The prevalence of epilepsy in rural China: a decreasing trend over 12 years

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Abstract

Objective To evaluate the prevalence of epilepsy and to assess secular trends in the life-time prevalence of epilepsy in rural China over a 12-year period.

Methods In 2000-2002 and in 2012-2013, two independent cross-sectional epidemiological surveys, using an identical protocol, were conducted in rural areas in Shanghai, Shanxi Province, and Ningxia Hui Autonomous Region. The survey procedure included two stages: screening and ascertaining epilepsy cases in the target population. The initial screening was conducted by trained rural physicians and the diagnosis was confirmed or rejected by neurologists in the second stage. The age structure of the Chinese rural population in 2012 was used for standardization.

Results The 2000-2002 survey included 32,680 people and the standardized life-time prevalence was 6.79‰ (95% confidence interval [CI], 5.96-7.74‰). In 2012-2013, in a population of 16,873, the standardized life-time prevalence rate was 3.97‰ (95%CI, 3.13-5.04‰). The overall prevalence decreased by 41% over 12 years ($P<0.001$). The decreasing trend of life-time prevalence was found in each site and nearly all age-specific groups.

Conclusions Life-time prevalence of epilepsy seems to have significantly decreased in rural China over a 12-year period. We hypothesize that it may be attributed to decreased incidence and increased premature mortality.

Introduction

Epilepsy affects up to 70 million people worldwide.[1] More than 80% of the global burden of epilepsy is found in resource-poor settings where the condition is largely untreated.[2] In China, epilepsy prevalence estimates ranged from 0.90‰ to 8·50‰ during the 1980s and 2000s.[3] In 2003, it was estimated there were at least 9 million people with epilepsy in China.[3] In the last two decades there has been significant economic growth, rapid urbanization and demographic changes with an increase aging of the population. Epilepsy awareness has also increased. These social changes may have impacted epilepsy prevalence.

Recently, a systematic review[4] using modeling suggested that the life-time epilepsy prevalence in China increased substantially between 1990 and 2015, with prevalence having more than doubled and the number of people with epilepsy more than tripled (with an overall increase in the Chinese population). This is not consistent with the notion that epilepsy is a condition with a generally low prevalence.[5] A recent review focusing on epilepsy in Asia only referenced the few Chinese epidemiological surveys published in English, omitting many more studies reported in Chinese, thus introducing a publication bias.[6]

In 2000-2002 and in 2012-2013, we conducted two cross-sectional population-based surveys to determine the life-time prevalence of epilepsy with identical protocols in the same areas of rural China. It offered us the opportunity to re-examine the prevalence of epilepsy in rural China, and to assess the secular trend in the recent past.

Methods

Study design and participants

We applied a multi-stage random cluster sampling based on Chinese census units in rural areas in Shanghai, Shanxi province and Ningxia Hui Autonomous Region, which represented not only different geographical areas (east [Shanghai], middle [Shanxi] and west [Ningxia]), and multiple ethnicities (Han [Shanghai and Shanxi] and Hui [Ningxia]), but also diverse economic levels (high [Shanghai], middle [Shanxi] and low [Ningxia] (Figure 1). Participants were enrolled if they met residency criteria: living in the area regardless of household registration for more than a month. Those with household registration were also enrolled if they had temporarily left the area for less than 1 month at the time of the survey. Lists of residents were extracted from the local population registration system. Guardians or relatives of children younger than 15 years and of people aged over 70 years, as well as those with learning disabilities, were interviewed to obtain accurate data.

Survey procedure

The survey procedure included two stages of screening and ascertaining epilepsy cases in the target population. At the screening stage, well-trained local village physicians and health workers performed door-to-door interviews to enroll participants to complete the screening questionnaire. The questionnaire was based on the WHO screening questionnaires previously used in China and on the International Community-based Epilepsy Research Group (ICBERG) screening instrument with specificity (78.5%) and sensitivity (100%) previously validated in China.[7] In the diagnosis-ascertaining stage, “definitive” or “suspected” epilepsy cases reported from the first stage were reviewed in person by a supervising neurologist from the provincial hospital in the study area. Neurologists confirmed or refuted the diagnosis of epilepsy based on medical history, clinical symptoms and examination of each individual who had screened positive. Difficult cases were resolved by consensus after an expert panel discussion.

