	Rheumatoid arthritis
N040L00	Rheumatoid arthritis of lesser MTP joint	Rheumatoid arthritis
N040M00	Rheumatoid arthritis of IP joint of toe	Rheumatoid arthritis
N040N00	Rheumatoid vasculitis	Rheumatoid arthritis
N040Q00	Rheumatoid bursitis	Rheumatoid arthritis
N040R00	Rheumatoid nodule	Rheumatoid arthritis
N040S00	Rheumatoid arthritis - multiple joint	Rheumatoid arthritis
N040T00	Flare of rheumatoid arthritis	Rheumatoid arthritis
N041.00	Felty's syndrome	Rheumatoid arthritis
N042.00	Other rheumatoid arthropathy + visceral/systemic involvement	Rheumatoid arthritis
N042000	Rheumatic carditis	Rheumatoid arthritis
N042100	Rheumatoid lung disease	Rheumatoid arthritis
N042200	Rheumatoid nodule	Rheumatoid arthritis
N042z00	Rheumatoid arthropathy + visceral/systemic involvement NOS	Rheumatoid arthritis
N043.00	Juvenile rheumatoid arthritis - Still's disease	Rheumatoid arthritis
N043000	Juvenile rheumatoid arthropathy unspecified	Rheumatoid arthritis
N043100	Acute polyarticular juvenile rheumatoid arthritis	Rheumatoid arthritis
N043200	Pauciarticular juvenile rheumatoid arthritis	Rheumatoid arthritis
N043300	Monarticular juvenile rheumatoid arthritis	Rheumatoid arthritis
N043z00	Juvenile rheumatoid arthritis NOS	Rheumatoid arthritis
N044.00	Chronic post-rheumatic arthropathy	Rheumatoid arthritis
N044.11	Jaccoud's syndrome	Rheumatoid arthritis
N044.12	Nodular fibrositis of chronic rheumatic disease	Rheumatoid arthritis
N045.00	Other juvenile arthritis	Rheumatoid arthritis
N045000	Juvenile ankylosing spondylitis	Rheumatoid arthritis
N045100	Juvenile seronegative polyarthritis	Rheumatoid arthritis
N045200	Juvenile arthritis in psoriasis	Rheumatoid arthritis
N045300	Juvenile arthritis in Crohn's disease	Rheumatoid arthritis
N045400	Juvenile arthritis in ulcerative colitis	Rheumatoid arthritis
N045500	Juvenile rheumatoid arthritis	Rheumatoid arthritis
N045600	Pauciarticular onset juvenile chronic arthritis	Rheumatoid arthritis
N047.00	Seropositive errosive rheumatoid arthritis	Rheumatoid arthritis
N04X.00	Seropositive rheumatoid arthritis, unspecified	Rheumatoid arthritis
N04y.00	Other specified inflammatory polyarthropathy	Rheumatoid arthritis
N04y011	Caplan's syndrome	Rheumatoid arthritis
N04y012	Fibrosing alveolitis associated with rheumatoid arthritis	Rheumatoid arthritis
N04yz00	Other specified inflammatory polyarthropathy NOS	Rheumatoid arthritis
N04z.00	Inflammatory polyarthropathy NOS	Rheumatoid arthritis
Nyu1100	[X]Other seropositive rheumatoid arthritis	Rheumatoid arthritis
Nyu1200	[X]Other specified rheumatoid arthritis	Rheumatoid arthritis
1464.00	H/O: schizophrenia	Schizophrenia
212W.00	Schizophrenia resolved	Schizophrenia

