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The descriptive epidemiology of epilepsy-a review

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Abstract

Epilepsy is a chronic disease experienced by millions and a cause of substantial morbidity and mortality. This review summarizes prevalence and incidence studies of epilepsy that provided a clear definition of epilepsy and could be age-adjusted: requirements if comparisons across studies are to be made. Although few exceptions, age-adjusted prevalence estimates from record-based studies (2.7 to 17.6 per 1000), are lower than those from door-to-door surveys (2.2 to 41.0 per 1000). Age-adjusted incidence ranged from 16 to 51 per 100,000, with one exception in Chile, where incidence was 111 per 100,000. Variation in reported prevalence and incidence may be related to factors such as access to health care, regional environmental exposures, or socioeconomic status. A higher proportion of epilepsy characterized by generalized seizures was reported in most prevalence studies. Epilepsy characterized by partial seizures accounted for 20% to 66% of incident epilepsies. Virtually all prevalence and incidence studies report a preponderance of seizures of unknown cause. Additional prevalence studies are needed in regions where data does not exist, and additional incidence studies in all regions. Interpretation of differences in prevalence and incidence will require understanding of the role of cultural, social and economic factors influencing epilepsy and its care.

Keywords

Prevalence; Incidence; Epilepsy; Seizure; Review

1. Introduction

Epilepsy is one of the oldest conditions known to mankind (WHO, 2001a) and still the most common neurological condition affecting individuals of all ages. At any given time, it is estimated that 50 million individuals worldwide have a diagnosis of epilepsy (WHO, 2001b). However, the heavy burden of this disease is not evenly distributed, and according to available data, there are disparities in reported prevalence and incidence across the world. Many of the reported differences can be attributed to variations in study methodology (e.g. case definition,

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ascertainment) and population structure (e.g., age). Increased prevalence and incidence may be related to factors such as low socioeconomic status, limited access to health care and environmental exposures such as neurocysticercosis. Prevalence or incidence may be underestimated in areas where the condition is greatly stigmatized and cultural beliefs about the causes of epilepsy or negative attitudes toward those with epilepsy lead to the concealing of symptoms of epilepsy, or its diagnosis.

In this review, all primary population-based studies of prevalence and incidence of epilepsy published in English, and accessible through Medline since 1965 are examined. The PubMed database was searched using three keyword combinations: “epilepsy epidemiology” (n=5,314), “epilepsy incidence” (n=6,534) and “epilepsy prevalence” (n=5,749). Additional references were found using reference lists from selected studies (n=57). Studies were then limited to total population studies that provided a clear definition of epilepsy and could be age-adjusted (n=68; 48 prevalence and 20 incidence).

1.1. Definitions

1.1.1. Epilepsy—Epilepsy is defined as a condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause (Hauser and Kurland, 1975; ILAE, 1993). Multiple seizures occurring in a 24-hour period or an episode of status epilepticus (SE) are considered a single event. Individuals who have had only febrile seizures or only neonatal seizures (seizures in the first 30 days of life), and people with acute symptomatic seizures, (seizures associated with acute systemic illness, intoxication, substance abuse or withdrawal, or acute neurological insults), and individuals with a single unprovoked seizure, are excluded from this category.

In some studies, “epilepsy” is defined as the above plus those with a single unprovoked seizure, any afebrile seizure, or febrile seizures. For some studies using computerized record search alone, there is uncertainty as to the inclusion or exclusion of any of the above features. This review has focused on studies of epilepsy defined as recurrent unprovoked seizures. For completeness, studies using other definitions are also reviewed.

1.1.2. Prevalence—Prevalent epilepsy is defined as a diagnosis of epilepsy (recurrent unprovoked seizures) at some point prior to the prevalence period or date. An active prevalence case is one that continues to experience the burden of epilepsy based either on recency of seizure (generally in the year prior to the prevalence date or within 5 years of the prevalence date, depending on the study) and/or recency of anti-seizure medication use. Point prevalence reflects the number of cases of active epilepsy on prevalence day, divided by the total population under study on that prevalence day. In this review, prevalence is expressed as active cases per 1,000 persons. Active prevalence differs from life-time prevalence, which includes those having a history of epilepsy regardless of recency of seizures or of use of anti-seizure medication.

1.1.3. Incidence—Incidence of epilepsy is defined as the number of new cases of epilepsy over a specified time period. In this review, the incidence is the number of new cases per year divided by the average susceptible population under study during a specified time period and is expressed as new cases per 100,000 persons per year.

1.1.4. Age adjustment—Since the incidence and prevalence of epilepsy vary with age, overall population incidence and prevalence cannot be compared unless the age structures of the populations are identical. Thus, we have only included studies that provide age-adjusted or age-specific estimates. For studies which provided age-specific estimates, we performed

age-adjustment using the direct method to the 2000 US standard population (Health Statistics, 2006).

1.1.5. Seizure type—The two major categories of seizure type classified by the International League Against Epilepsy (ILAE) in 1981 are epilepsy characterized by partial seizures and epilepsy characterized by generalized seizures. Epilepsy characterized by partial (focal) seizures is that in which seizures begin in a local area of the brain. This seizure type is further subdivided into simple partial (no alteration in consciousness) and complex partial seizures (alteration of consciousness). Epilepsy characterized by generalized seizures may also be categorized as partial with secondary generalization if a clinical description of an antecedent symptom (aura), or a clear electroencephalographic signature of focality is indicated. Epilepsy characterized by generalized onset seizures conceptually involves the entire brain simultaneously. Individual generalized seizure types include absence, myoclonic, tonic-clonic, atonic, tonic, and clonic symptoms. In many studies, it is not clear that “generalized seizure” is synonymous with generalized onset seizure, leading to some ambiguity in classification by seizure type. Since some seizure types co-exist, it is assumed that the classifications represent the predominant seizure type. This is seldom clear, however, and in some cases, seizure type may remain unclassifiable.

1.1.6. Etiology—Broad etiologic categories included idiopathic, symptomatic, and cryptogenic (ILAE, 1989). Idiopathic epilepsies are assumed to have a genetic basis and generally have onset during childhood. Symptomatic epilepsies typically follow an identified brain insult. For cryptogenic epilepsies, the cause of the epilepsy is unknown but many presume that a cause could be identified with sufficient investigation.