The first epidemiological survey was carried out in rural areas of Shanghai, Shanxi province, and Ningxia Hui Autonomous Region during 2000 and 2002. During 2012 and 2013, we carried out the second survey in the same general areas with identical protocol and questionnaire as used in the 2000-2002 survey. Survey populations in each site in the two surveys did not necessarily overlap but were in adjacent communities. Some datasets from the first survey were previously analyzed and reported,[3] but for this study we obtained the raw data and re-analyzed it.

Operational definitions

Following guidelines for epidemiologic studies,[8,9] epilepsy was defined as having two or more epileptic seizures occurring >24 hours apart, unprovoked by any immediate identified cause. Individuals with only febrile seizures or only neonatal seizures were excluded.

The concept of prevalence in this study refers to the life-time prevalence of epilepsy, which is the proportion of the population with a diagnosis of epilepsy from birth to the time of the investigation, regardless of treatment status or recentness of seizures. Different from the prevalence of active epilepsy, this includes individuals who were in remission on the survey day. Individuals diagnosed after the survey date were excluded.[8]

Statistical analysis

The minimal sample size for each site was estimated at 2052, using PASS version 11.0 Software and the formula for population surveys. We used an expected prevalence of 2.89‰ provided by a systematic review[10], a 95% confidence interval (CI) and a 5‰ expected CI Width (two-sided).

The life-time prevalence rate of epilepsy was estimated as the number of people having had epilepsy at any point in their lifetime, divided by the number of participants, and described as “number ‰” with 95%CI. This was estimated for the entire population, and for age group and site. The standardized prevalence was calculated by the direct method using the population age structure reported in the 2012 national population census as the reference population.[11] Chi-squared tests or Fisher’s exact tests were used to explore the differences between the prevalence rates in the two surveys.

The 95% CIs were derived from the Wilson Score tests.[12] P-values and 95% CIs were estimated in a two-tailed fashion. Differences were considered to be statistically significant at $p<0.05$. All statistical analyses were performed using SPSS 22.0 software for Windows (SPSS Inc., Chicago, IL, USA).

Results

The 2000-2002 survey included 32,680 people of whom 224 were confirmed as having definite epilepsy (see Table1), providing a standardized life-time prevalence of 6.79‰ (95%CI, 5·96-7.74‰). The 2012-2013 survey included a population of 16,873, and identified 71 people with a definite history of epilepsy, yielding a standardized life-time prevalence of 3.97‰ (95%CI, 3·13-5.04‰), a decrease of 41% over 12 years ($P<0.001$). In the 2000-2002 survey, the standardized life-time prevalence was 5.75‰ (95%CI, 4.49-7.37‰) in Shanghai, 6.13‰ (95%CI, 4.80-7.84‰) in Shanxi, and 7.48‰ (95%CI, 6.07-9.22‰) in Ningxia. The standardized life-time prevalence 12-years later decreased by 40% in Shanghai and by 16% in Shanxi. In Ningxia it decreased by 52% (P<0·001) (Table 1).

Table 1 Crude and standardized life-time epilepsy prevalence in 2000-2002 and 2012-2013 surveys

	2000-2002 survey				2012-2013 survey				
Study site	Population	Number of cases	Crude prevalence, ‰ (95%CI)	Standardized prevalence*, ‰ (95%CI)	Population	Number of cases	Crude prevalence, ‰ (95%CI)	Standardized prevalence *, ‰ (95%CI)	P value**
Shanghai	10777	65	6.03 (4.74-7.68)	5.75 (4.49-7.37)	3454	13	3.76 (2.20-6.43)	3.47 (1.99-6.06)	0.105
Shanxi	10273	60	5.84 (4.54-7.51)	6.13 (4.80-7.84)	4454	23	5.16 (3.44-7.74)	5.16 (3.44-7.74)	0.479
Ningxia	11630	99	8.51 (7.00-10.35)	7.48 (6.07-9.22)	8965	35	3.90 (2.81-5.42)	3.57 (2.53-5.03)	<0.001
Total	32680	224	6.85 (6.02-7.81)	6.79 (5.96-7.74)	16873	71	4.21(3.34-5.30)	3.97(3.13-5.04)	<0.001

*Standardized prevalence was calculated by the direct method according to the Chinese rural population age structure in 2012.
** Comparison of standardized prevalence rates between two surveys.