E10..00	Schizophrenic disorders	Schizophrenia
E100.00	Simple schizophrenia	Schizophrenia
E100.11	Schizophrenia simplex	Schizophrenia
E100000	Unspecified schizophrenia	Schizophrenia
E100100	Subchronic schizophrenia	Schizophrenia
E100200	Chronic schizophrenic	Schizophrenia
E100300	Acute exacerbation of subchronic schizophrenia	Schizophrenia
E100400	Acute exacerbation of chronic schizophrenia	Schizophrenia
E100500	Schizophrenia in remission	Schizophrenia
E101.00	Hebephrenic schizophrenia	Schizophrenia
E101000	Unspecified hebephrenic schizophrenia	Schizophrenia
E101100	Subchronic hebephrenic schizophrenia	Schizophrenia
E101200	Chronic hebephrenic schizophrenia	Schizophrenia
E101300	Acute exacerbation of subchronic hebephrenic schizophrenia	Schizophrenia
E101400	Acute exacerbation of chronic hebephrenic schizophrenia	Schizophrenia
E101500	Hebephrenic schizophrenia in remission	Schizophrenia
E101z00	Hebephrenic schizophrenia NOS	Schizophrenia
E102.00	Catatonic schizophrenia	Schizophrenia
E102000	Unspecified catatonic schizophrenia	Schizophrenia
E102100	Subchronic catatonic schizophrenia	Schizophrenia
E102200	Chronic catatonic schizophrenia	Schizophrenia
E102300	Acute exacerbation of subchronic catatonic schizophrenia	Schizophrenia
E102400	Acute exacerbation of chronic catatonic schizophrenia	Schizophrenia
E102500	Catatonic schizophrenia in remission	Schizophrenia
E102z00	Catatonic schizophrenia NOS	Schizophrenia
E103.00	Paranoid schizophrenia	Schizophrenia
E103000	Unspecified paranoid schizophrenia	Schizophrenia
E103100	Subchronic paranoid schizophrenia	Schizophrenia
E103200	Chronic paranoid schizophrenia	Schizophrenia
E103300	Acute exacerbation of subchronic paranoid schizophrenia	Schizophrenia
E103400	Acute exacerbation of chronic paranoid schizophrenia	Schizophrenia
E103500	Paranoid schizophrenia in remission	Schizophrenia
E103z00	Paranoid schizophrenia NOS	Schizophrenia
E104.00	Acute schizophrenic episode	Schizophrenia
E106.00	Residual schizophrenia	Schizophrenia
E106.11	Restzustand - schizophrenia	Schizophrenia
E10y.00	Other schizophrenia	Schizophrenia
E10y.11	Cenesthopathic schizophrenia	Schizophrenia
E10y000	Atypical schizophrenia	Schizophrenia
E10y100	Coenesthopathic schizophrenia	Schizophrenia
E10yz00	Other schizophrenia NOS	Schizophrenia
E10z.00	Schizophrenia NOS	Schizophrenia
Eu20.00	[X]Schizophrenia	Schizophrenia
Eu20000	[X]Paranoid schizophrenia	Schizophrenia

Eu20011	[X]Paraphrenic schizophrenia	Schizophrenia
Eu20100	[X]Hebephrenic schizophrenia	Schizophrenia
Eu20111	[X]Disorganised schizophrenia	Schizophrenia
Eu20200	[X]Catatonic schizophrenia	Schizophrenia
Eu20211	[X]Catatonic stupor	Schizophrenia
Eu20212	[X]Schizophrenic catalepsy	Schizophrenia
Eu20213	[X]Schizophrenic catatonia	Schizophrenia
Eu20214	[X]Schizophrenic flexibilatis cerea	Schizophrenia
Eu20300	[X]Undifferentiated schizophrenia	Schizophrenia
Eu20311	[X]Atypical schizophrenia	Schizophrenia
Eu20400	[X]Post-schizophrenic depression	Schizophrenia
Eu20500	[X]Residual schizophrenia	Schizophrenia
Eu20511	[X]Chronic undifferentiated schizophrenia	Schizophrenia
Eu20512	[X]Restzustand schizophrenic	Schizophrenia
Eu20600	[X]Simple schizophrenia	Schizophrenia
Eu20y00	[X]Other schizophrenia	Schizophrenia
Eu20y11	[X]Cenesthopathic schizophrenia	Schizophrenia
Eu20y12	[X]Schizophreniform disord NOS	Schizophrenia
Eu20y13	[X]Schizophrenifrm psychos NOS	Schizophrenia
Eu20z00	[X]Schizophrenia, unspecified	Schizophrenia
ZV11000	[V]Personal history of schizophrenia	Schizophrenia
E122.00	Paraphrenia	Schizophrenia