2. Methods of case ascertainment

The spectrum of methods of case ascertainment in population-based studies of epilepsy reviewed included community surveillance, community survey, key informants, record-based review and administrative database search. Most studies used combinations of these methodologies in order to capture and properly classify cases.

Surveillance methodology typically involved systematic identification of potential cases of epilepsy at multiple points of contact. Generally, a broad case definition for case identification is initially used but subsequently refined to only include cases meeting specific criteria.

Surveys sometimes involve direct interviews with people in populations of interest but may use other methods to obtain information, such as telephone or mail questionnaires. Surveys were almost always supplemented by additional evaluation in those individuals who initially screened positive for epilepsy. While cost-effective, telephone and mail surveys are frequently plagued with a low response rate. In some geographic areas, mail or phone surveys could not be considered since they require certain economic and social infrastructure in order to be feasible.

In studies that used record-based methodology, records were ascertained from all medical facilities, including neurology practices and EEG laboratories in specified catchment areas. This methodology identified those who had contact for medical care for their condition (epilepsy) but may not always capture individuals who did not have access to health care. Some studies used databases established for purposes other than the study of epilepsy. In these databases, search methodology for the epilepsy-related data included review of use of epilepsy-related prescription medications or review of diagnostic codes for seizures or epilepsy. In some cases, these diagnostic codes may not have been specific for epilepsy, resulting in uncertainty in actual diagnosis.

Regardless of methodology used, there were many ways in which a study may have underestimated the number of people with epilepsy. Missing cases could be due to individuals or their families hiding the condition of epilepsy, either because of fear of social stigma, or loss of employment or loss of driver's license. Under ascertainment could also occur as a result of not identifying individuals with epilepsy who did not regularly access health care for their condition.

3. Prevalence in studies of epilepsy (recurrent unprovoked seizures)

Forty-eight population-based studies including individuals of all ages, and for which prevalence could be age-adjusted, were identified for this review. Of these studies, twenty-nine used door-to-door survey methodology (Table 1), 14 studies used record-based methodology (Table 2), and five used self-report or computerized database methodology (Table 3).

3.1 Prevalence studies of epilepsy using door-to-door methodology

Age-adjusted prevalence in studies that used door-to-door survey methodology ranged from 2.2 in India (Koul et al., 1988) to 41.0 in Nigeria (Osuntokun, 1982). In the North American studies, the age adjusted prevalence was 5.0 in the study conducted by Kelvin et al (2007) in New York and 7.1 per 1000 (Haerer et al., 1986) in Mississippi.

In Central and South America, the overall age-adjusted prevalence ranged from 3.7 per 1000 in Argentina (Melcon et al, 2007) to 22.2 per 1000 in Ecuador (Cruz et al., 1985). The study performed by Cruz et al. was conducted among a population with a high prevalence of endemic goiter. The South American study most recently completed at the time of this review reports the lowest age-adjusted prevalence of 3.7 (Melcon et al., 2007).

Real differences in prevalence may be related to the presence of endemic conditions such as neurocysticercosis or malaria, the medical infrastructure in place, including availability of preventive regional health programs, and accessible local medical care. A region which has eradicated the porcine tapeworm, has established effective malaria prevention strategies, or has established immunization programs, can reduce or minimize risk factors associated with epilepsy.

In Europe, age-adjusted prevalence was low, 2.7 per 1000 and 3.3 per 1000, respectively in each study conducted in Italy (Reggio et al., 1996; Rocca et al., 2001), when compared to a prevalence of 7.0 per 1000 in the study conducted in the European region of Turkey (Onal et al., 2002).

In contrast to the majority of studies conducted in Asia, the age-adjusted prevalence of 10.2 per 1000 in Asian Turkey (Karaagac et. al, 1999) was higher than both the age-adjusted prevalence of 6.6 per 1000 and 9.8 per 1000 in the studies conducted in Asian Turkey and Pakistan by Aziz et al (1997). This prevalence was much higher than the age-adjusted prevalence reported in studies conducted in India and China, where prevalence ranged between 2.2 and 4.4 per 1000 (Koul et. al, 1988; Bharucha et al., 1988; Radhakrishnan et al., 2000; Li et. al, 1985).

The highest reported age-adjusted prevalence is from a study conducted in a rural area of Nigeria (Osuntokun et al., 1982). In another study conducted in Nigeria five years later by the same investigators, age-adjusted prevalence is 4.9 per 1000 (Osuntokun et al., 1987). Excluding the 1982 study, age-adjusted prevalence in Africa ranged from 3.9 per 1000 in Tunisia (Attia-Romdhane et al., 1993) to 13.2 per 1000 in Zambia (Birbeck and Kalichi, 2004).

3.2. Prevalence studies of epilepsy using record-based methodology

Prevalence studies that used record-based methodology require a more sophisticated medical infrastructure and are typically conducted in developed countries. In the Rochester, Minnesota studies (Hauser et al., 1991), age-adjusted prevalence increased from 2.7 in 1940 to 7.1 in 1980. These changes over time may be in part due to changes in incidence and survival, but are also related to inclusion of cases with active epilepsy identified at an earlier time, residing in the community on later prevalence days, and taking anti-seizure medications. Many of these cases would have been missed in cross-sectional surveys. In 1980 for example, the prevalence from a cross-sectional survey would have been 20% lower had the active prevalence been limited to those identified through screening of recent diagnostic entries for epilepsy.

In the only record-based study conducted in South America, the age-adjusted prevalence of active epilepsy in Chile was 17.6 per 1000 (Lavados et al., 1992). This prevalence is within the range derived from studies using door-to-door methodology in this region.

In European studies using record-based methodology, age-adjusted prevalence ranged from 3.0 per 1000 in a study conducted in the Aeolian Islands (Gallitto et al., 2005) to 7.7 per 1000, reported from a study in the Faroes (Joensen, 1986).

Only one record-based study has been completed in Asia (Asawavichienjinda et al., 2002). This study, conducted in Thailand, reported a higher age-adjusted prevalence (7.1 per 1000) than some other studies conducted in Asia using door-to-door methodology.

3.3. Prevalence reported in studies in which diagnostic criteria are not established

Five studies without strict criteria for epilepsy were included in this review (Table 3). Age-adjusted Prevalence was estimated to be 5.0 (Tellez-Zenteno et al., 2004) and 5.2 (Wiebe et al., 1999) per 1000 in two studies conducted in Canada, which used self reported data from an interview. In these studies, there was lack of any verifiable medical information regarding diagnosis of seizures or epilepsy.

In three studies, algorithms were developed to combine pharmacy data with diagnostic entries in order to enumerate individuals with epilepsy within a database, and age-adjusted prevalence ranged from 4.0 in Italy (Beghi et al., 1991) to 5.5 in per 1000 in Denmark (Christensen et al., 2007). In the studies that relied on computerized databases, it may be impossible to distinguish individuals being treated after single unprovoked seizure or following acute symptomatic seizure (including febrile seizure), from those with epilepsy (recurrent unprovoked seizure).

3.4. Age-specific prevalence

Although studies are not in perfect concordance, most reports show a general trend towards an increase in epilepsy prevalence during adolescence or early adulthood (Lavados et al., 1992; Basch et al., 1997; Olafsson and Hauser, 1999; Birbeck and Kalichi, 2004). In developed countries, most studies show the prevalence of epilepsy to be stable in the adult age groups and to increase with age after 50 (Forsgren, 1992; Olafsson and Hauser, 1999). In most studies in developing countries, prevalence of epilepsy remains stable in the third and fourth decades and typically drops after the fifth decade of life. In a few studies, prevalence then again increases after age 60 (Lavados et al., 1992; Basch et al., 1997; Birbeck and Kalichi, 2004).

3.5. Gender

Prevalence is higher in males than females in 16 of 29 door-to-door studies (Table 1) and 11 of 16 record-review studies for which data was provided (Table 2). However, absolute difference in gender-specific prevalence is minimal. The most extreme example of a male excess was reported in a study conducted in India, in which prevalence of males (5.1 per 1000)

was significantly higher than females (2.2 per 100) (Bharucha et al., 1988). In this population, women with epilepsy are felt to be unmarriageable and this may have led to active concealment of symptoms or diagnosis among women.

3.6. Race and ethnicity

Few studies have examined prevalence of epilepsy comparing race or ethnic group. The largest racially diverse prevalence study comes from Copiah County, Mississippi, USA (Haerer et al., 1986). Haerer et al. assessed the prevalence of epilepsy in 23,957 inhabitants and tabulated them according to gender, age, and race (African American/Caucasian) and found age-adjusted prevalence was higher for African-Americans (8.2 per 1000) as compared to Caucasians (5.4 per 1000). While this study suggests a higher prevalence of epilepsy among African-Americans, a serious limitation was failure to control for socioeconomic status.

A study in UK examined racial differences between South Asians and non-South Asians, and found prevalence of active epilepsy to be lower in South Asians in comparison to Non South-Asians (Wright et al., 2000). In this study, cases were ascertained through review of medical records which were identified by searching practice databases using diagnostic codes combined with repeat prescribing data. South Asians were classified by computer analysis of their names. The study estimated the age-standardized rate for all patients of South Asian origin to be 3.6 per 1000, as compared to the age-standardized estimated rate of 7.8 per 1000 for Non South-Asians (OR=0.46; 95% CI: 0.38, 0.57).

3.7. Socioeconomic status

Three recent studies conducted in different parts of the world have reported an association between SES and prevalence (Noronha et al., 2007, Birbeck et al., 2007, Kelvin et al., 2007). In a study conducted in Brazil, the prevalence of active epilepsy was higher in those with lower SES (7.5 per 1000) compared with prevalence in more affluent groups (1.6 per 1000), even after accounting for a potential treatment gap among socioeconomic levels (Noronha et al., 2007). In a cross-sectional study conducted in Zambia, individuals with epilepsy were found to have substantially poorer social and economic status, as exemplified by living in suboptimal housing, income level and occupational status in comparison to age-matched peers with other chronic medical conditions (Birbeck et al., 2007). The results of the third study were not consistent with results of the other two. In a community-based prevalence study conducted in New York City using a random-digit dial phone survey, prevalence of epilepsy was highest in those with highest income (Kelvin et al., 2007). This finding is not readily explained aside from potential bias created by the study design which required a household telephone. All three studies, by nature of a cross-sectional design, do not provide information about the direction of influence between SES and epilepsy.

3.8. Seizure type

Classification of seizure type is dependent on accuracy of history, availability and sophistication of diagnostic tests used, and age at which the patient's seizure type was classified. Twenty-five studies provide data regarding prevalence by seizure type (Table 4). A higher proportion of epilepsy characterized by generalized seizure was reported in half of the studies. One might expect epilepsy characterized by partial seizures to predominate in areas with increased medical sophistication and in populations limited to adults. While this is in part true, it does not seem consistent in all studies. For example, in Italian studies (Granieri et al., 1983; Giuliani et al., 1992; Rocca et al., 2001), a preponderance of epilepsy characterized by generalized seizures was reported. The studies conducted in Mississippi (Haerer et al., 1986) and in Minnesota (Hauser et al., 1991) were conducted in contemporaneous populations yet dramatic differences are present in distribution of cases by seizure type. Prevalence studies relying on information acquired from door-to-door studies without availability of diagnostic

tests may underestimate epilepsy characterized by partial seizures. Since criteria used for classification by seizure type were seldom specified, misclassification of cases by seizure type is difficult to estimate.

3.9. Etiology

Seventeen studies provided information of prevalence by etiology (Table 5). Virtually all studies report preponderance of seizures of unknown cause. When a more detailed account of etiology has been provided, cryptogenic seizures predominate in those with unknown etiology. In studies in Africa, a higher proportion of cases of unknown etiology were reported when compared to studies conducted in North America and in Europe. Although criteria are only occasionally specified, most recent studies typically referred to the recommendations of the ILAE commission for epidemiological studies (ILAE, 1993). These studies have attempted to separate cases of unknown cause into idiopathic (presumed genetic) and cryptogenic types. This may be due to a greater likelihood of having sophisticated diagnostic tools (EEG, imaging) available or a greater likelihood of getting appropriate information from a patient's history to classify etiology.

4. Incidence in studies of epilepsy, all unprovoked seizures and all afebrile seizures

While prevalence studies are useful in estimating the burden of disease, and making economic and other public health predictions, incidence studies provide a better understanding of the etiology and natural history of epilepsy. Due to the difficulty and expense of identifying an incidence cohort, incidence studies are conducted less often than prevalence studies.