Appendix 15: The generalized linear model (GLM) - an overview[277]

The standard linear regression model (e.g. OLS) relies on several assumptions, among which are the following:

1. Each observation of the response variable is characterized by the normal or Gaussian distribution;
   $y_i \sim N(\mu_i, \sigma^2_i)$.
2. Homoscedasticity, the distributions for all observations have a common variance: $\sigma^2_i = \sigma^2$ for all i.
3. There is a direct or "identical" relationship between the linear predictor (linear combination of covariate values and associated parameters) and the expected values of the model; $x_i\beta = \mu_i$

Common characteristics of many outcome variables (y) in health economics and biostatistics are heteroscedasticity, heavy skewness in the right tail, and kurtotic distributions in which the OLS is inefficient [276]. The regression of logarithmic transformation of y using the OLS is a way to overcome the problems of heteroscedasticity and severe skewness. However, the transformation of heavy skewed data is most often not sufficient to normalise the data. When the log-scale residuals showed evidence of heteroscedasticity, estimates based on OLS can produce a biased assessment of the impact of covariates on expected values of y on raw scale. In such case, an alternative approach is one of the GLM models [275].

The purpose of GLMs is to specify the relationship between the observed response variable and some number of covariates. By restructuring the relationship between the linear predictor and the fit, relationships that initially seem to be nonlinear can be linearised. The traditional linear model is not appropriate when data are not normally distributed or if the response variable has a limited outcome set.

The models placed under the GLM framework had been fitted using a developed general algorithm for maximum likelihood estimation. Whereas the linear model conceptualizes the outcome y as the sum of its mean μ and a

random variable ε, each GLM family member were linearised by means of a link function. The GLMs specify a relationship between the mean of the random variable y and a function of the linear combination of the predictors. The outcome dependent variable y is assumed to be generated from a particular distribution function in the exponential family which include a large range of probability distributions. In fact, the exponential family admits a model specification that allows modelling continuous, discrete, proportional, count and binary outcomes. Among continuous distributions is the Gaussian, log-normal, inverse-Gaussian, exponential, gamma, Weibull, etc. Among discrete distributions is the Bernoulli, binomial, Poisson, geometric, negative binomial, etc.

The estimation algorithm allowed researchers to more easily estimate many models previously considered to be non-linear by constructing them into GLMs.

Model components

The GLMs consist of some elements which can be listed as follow:

1. A random component for the response, y, which has a distribution following the exponential family.
2. A linear systematic component, relating the linear predictor, $\eta=X\beta$, to the independent (explanatory) variables X and the parameters β.
3. A known monotonic, one-to-one, differentiable link function g(-) relating the linear predictor to the fitted values. Since the function is one-to-one, there is an inverse function relating the mean expected response, E(y)=μ, to the linear predictor.
4. The variance may change with the covariates only as a function of the mean.
5. There is one IRLS (Iteratively Reweighted Least Squares) algorithm that suffices to fit all members of the class.

Assumptions of GLMs

The link function relates the mean μ=E(y) to the linear predictor Xβ and the variance function relates the variance as a function of the mean V(y)= a(φ)V(μ), where a(φ) is the scale parameter.

The critical assumptions in the GLM framework may be expressed as follows:

1. Statistical independence of the n observations.
2. The variance function V(μ) is correctly specified.
3. The a(φ) is correctly specified (1 for Poisson, binomial, and negative binomial).
4. The link function is correctly specified.
5. Explanatory variables are of the correct form.
6. There is no undue influence of the individual observations on the fit.