4.1. Incidence studies of epilepsy

A total of fifteen population-based studies in all ages for which incidence of epilepsy could be age-adjusted have reported incidence of epilepsy, defined as recurrent unprovoked seizures (Table 6). In North America, age-adjusted incidence of epilepsy ranged from 16 per 100,000 person-years (Benn et al., 2008) to 51 per 100,000 person-years (Hauser et al., 1993).

The only incidence study of epilepsy, defined as recurrent unprovoked seizures, that could be age-adjusted in South America, conducted in rural Chile (Lavados et al., 1992), reported the highest age-adjusted incidence in the world (111 per 100,000 person-years).

Age adjusted incidence of epilepsy in European studies ranged from 26 per 100,000 person-years in Norway (De Graaf, 1974) to 47 per 100,000 person years in England (MacDonald et al., 2000).

Only one incidence study of epilepsy that could be age-adjusted was conducted in Asia (Mani et al., 1998). This study, carried out in India, and reported an age-adjusted incidence of 35 per 100,000 person years.

There were two studies of incidence of epilepsy conducted in Africa. In Tanzania (Rwiza et al., 1992), crude incidence was 73 per 100,000 and age-adjusted incidence was 51 per 100,000. In Ethiopia (Tekle-Haimanot et al., 1997), crude incidence of epilepsy was 64 per 100,000 while age-adjusted incidence of epilepsy was 43 per 100,000.

4.2. Incidence studies of all unprovoked seizures

The incidence of all unprovoked seizures was available from seven studies (Table 7). The childhood study of Sidenvall and the adult study of Forsgren from the same region were combined. Age adjusted incidence of all unprovoked seizures ranged from 41 per 100,000 in

New York (Benn et al., 2008) to 69 per 100,000 person-years in Minnesota (Hauser et al., 1993).

4.3. Incidence studies of all afebrile seizures

Five studies reported age-adjusted incidence of all afebrile seizures (Table 8). In these studies, incidence ranged from 30 per 100,000 person-years in Denmark, (Juul-Jensen and Foldspang, 1983) to 174 (Placencia, 1992) per 100,000 person-years in Ecuador. As would be expected, the incidence of all afebrile seizures is generally higher than the incidence of epilepsy (recurrent unprovoked seizures) (Table 6).

4.4. Age-specific incidence

In developed countries, studies showed epilepsy incidence to be high in the first year of life, and early childhood, stabilizing after adolescence, and generally lowest in the adult years through the fifth decade of life (Forsgren et al, 1996; Granieri et al, 1983; Hauser et al., 1993; Olafsson et al., 2005; Sidenvall et al, 1993). Incidence then increased in the oldest age groups. In developing countries, incidence was high in the childhood years but an increase in the older age groups was generally not seen (Lavados et. al, 1992; Mani et al., 1998; Rwiza et al., 1992; Tekle-Haianot et al., 1997).

4.5. Secular trends

A few studies have analyzed secular trends incidence of epilepsy. Cockerell et al. (1995) analyzed first attendance data, (first physician visit at which a definite epileptic seizure was diagnosed) in a general practice in South East England. They noted that first attendance declined in children over time from 152 per 100,000 between 1974 and 1983 to 61 per 100,000 between 1984 and 1993.

The Rochester study(Hauser et al., 1993) reported some fluctuation between 1935 and 1984, but no significant difference in age-adjusted incidence over time. However, there were time trends by age group. Incidence fell in children (less than 10 years) between 1935 and 1974 and increased between 1974 and 1984. This change was counterbalanced by an increasing incidence in the elderly between 1935 and 1984.

In an incidence study in children (Heijbel, 1975) in Northern Sweden, the incidence of first unprovoked seizure for individuals between the ages of 0 to 15 years was 134 per 100,000. In a follow-up study conducted three years later(Blom et al., 1978), the incidence fell to 82 per 100,000. Approximately eight years after this follow-up study, Sidenvall et al (1993) again investigated the incidence of epilepsy in Northern Sweden and found that incidence was 89 per 100,000 over a 20-month study period. When neonatal seizures are excluded, incidence in the Heijbel study is approximately 124 per 100, 000 and it is 79 per 100,000 in the Sidenvall study.

It is hypothesized that the decrease in incidence of children's cases is related to better prenatal care and immunization programs. The increasing incidence in children found in Rochester after 1975 may be related to improved survivorship of very low birth weight babies, leading to a higher proportion of children with neurological deficits. The increasing incidence in the elderly are hypothesized to be related to improved survival in persons with cerebrovascular disease.

4.6. Gender

Many studies report a higher incidence in males than females but seldom has this difference been significant (Hauser et al., 1993). Cumulative incidence for all unprovoked seizures reported in Iceland and US demonstrated a significant male excess (Hauser et al., 1993; Olafsson et al., 2005).

4.7. Race and ethnicity

Few studies provide information on variation in incidence by race or ethnicity. One of the only incidence studies to provide data on a racially diverse adult population (Annegers et al., 1999) was conducted in Houston, Texas. This study was based on health maintenance organization (HMO) enrollees and their families. There were no statistically significant differences in incidence among non-Hispanic whites, African-Americans, Hispanics, and Asians. The use of an HMO population eliminates much of the influence of socioeconomic status. In a study estimating incidence of epilepsy in an urban community, incidence among Hispanics was found to be similar to that of both Whites and African Americans (Benn et al., 2008).

4.8. Socioeconomic status

Studies show an increase in incidence of epilepsy in lower SES groups when compared with more affluent populations. In Great Britain, findings from a prospective surveillance study of twenty general practices demonstrated that those in the lowest SES group were over two times more likely to develop epilepsy in comparison to the highest SES group (Heaney et al., 2002). In a population-based incident case control study examining the association between low socioeconomic status and risk of epilepsy in Iceland, results showed that in adults, low SES, as indexed by low education or lack of home ownership, was a risk factor for epilepsy. This association was not accounted for by established risk factors for epilepsy (e.g., head injury, stroke), which also have a higher incidence in low SES populations (Hesdorffer et al., 2005). In another study examining population-based data in Sweden, an increased risk of epilepsy was observed in men in who held occupations such as waiter, construction worker, or dry cleaner (Li et al., 2008) when compared to “white-collar” occupations. Those with low SES may be differently exposed to certain occupational, residential or lifestyle factors, which individuals in higher SES groups are not.

4.9. Seizure type

Eight incidence studies provided information on seizure type (Table 9). Epilepsy characterized by partial or localization-related epilepsies account for 20% to 66% of incident epilepsies in population-based studies of all ages. Studies of seizure type reporting a high proportion of cases as “unclassifiable” or “unknown” probably classify people with tonic-clonic seizures alone and with no other distinguishing features as unknown. The incident studies performed in developing countries, particularly in Africa, reported a greater proportion of individuals to have epilepsy characterized by generalized onset seizures than epilepsy characterized by partial seizures.

4.10. Etiology

There was surprising consistency in the proportional distribution of broad etiologic classification regardless of the country in which the study has been conducted or medical sophistication of evaluation available to investigators (Table 10). In studies which include all ages, an identified cause is present in 14% to 39% of cases, while the majority has no obvious identifiable cause.

The 1993 ILAE recommendations for epidemiologic studies suggested dividing symptomatic epilepsy into “remote” and “progressive”, where remote symptomatic epilepsies encompass cases developing following insults resulting in static lesions (such as those attributable to conditions such as stroke or CNS infections), and progressive symptomatic epilepsy encompass epilepsies associated with non-static conditions (such as brain tumors or degenerative disease). This more detailed classification has been used in several studies performed since 1995. Classification using these definitions is also possible in some earlier studies. In general, all of

these studies have reported relatively similar distributions of etiologic categories. A few studies also allow distinction between idiopathic (presumably genetic) and cryptogenic among those with epilepsy of unknown causes. In these studies, idiopathic cases account for about 10% of all epilepsies.

5. Discussion

Findings from studies are most comparable when the definition of epilepsy is the same and population age structure differences are minimized through age-adjustment. When comparing age-adjusted estimates of studies using the same definition of epilepsy in this review, overall prevalence and incidence of epilepsy tended to be lower in developed regions (United States and Europe) in comparison to developing regions (Latin America and Africa), with Asia reporting the lowest frequency of epilepsy. The studies with the highest prevalence from door-to-door studies (Nigeria and Ecuador), were performed in rural villages. Further, the populations studied in these reports were relatively small and the low numbers of cases identified may have lead to some instability in prevalence estimates. If one considers only studies with a larger number of cases, there remains substantial variation in prevalence estimates. The high prevalence in the record based study in Chile is unexplained. Prevalence of epilepsy is low in Asia, but the condition is highly stigmatized in this region and the low prevalence may be a reflection of the culture.

Incidence, just as prevalence, is also generally lower in developed regions in comparison to developing regions. The highest reported incidence of epilepsy from the study conducted in Chile (1992), is largely unexplained. Only one study reported incidence in Asia, and this is low when compared to reported incidence in the United States and Europe.

The need for use of standard definitions is best demonstrated by contrasting the incidence of all afebrile seizures reported from Ecuador by Placenia (1992) and colleagues (age adjusted 174 per 100,000) with the only incidence study of epilepsy reported from South America conducted in Chile (Lavados et al., 1992) with an age adjusted incidence of 111/100,000. At first it would seem the incidence in Ecuador is exceedingly high. In fact the Ecuadorian study provides by far the highest estimate of incidence of any study reviewed. However, if one considers that the definition used in which incidence was derived by combining individuals with single unprovoked seizures and acute symptomatic seizures, in addition to recurrent unprovoked seizures (epilepsy), it becomes evident that these studies cannot be readily compared.

The need for age-adjustment is best demonstrated by studies of epilepsy incidence conducted in Africa, where the age distribution of the population differs substantially from that in developed countries. In the study conducted by Rwiza and colleagues in Tanzania (1992), crude incidence of epilepsy was 73 per 100,000 but age-adjusted incidence was 51 per 100,000. In Ethiopia, the crude incidence of epilepsy of 64 per 100,000 was reduced to 43 per 100,000 after age-adjustment (Tekle Haimmanot et al., 1997). Thus, what appears to be a high incidence if crude rates are considered is dramatically reduced when the age adjusted incidence is calculated, and is comparable to incidence of epilepsy seen in developed countries. While there still may be differences in underlying etiologies of epilepsy, the apparent excessive burden of epilepsy in these developing countries based on a high crude incidence is put into perspective after age adjustment.

Prevalence and incidence of epilepsy differ by demographic factors including age, gender, race and socioeconomic status. In developed countries, the prevalence of epilepsy increases as age increases. In developing countries, prevalence of epilepsy generally peaks in adolescence and early adulthood. In both developed and developing countries, the incidence of epilepsy is high

in infancy and early childhood. In developed countries, incidence is several times higher in the elderly than in the adult age groups.

Most studies report differences by gender, although almost no study reports these differences to be statistically significant. The majority of prevalence studies report an excess of males. There is less consistency in incidence studies although most report non-statistically significantly higher incidence for males compared to females.

The association between race and epilepsy is largely unknown. There are few studies comparing racial or ethnic differences in the same population in any region of the world other than those conducted in North America and Great Britain. Prevalence studies conducted in the United States suggest that African-American race is associated with higher prevalence of epilepsy. Two incidence studies conducted in the United States and stratify findings by race report no differences when racial or ethnic groups are compared.

Some but not all prevalence studies have shown an association between epilepsy and lower socioeconomic status. Prevalence studies do not establish direction of causality. Directionality can only be established in incidence studies. Lower socioeconomic status is associated with higher incidence of epilepsy in adults but not children. This finding is surprising since low socioeconomic status is associated with a number of health conditions affecting both adults and children (e.g. birth defects, infection, injury, poor nutrition, low educational attainment and suboptimal housing), and all of these factors may in turn influence risk of developing epilepsy.

The few studies analyzing time trends show a recent decrease in the incidence of childhood epilepsy and an increase incidence of epilepsy in the elderly. Reasons for these trends are not fully understood.

There are almost no total population studies providing data regarding epilepsy syndromes although some information may be gleaned from assessment of seizure type and etiology. A number of studies provided information on seizure type. Classification of seizure type is largely dependent on the availability of medically sophisticated technology and without the use of such techniques, misclassification might be expected. Thus, there is little consistency across studies regarding distribution of seizure type. Virtually all prevalence and incidence studies, regardless of time or region of study, report preponderance of epilepsy to be of unknown etiology, suggesting use of sophisticated medical infrastructure such as imaging technology, does not always increase ability to detect a cause of epilepsy.