The distribution function is derived from the exponential family and has the form:

$$f(y) = \exp\left[\frac{\theta y - b(\theta)}{a(\varphi)} + c(y, \varphi)\right]$$

Where θ is the canonical (natural) parameter that determines the location of distribution and φ is the scale parameter required to produce standard errors following a distribution in the exponential family of distributions.
The joint probability density function may be expressed as a function of θ and φ and is called the likelihood, L. Given the product in the likelihood, it is more convenient to work with the log likelihood. The estimates with GLMs aim to find values of θ and φ that maximise the likelihood and hence maximise the log likelihood.

Goodness of fit

The fit of the GLM model to the data is measured as twice the difference between the log likelihoods of the model of interest, and a saturated model. Since this difference is a measure of the deviation of the model of interest from a perfectly fitting model, the measure is called the "deviance". The deviance is quantified as twice the negative log likelihood.
deviance= $-2 \log \ell$
The main goal in modelling is to find the simplest model (fewest parameters) that has the smallest deviance (reproduces the data). The values of the parameters that minimize the deviance are the same as the values of the parameters that maximize the likelihood.

Two other criteria can be used to compare competing models which are Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC). A comparison may be made to non-nested models or models calculated across different samples. The AIC is such that the lower the value, the better fitting the model. Moreover, a difference of greater than two indicates a marked preference for the model with the smaller criterion measure. Like the AIC statistic, the better fitting the model is the one having the smaller BIC value. The BIC is often negative, thus, the model having the most negative value is preferred.

GLM- the gamma family

The gamma model is used for data situations in which the response can take only values greater than or equal to 0. The GLM gamma family is used primarily with continuous-response data and can be also used with count data. Ideally, the gamma model is best used with positive responses having a constant coefficient of variation. However, the model is robust to wide deviations from the latter criterion. In fact, because the shape of the two-parameter gamma distribution is flexible and can be parameterized to fit many response shapes, it may be preferable over the Gaussian model for many strictly positive response data situations.

As with other GLM families, there are many commonly used link functions to provide the relationship between the linear predictor and the mean of the distribution function. The choice between different links of the same model family may sometimes be hard. Choosing the model having the least value for the deviance may be preferable.

The log-linked gamma represents the log-rate of the response. The log-gamma model, like its reciprocal counterpart, is used with data in which the response is greater than 0. Log-gamma technique is used now to model data which were generally modelled using Gaussian regression with a log-transformed response. Although the results are usually similar between the two methods, the log-gamma, which requires no external transformation, is easier to interpret and comes with a set of residuals with which to evaluate the worth of the model.

Appendix 16: Generalized estimating equations (GEE) for longitudinal data analysis

A major challenge comes in analysing longitudinal data is the correlation of observations within subjects, in which data are clustered within related subjects (subgroups). Failure to incorporate correlation of responses can lead to incorrect estimation of regression model parameters, particularly when such correlations are large [366]. The regression estimates (βs) are less efficient, that is, they are more widely scattered around the true population value than they would be if the within subject correlation were incorporated in the analysis [366].

Unlike the Gaussian data, the traditional maximum likelihood approaches cannot be used for non-Gaussian data as the integral does not have a closed form. To overcome these problems, Liang and Zeger introduced the Generalized Estimating Equation (GEE) to produce more efficient and unbiased regression estimates for use in analyzing longitudinal or repeated measures research designs with non-normal response variables [283]. The GEE models are an extension of generalized linear models, which facilitate regression analyses on dependent variables that are not normally distributed [367]. The GEE models are consistent and can handle a variety of correlated data even if the correlation structure is misspecified [284].

The GEE tests hypotheses regarding the influence of factors on binary and other exponentially (e.g., Poisson, Gamma, negative binomial) distributed response variables collected within subjects across time.

The GEE method is based on multivariate quasi likelihood theory and it can handle the complexities of longitudinal data which takes into account the correlation arising due to a longitudinal study design, resulting in increased efficiency of standard error estimates [366].