Future studies which include individuals from different age groups, racial and socioeconomic backgrounds, will provide information on the role of factors such as age, gender, race, and socioeconomic status upon prevalence and incidence of epilepsy. Additional prevalence studies would be useful in regions for which there is still no prevalence estimate. The need for more incidence studies, which are essential to learning more about the etiology of epilepsy, cannot be overstated. Interpretation of findings from all studies will be facilitated if culture and stigmatization, health care policies and access to health care, are fully considered.

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Table 1

Prevalence of recurrent unprovoked seizures in population based door-to-door survey studies of all ages

Region	Reference (First Author)	Publication Date	Gender	Population	Number of cases	Prevalence (per 1000)	
						crude	age-adjusted to 2000 US Standard Population
North America							
Mississippi	Haerer (Haerer et al., 1986)	1986	M>F	23,597	160	6.8	7.1
New York	Kelvin (Kelvin et al., 2007) *	2007	M<F	208,301	42	5.2	5.0
Central and South America							
Ecuador	Cruz (Cruz et al., 1985)	1985	M<F	1,113	19	17.1	22.2
Ecuador	Placencia (Placencia et al., 1992)	1992	M<F	72,121	575	8.0	9.1
Ecuador	Basch (Basch et al., 1997)	1997	M>F	221	5~	22.6	11.4
Bolivia	Nicoletti (Nicoletti et al., 1999)	1999	M<F	10,124	112	11.1	14.0
Honduras	Medina (Medina et al., 2005)	2005	M<F	6,473	100	15.4	16.0
Argentina	Melcon (Melcon et al., 2007)	2007	M<F	17,049	64	3.8	3.7
Europe							
Italy	Reggio (Reggio et al., 1996)	1996	M<F	9,956	27	2.7	2.7
Italy	Rocca (Rocca et al., 2001)	2001	M>F	24,496	81	3.3	3.3
Turkey	Onal (Onal et al., 2002)	2002	M>F	2,817	17	6.0	7.0
Asia							
China	Li (Li et al., 1985)	1985	M>F	63,195	289	4.6	4.4
India	Koul (Koul et al., 1988)	1988	M>F	63,645	157	2.5	2.2
India	Bharucha (Bharucha et al., 1988)	1988	M>F	14,010	50	3.6	3.6
Pakistan	Aziz (Aziz et al., 1997)	1997	M<F	24,130	241	9.9	9.8
Turkey**	Aziz (Aziz et al., 1997)	1997	M>F	11,497	81	7.0	6.6
Turkey**	Karaagac (Karaagac et al., 1999)	1999	M>F	4,803	49	10.2	10.2
India	Radhakrishna (Radhakrishnan et al., 2000)	2000	M>F	238,102	1,175	4.9	4.4
Saudi Arabia	Al Rajeh (Al Rajeh et al., 2001)	2001	M>F	23,700	155	6.5	5.1

Region	Reference (First Author)	Publication Date	Gender	Population	Number of cases	Prevalence (per 1000)	
						crude	age-adjusted to 2000 US Standard Population
<i>Africa</i>							
Nigeria	Osuntokun (Osuntokun, 1982)	1982	M<F	903	33	37	41.0
Nigeria	Osuntokun (Osuntokun et al., 1987)	1987	M<F	18,954	101	5.3	4.9
Nigeria	Longe (Longe and Osuntokun, 1989)	1989	M<F	2,925	18	6.2	4.7
Ethiopia	Tekle-Haimanot (Tekle- Haimanot et al., 1990)	1990	M>F	60,820	316	5.2	5.4
Tanzania	Rwiza (Rwiza et al., 1992)	1992	M<F	18,183	185	10.2	12.5
Tunisia	Attia-Romdhane (Attia-Romdhane et al., 1993)	1993	M>F	35,370	141	4.0	3.9
Kenya	Snow (Snow et al., 1994)	1994	M>F	7,450 (5+)	30	4.0	3.7
Uganda	Kaiser (Kaiser et al., 1996)	1996	M<F	4743	61	12.9	9.2
Zambia	Birbeck (Birbeck and Kalichi, 2004)	2004	M>F	55, 000	799	14.5	13.2
Tanzania	Dent (Dent et al., 2005)	2005	M>F	4,905	42	8.6	6.8
<i>Pacific Islands</i>							
Guam	Mathai (Mathai et al., 1968)	1968	-	6,967	16	2.3	2.7

* This study was done using random-digit dial methodology in the Northern Manhattan community. A follow-up interview was administered to those who screened positive for epilepsy over the telephone. Epileptologists reviewed all information from interviews to determine whether each potential case was actually a case.

~ all 5 cases were between 7–14 years of age

** These studies were conducted in a region of Turkey that is geographically part of Asia. However, the population may be more comparable to the western region of Turkey, which is part of Europe.

Table 2
Prevalence of epilepsy in population based interview or record-based studies of adults of all ages

Region	Reference (First Author)	Publication Date	Gender	Population (age)	Number of cases	Prevalence (per 1000)	
						crude	age-adjusted to 2000 US Standard Population
North America							
Rochester, MN 1940	Hauser (Hauser et al., 1991)	1991	M>F	24764	66	2.7	2.7
Rochester, MN 1950	Hauser (Hauser et al., 1991)	1991	M>F	28,241	124	4.4	4.5
Rochester, MN 1960	Hauser (Hauser et al., 1991)	1991	M>F	39005	198	5.1	5.5
Rochester, MN 1970	Hauser (Hauser et al., 1991)	1991	M>F	52629	285	5.4	5.7
Rochester, MN 1980	Hauser (Hauser et al., 1991)	1991	M<F	56,477	383	6.8	7.1
Central and South America							
Chile	Lavados (Lavados et al., 1992)	1992	M<F	17,694	314	17.7	17.6
Europe							
England	Brewis (Brewis, 1966)	1966	-	497,707	340	4.8	5.5
Norway	De Graaf (de Graaf, 1974)	1974	M=F	213,116	749	3.5	3.6
Italy	Granieri (Granieri et al., 1983)	1983	M>F	45,153	278	6.2	6.3
Faroes	Joensen (Joensen, 1986)	1986	M>F	43,609	333	7.6	7.7
Italy	Marenmani (Marenmani et al., 1991)	1991	M>F	9,549	51	5.1	5.2
Sweden	Sidenvall (Sidenvall et al., 1996)/Forsgren (Forsgren, 1992)	1992	M>F	129,005	868	5.2	5.1
Italy	Giuliani (Giuliani et al., 1992)	1992	M>F	45,258	235	5.2	5.3
Iceland	Olafsson (Olafsson and Hauser, 1999)	1999	M>F	89,656	428	4.8	4.3
Spain	Luengo (Luengo et al., 2001)	2001	-	98,405	394	4.0	4.1
Aeolian Islands	Gallitto (Gallitto et al., 2005)	2005	M<F	13,431	42	3.1	3.0
Croatia	Bielen (Bielen et al., 2007)	2007	M>F	212,069	1022	4.8	4.8