Inference about the mean of the outcome as a function of a set of covariates is the main focus of the GEE [276]. It specifies the marginal expectations and the marginal covariance matrix of the responses for longitudinal or clustered data as a function of the covariates [282]. The marginal effect is the population average rate of change in the mean of response with respect to covariates [276]. In

other words, for every one-unit increase in a covariate across the population, GEE tells the user how much the average response would change [285]

This method avoids the use of multivariate distribution by assuming a functional form for marginal distribution at each time, making it useful for non-Gaussian outcomes. The advantage of using the GEE method is that the solutions are consistent, i.e. the estimate of β are nearly efficient and asymptotically Gaussian, even when the time dependence is misspecified [285].

Appendix 17: Read codes list for outpatient attendances including paediatric neurology

Medical code	Description
64QZ.00	Child specific referral NOS
6613.00	Next hospital appointment
8H4..00	Referral to physician
8H42.00	Referral to paediatrician
8H42.11	Paediatric referral
8H46.00	Neurological referral
8H49.00	Psychiatric referral
8H4f.00	Referral to learning disabilities psychiatrist
8H4h.00	Referral to neurologist
8H4M.00	Referral to community paediatrician
8H4O.00	Referral to paediatric neurologist
8H4P.00	Referral to child psychiatrist
8H4Y.00	Referral to neurology special interest general practitioner
8H4Z.00	Referral to physician NOS
8H55.00	Neurosurgical referral
8H65.00	Refer to hospital registrar
8H7a.00	Refer to hospital
8H7b.00	Refer to day hospital
8Hh..00	Self-referral
8Hi..00	Earlier referral for specialist review
8HJ3.00	Psychiatric self-referral
8HJ5.00	Paediatric self-referral
8HJE.00	Neurology self-referral
8HkS.00	Referral to clinical neurophysiology service
8HlB.00	Urgent referral to psychiatrist
9b89.00	Neurosurgery
9b9K.00	Neurology
9b9N.00	Paediatrics
9b9O.00	Paediatric neurology
9bA..00	Psychiatry
9bA2.00	Child and adolescent psychiatry
ZL18P00	Under care of neurologist
ZL19.00	Under care of paediatrician
ZL19300	Under care of paediatric neurologist
ZL1B.00	Under care of psychiatrist
ZL1B100	Under care of child and adolescent psychiatrist
ZL1GK00	Under care of neurosurgeon
ZL57.00	Referral to paediatrician
ZL57100	Referral to community paediatrician
ZL57300	Referral to paediatric neurologist

ZL59300	Referral to neuropathologist
ZL5A.00	Referral to physician
ZL5A900	Referral to clinical neurophysiologist
ZL5AO00	Referral to neurologist
ZL5B.00	Referral to psychiatrist
ZL5B100	Referral to child and adolescent psychiatrist
ZL5B111	Referral to child psychiatrist
ZL5GL00	Referral to neurosurgeon
ZL87.00	Referral to speech and language therapist
ZL87.11	Refer to speech therapist
ZL87100	Referral to community-based speech and language therapist
ZL87111	Referral to community speech and language therapist
ZL97.00	Seen by paediatrician
ZL97300	Seen by paediatric neurologist
ZL9AP00	Seen by neurologist
ZL9D.00	Seen by psychiatrist
ZL9GJ00	Seen by neurosurgeon
ZLD2V00	Discharge by paediatric neurologist
ZLD3900	Discharge by clinical neurophysiologist
ZLD3P00	Discharge by neurologist
ZLD4E00	Discharge by neurosurgeon

Appendix 18: Code list of inpatient and emergency hospital care

Medical code	Description
6611.00	Last hospital in-patient
9116.11	Emergency treatment registration
9144.00	Patient in hospital
9451.00	Death notification from hospital
9495.00	Patient died in hospital
13F8.00	Hospital patient
13F8.11	Hospital inpatient
13F8100	Long stay hospital inpatient
13F8200	Previous multiple hospital admissions
13FS.00	Long stay hospital inpatient
667W.00	Emergency epilepsy treatment since last appointment
8B1..00	Emergency treatment
8B11.00	Emergency dressing
8B1Z.00	Emergency treatment NOS
8CO..00	Inpatient care
8H1..00	Admit to intensive care unit
8H1..11	Admit to I.T.U.
8H13.00	Admit to neurological ITU
8H16.00	Admission to special care baby unit
8H1Z.00	Admit to intensive CU. NOS
8H2..00	Emergency hospital admission
8H21.00	Admit medical emergency unsp.
8H22.00	Admit surgical emergency unsp.
8H23.00	Admit psychiatric emergency
8H23000	Emergency psychiatric admission MHA
8H25.00	Admit paediatric emergency
8H2A.00	Admit trauma emergency
8H2E.00	Admit neurology emergency
8H2N.00	Admit neurosurgical emergency
8H2Z.00	Admit hospital emergency NOS
8H3..00	Non-urgent hospital admission
8H31.00	Non-urgent hospital admission unspecified
8H36.00	Non-urgent medical admission
8H38.00	Non-urgent psychiatric admission
8H3J.00	Non-urgent neurology admission
8H3S.00	Non-urgent neurosurgical admission
8H3Z.00	Other hospital admission NOS
8Ha..00	Voluntary admission
8Hb..00	Involuntary admission
8HC..00	Refer to hospital casualty
8HCZ.00	Refer to hospital casualty NOS

8Hd..00	Admission to hospital
8Hd0.00	Admission to community hospital
8HE..00	Discharged from hospital
8HE7.00	Discharged from hospital within 6 hours of delivery
8HE8.00	Discharged from accident and emergency
8HF..12	Transferred from hospital
8HG..00	Died in hospital
8HG..11	Death in hospital
8HJJ.00	Self-referral to accident and emergency department
8HM6.00	Listed for Neurology admission
8HTF.00	Referral to emergency clinic
945..00	Hospital death discharge notification
945Z.00	Hospital death discharge NOS
949B.00	Patient died in community hospital
94D..00	Hospital notified of death
9b00.00	A&E report
9b09.00	Day case report
9b0A.00	Discharge report
9b0B.00	Discharge summary report
9b0C.00	Emergency consultation note
9b0K.00	Hospital admission note
9b0L.00	Hospital inpatient report
9b0l.00	Surgery consultation note
9b8D.00	Accident & emergency
9Ee0F00	Admission history and physical report
9N58.00	Emergency appointment
9N62.00	Referred by hospital doctor
9NM4.00	Attending day hospital
9NNQ.00	Under care of hospital psychiatric team
9R6..00	Hospital reference number:
9U4..00	Formal complaint about hospital care
9U5..00	Formal complaint about hospital care RE: self
9U6..00	Formal complaint about hospital care RE: relative
Eu43213	[X]Hospitalism in children
Z177800	Inpatient care
ZIF3.00	Ensuring patient's carer prepared for hospital discharge
ZL11.00	Under care of accident and emergency doctor
ZL11.11	Under care of A & E doctor
ZL11.12	Under care of casualty doctor
ZL16.00	Under care of intensive care specialist
ZL16.11	Under care of ITU specialist
ZL51.00	Referral to accident and emergency doctor
ZL51.12	Referral to A & E doctor
ZL51.13	Referral to casualty doctor

ZL56.00	Referral to intensive care specialist
ZL56.11	Referral to ITU specialist
ZL56200	Referral to paediatric intensive care specialist
ZL56211	Referral to paediatric ITU specialist
ZL87200	Referral to hospital-based speech and language therapist
ZL87211	Referral to hospital speech and language therapist
ZL91.00	Seen by accident and emergency doctor
ZL91.11	Seen by A & E doctor
ZL91.12	Seen by casualty doctor
ZLD2100	Discharge by accident and emergency doctor
ZLD2111	Discharge by casualty doctor
ZLD2112	Discharge by A & E doctor
ZLD2a00	Discharge by psychiatrist
ZLD2b00	Discharge by child and adolescent psychiatrist
ZLD2R00	Discharge by paediatrician
ZLDP.00	Discharge by speech and language therapist
ZLDP200	Discharge by hospital-based speech and language therapist
ZLDP211	Discharge by hospital speech and language therapist
ZLEL100	Discharge from hospital speech and language therapy service
ZLEL200	Discharge from hospital speech and language therapy service
ZLF1100	Discharge from hospice day hospital
ZLF2.00	Discharge from hospital
ZLF2100	Discharge from day hospital
ZLF2200	Discharge from psychiatry day hospital
ZLF3.00	Discharge from ward
ZLF3100	Discharge from day ward
ZLG6.00	Discharge to hospital
ZLG6100	Discharge to long stay hospital
ZLG6200	Discharge to community hospital
ZLG6300	Discharge to GP hospital
ZLG6400	Discharge to tertiary referral hospital
ZLG6411	Discharge to tertiary referral centre
ZLG6500	Discharge to tertiary referring hospital
ZLG8.00	Discharge to ward
ZLG8100	Discharge to day ward