Region	Reference (First Author)	Publication Date	Gender	Population (age)	Number of cases	Prevalence (per 1000)	
						crude	age-adjusted to 2000 US Standard Population
Asia Thailand	Asawavichienjinda (Asawavichienjinda et al., 2002)	2002	M<F	2,069	15	7.2	7.1

Table 3
Prevalence of epilepsy in studies in which diagnostic criteria cannot be established

Region	Reference (First Author)	Publication Date	Method	Population	Number of cases	Prevalence (per 1000)	
						Crude	Age-adjusted
North America							
Canada	Wiebe (Wiebe et al., 1999)	1999	Door-to-door; Self-report	-	313	5.8	5.2
Canada	Tellez-Zentano (Tellez-Zenteno et al., 2004)	2004	Door-to-door; Self-report	49,026	241	4.9	5.0
Europe							
Italy	Beghi (Beghi et al., 1991)	1991	Computerized Database	51,220	199	3.9	4.0
England	Wallace (Wallace et al., 1998)	1998	Computerized Database	2,052,922	10,564	5.1	5.1
Denmark	Christensen (Christensen et al., 2007)	2007	Computerized Database	4,977,482	28,303	5.7	5.5

Table 4
Classification of seizure type in population based prevalence studies of all ages

Region	Reference (First Author)	Publication Date	Partial (%)	Generalized (%)	Unclassifiable/ (%)
<i>North America</i>					
Mississippi	Haerer (Haerer et al., 1986)	1986	12	75	14
Minnesota	Hauser (Hauser et al., 1991)	1991	59	38	3
<i>Central and South America</i>					
Ecuador	Cruz (Cruz et al., 1985)	1985	21	74	5
Chile	Lavados (Lavados et al., 1992)	1992	55	40	5
Ecuador	Basch (Basch et al., 1997)	1997	20	80	-
Bolivia	Nicoletti (Nicoletti et al., 1999)	1999	53	47	2
Honduras	Medina (Medina et al., 2005)	2005	92	6	2
<i>Europe</i>					
Italy	Granieri (Granieri et al., 1983)	1983	33	60	7
Faroes	Joensen (Joensen, 1986)	1986	51	38	11
Italy	Cornaggia (Cornaggia et al., 1990)	1990	48	46	6
Sweden	Forsgren (Forsgren, 1992)*	1992	60	32	8
Italy	Giuliani (Giuliani et al., 1992)	1992	18	74	8
Iceland	Olafsson (Olafsson and Hauser, 1999)	1999	35	63	2
Spain	Luengo (Luengo et al., 2001)	2001	63	37	-
Italy	Rocca (Rocca et al., 2001)	2001	23	74	3
Turkey	Onal (Onal et al., 2002)	2002	41	47	12
Aeolian Islands	Gallitto (Gallitto et al., 2005)	2005	62	38	-
<i>Asia</i>					
China	Li (Li et al., 1985)	1985	8	90	2
India	Bharucha (Bharucha et al., 1988)	1988	54	46	-
India	Koul (Koul et al., 1988)	1988	12	79	9
Turkey**	Karaagac (Karaagac et al., 1999)	1999	53	41	6

Region	Reference (First Author)	Publication Date	Partial (%)	Generalized (%)	Unclassifiable/ (%)
<i>Africa</i>					
Nigeria	Osuntokun (Osuntokun et al., 1987)	1987	55	26	19
Ethiopia	Tekle-Haimanot (Tekle-Haimanot et al., 1990)	1990	20	75	5
Tanzania	Rwiza (Rwiza et al., 1992)	1992	32	58	10
Tunisia	Attia-Romdhane (Attia-Romdhane et al., 1993)	1993	3	97	-
Tanzania	Dent (Dent et al., 2005)	2005	71	27	-

*** These studies were conducted in a region of Turkey that is geographically part of Asia. However, the population may be more comparable to the western region of Turkey, which is part of Europe

Table 5
Etiology of epilepsy in population based prevalence studies of all ages

Region	Reference (First Author)	Publication Date	Symptomatic (%)	Remote	Idiopathic	Unknown (%)	Unclassified (%)
<i>North America</i>							
Mississippi	Haerer (Haerer et al., 1986)	1986	37			63	-
Minnesota	Hauser (Hauser et al., 1991)	1991	24			76	-
<i>Central and South America</i>							
Chile	Lavados (Lavados et al., 1992)	1992	30			70	-
Bolivia	Nicoletti (Nicoletti et al., 1999)	1999	21			79	-
Honduras	Medina (Medina et al., 2005)	2005	62		8	30	-
<i>Europe</i>							
Italy	Granieri (Granieri et al., 1983)	1983	40			60	-
Sweden	Forsgren (Forsgren, 1992)*	1992	35			65	-
Italy	Giuliani (Giuliani et al., 1992)	1992	34			66	-
Iceland	Olafsson (Olafsson and Hauser, 1999)	1999	7	31		62	-
Spain	Luengo (Luengo et al., 2001)	2001	28		33	36	3
Aeolian Islands	Gallitto (Gallitto et al., 2005)	2005	13			87	-
<i>Asia</i>							
India	Bharucha (Bharucha et al., 1988)	1988	2	21		77	-
Turkey	Karaagac (Karaagac et al., 1999)	1999	2	20		78	-
<i>Africa</i>							
Nigeria	Osuntokun (Osuntokun, 1982)	1987	9			91	-
Tanzania	Rwiza (Rwiza et al., 1992)	1992	12			88	-
Tunisia	Attia-Romdhane (Attia-Romdhane et al., 1993)	1993	23			76	-
Tanzania	Dent (Dent et al., 2005)	2005	26			74	-

Region	Reference (First Author)	Publication Date	Symptomatic (%)	Progressive	Remote	Idiopathic	Unknown (%)	Unclassified (%)

Table 6
Incidence of recurrent unprovoked seizures in population based studies of all ages

Region	Reference (First Author)	Publication Date	Gender	Population/Person-Years	Number of cases	Incidence (per 100,000)	
						Crude	Age-adjusted
North America							
Rochester, MN 1935-44	Hauser (Hauser et al., 1993)	1993	M>F	245,969	94	38	41
Rochester, MN 1945-54	Hauser (Hauser et al., 1993)	1993	M>F	282,452	142	50	49
Rochester, MN 1955-64	Hauser (Hauser et al., 1993)	1993	M>F	384,881	187	45	44
Rochester, MN 1965-74	Hauser (Hauser et al., 1993)	1993	M>F	516,903	182	35	36
Rochester, MN 1975-84	Hauser (Hauser et al., 1993)	1993	M>F	573,152	275	48	51
Texas	Annegers (Annegers et al., 1999)	1999	M>F	601,448	197	33	28
New York	Benn (Benn et al., 2008)	2008	M>F	279,677	82	15	16
Central and South America							
Chile	Lavados (Lavados et al., 1992)	1992	M>F	90,596	102	113	111
Europe							
England	Brewis (Brewis, 1966)	1966	-	497,707	141	29	28
Norway	De Graaf (de Graaf, 1974)	1974	M>F	213,116	70	33	26
Italy	Granieri (Granieri et al., 1983)	1983	M>F	697,000	230	33	33
Faroes	Joensen (Joensen, 1986)	1986	M>F	452,584	194	43	37
Iceland	Olafsson (Olafsson et al., 1996)	1996	M>F	90,237	42	47	43
England	MacDonald (MacDonald et al., 2000)	2000	-	100,230	46	46	47
Netherlands	Kotsopoulos (Kotsopoulos et al., 2002)	2002	M>F	316,828	94	30	29

Region	Reference (First Author)	Publication Date	Gender	Population/Person-Years	Number of cases	Incidence (per 100,000)	
						Crude	Age-adjusted
Iceland	Olafsson (Olafsson et al., 2005)	2005	M>F	882,151	290	33	31
<i>Asia</i>							
India	Mani (Mani et al., 1998)	1998	M>F	64,963	32	49	35
<i>Africa</i>							
Tanzania	Rwiza (Rwiza et al., 1992)	1992	-	165,684	122	73	51
Ethiopia	Tekle-Haimanot (Tekle-Haimanot et al., 1997)	1997	M>F	215,901	139	64	43

Table 7
Incidence of all unprovoked seizures in population based studies of all ages

Region	Reference (First Author)	Publication Date	Gender	Population	Number of cases	Incidence (per 100,000)	
						Crude	Age-Adjusted
<i>North America</i>							
Minnesota 1975-1984	Hauser (Hauser et al., 1993)	1993	M>F	2,003,357	1208	61	69
Texas	Annegers (Annegers et al., 1999)	1999	-	601,448	275	46	48
New York	Benn (Benn et al., 2008)	2008	M>F	270,677	209	39	41
<i>Europe</i>							
Sweden	Sidenvall & Forsgren (Forsgren et al., 1996; Sidenvall et al., 1996)	1996	M<F	203,166	107	53	54
Iceland	Olafsson (Olafsson et al., 2005)	2005	M=F	882,151	501	57	52
Netherlands	Kotsopoulos (Kotsopoulos et al., 2002)	2005	M>F	316,828	174	55	48

Table 8
Incidence of all afebrile seizures in population based studies of all ages

Region	Reference (First Author)	Publication Date	Gender	Population	Number of cases	Incidence (per 100,000)	
						Crude	Age-Adjusted
North America							
Minnesota 1975-1984	Hauser (Hauser et al., 1993)	1993	M>F	573,152	644	112	113
Central and South America							
Ecuador	Placencia (Placencia et al., 1992)	1992	M<F	72,121	137	190	174
Europe							
Denmark	Juul-Jensen (Juul-Jensen and Foldspang, 1983)	1983	M>F	2,497,573	817	32	30
Switzerland	Jallon (Jallon et al., 1997)	1997	M>F	384,657	273	71	70
Martinique	Jallon (Jallon et al., 1999)	1999	M>F	383,596	309	81	83

Table 9
Classification of seizure type in population based studies incidence studies of all ages

Region	Reference (First Author)	Publication Date	Partial (%)	Generalized (%)	Unclassifiable (%)
<i>North America</i>					
Minnesota	Hauser (Hauser et al., 1993)	1993	57	40	3
<i>Central and South America</i>					
Chile	Lavados (Lavados et al., 1992)	1992	54	38	8
<i>Europe</i>					
Italy	Granieri (Granieri et al., 1983)	1983	32	59	9
Faroes	Joensen (Joensen, 1986)	1986	51	39	10
Iceland	Olafsson (Olafsson et al., 1996)	1996	31	69	-
Iceland	Olafsson (Olafsson et al., 2005)	2005	40	58	2
<i>Africa</i>					
Tanzania	Rwiza (Rwiza et al., 1992)	1992	32	58	10
Ethiopia	Tekle-Haimanot (Tekle-Haimanot et al., 1997)	1997	20	69	11

Table 10
Etiology in incident cases of epilepsy in population based studies of all ages

Region	Reference (First Author)	Publication Date	Symptomatic (%)			Unknown (%)		Unclassified (%)
North America								
Minnesota	Hauser (Hauser et al., 1993)	1993	8	25		66	-	
Texas	Annegers (Annegers et al., 1999)	1999		25		75	-	
Europe								
Italy	Granieri (Granieri et al., 1983)	1983		39		61		
Iceland	Olafsson (Olafsson et al., 1996)	1996	10	21		69	-	
Africa								
Tanzania	Rwiza (Rwiza et al., 1992)	1992		25		75	-	
Ethiopia	Tekle-Haimanot (Tekle-Haimanot et al., 1997)	1997		14		86	-	