Appendix 19: Code list of diagnostic imaging and laboratory investigations for epilepsy

Medical code	Description (diagnostic imaging)
3113000	EEG normal
3114000	EEG abnormal
3119.00	Electroencephalogram
31C..00	EEG observations
563..00	Tomography
5631.00	Tomography requested
5632.00	Tomography normal
5633.00	Tomography abnormal
5634.00	Tomography - head/neck
563Z.00	Tomography - NOS
567..00	Computerised axial tomography
567..11	CAT scan
567..12	Computer axial scan
567..13	Computerised tomography scan
5671.00	CAT scan requested
5672.00	CAT scan normal
5673.00	CAT scan abnormal
5675.00	CAT scan - brain
567B.00	CAT scan - whole body
567C.00	CAT scan brain - abnormal
567Z.00	CAT scan - NOS
569..00	Nuclear magnetic resonance
569..11	NMR Scan
569..12	Magnetic resonance imaging
5691.00	Nuclear magn.reson.requested
5692.00	Nuclear magnreson normal
5692.11	MRI scan normal
5693.00	Nuclear magn.reson. abnormal
5693.11	MRI scan abnormal
5694.00	Magnetic resonance imaging of brain abnormal
569F.00	Magnetic resonance imaging of brain normal
569K.00	Magnetic resonance imaging of head
569K.11	MRI of head
569K000	Magnetic resonance imaging of brain
569Z.00	Nuclear magnetic resonance NOS
7065000	Electroencephalography
7065600	Video EEG
7065611	EEG video telemetry
7065B00	Electroencephalography NEC

7P00000	Computed tomography of whole body
7P00100	Magnetic resonance imaging of whole body
7P00z00	Diagnostic imaging of whole body NOS
7P02000	Computed tomography of head
7P02100	Magnetic resonance imaging of head
7P02200	Functional magnetic resonance imaging of head
7P0J000	Magnetic resonance imaging NEC
7P10000	Electroencephalograph telemetry
8HQ3.11	Refer for MRI
8HR5.00	Refer for EEG
R140100	[D]Echoencephalogram abnormal
R140200	[D]Electroencephalogram (EEG) abnormal
7P0M100	Positron emission tomography with computed tomography
Medical code	Description (laboratory investigations)
44W2.00	Serum phenobarbitone level
44W3.00	Serum phenytoin level
44W3.11	Phenytoin: blood level
44W4.00	Serum sodium valproate level
44W4.11	Epilim: blood level
44W4.12	Sodium valproate: blood level
44W5.00	Serum carbamazepine level
44W5.11	Carbamazepine: blood level
44W6.00	Serum ethosuximide level
44W7.00	Serum primidone level
44Wf.00	Serum vigabatrin level
44Wg.00	Serum lamotrigine level
44Wn.00	Serum gabapentin level
44Ws.00	Plasma carbamazepine level
44Wt.00	Serum diazepam level
44u5.00	Serum clonazepam level
44uC.00	Serum topiramate level
44uF.00	Serum clobazam level
44vA.00	Serum levetiracetam level
8HP..00	Referral for laboratory tests
8HP1.00	Referral for haematology test
8HPZ.00	Referral for lab test NOS
44vA.00	Serum levetiracetam level
9bC3.00	Haematology (specialty)
9bC7.00	Neuropathology