Figure 1 shows that most age-specific prevalence rates were lower in the 2012-2013 survey than previously. There was a significant decrease in the 40-59 years' group in Shanghai (from7.11‰ to 1.87‰, p=0.049), in those aged 10-19 years (from 10.54‰ to 4.05‰, p=0.019) and 20-39 years (from 9.73‰ to 3.68‰, p=0.001) in Ningxia, and in those aged 10-19 years (from 8.15‰ to 3.56‰, p=0.015) and 20-39 years (from

6.44‰ to 3.72‰, p=0.020) in all participants. The biggest difference in prevalence in Shanxi, Ningxia and overall were found in the 10-19 years group, but in Shanghai the biggest difference was in the group aged 40-59 years. Different from other two areas, the lowest prevalence in both surveys in Ningxia was in people aged >60-years.

Discussion

We ascertained trends of life-time prevalence of epilepsy over a 12-year period through two epidemiological surveys using identical protocols. The life-time prevalence decreased significantly over the period and this was seen in all sites and most age-specific groups.

There are few longitudinal studies of secular changes of epilepsy prevalence. Work conducting decennial censuses in Minnesota from 1935 to 1984 showed that the life-time prevalence increased with each subsequent census.[13] A population of about 6000 people in Britain was assessed 10 years apart, and life-time prevalence increased slightly but without statistical significance.[14] In China, two door-to-door surveys conducted in 2000 and 2004 in the same six areas of rural China reported a decrease in life-time prevalence, though not statistically significant.[15] Recently, a systematic review[4] estimated the life-time epilepsy prevalence trends in China using modeling; the life-time prevalence estimations increased by nearly 260% in a 15- year period. This review has limitations. Firstly, the selected population-based surveys had large variations in study design, screening instruments, diagnostic criteria, and sampling locations, thus rendering the data unsuitable for pooling due to heterogeneity. Secondly, prevalence rates in 1990, 2000, and 2015 were not similar to contemporaneously reported multi-center population-based studies in China.[3,16–18]

Thirdly, among total participants, only about 5% specific data points based on age, sex and location provided the information on life-time epilepsy prevalence. These small numbers were used, leading to wide CIs in age groups especially in 2015. This suggests that the large increase in life-time epilepsy prevalence is in doubt.

We searched Pubmed and Chinese Databases for reports in either English or Chinese languages on door-to-door epidemiological surveys involving at least life-time prevalence in China since 2000 and extracted data when available (Table 2). In the table, though very few studies were conducted in the same areas, general downward trends in life-time prevalence, active prevalence and incidence can be seen.

Table 2 Literature review of door-to-door surveys for life-time epilepsy prevalence in China from 2000 to 2013

Study	Study site	Survey year	Total Population	Survey region	Screen tool	Definition of epilepsy	Seizure type	Life-time prevalence (‰)	Active Prevalence (‰)	Incidence (100,000 person-year)
Qin et al.(2001)[33]	Henan	2000	12457	rural	WHO&ICBERG SQ	common-2	all	4.7	3.5	32.1
Du et al.(2002)[34]	Ningxia	2000	11630	rural	WHO&ICBERG SQ	common-2	all	8.51	6.7	25.8
Xu et al.(2002)[35]	Shanxi	2000	10273	rural	WHO&ICBEGR SQ	ILAE 1993	all	5.8	3.3	38.9
Wang et al.(2002)[36]	Heilongjiang	2000	10151	rural	SQ	NS	all	7.98	NS	29.55
Zhang et al(2005)[37]	Jiangsu	2000-2001	11895	rural	SQ	NS	all	7.83	NS	53.40
Ding et al.(2004)[38]	Shanghai	2002	10777	rural	WHO&ICBEGR SQ	ILAE 1993	all	6.03	3.80	NS
Huang et al.(2008)[39]	Ningxia	2003	8316	rural	WHO&ICBEGR SQ	common-2	all	8.3	6.5	28.8
Wang et al.(2008)[15]	Heilongjiang/ Ningxia/Hena	2004	51644	rural	WHO&ICBEGR SQ	ILAE 1993	all	6.2	4.5	NS

	n/Shanxi /Jiangsu									
Ren et al.(2007)[40]	Yunnan	2005	4465	rural	WHO&ICBEGR SQ	common-2	all	3.58	2.69	22.39
Yu et al.(2009)[41]	Yunnan	2007-2008	10579	rural	WHO&ICBEGR SQ	ILAE 1989	all	1.80	1.51	18.99
Meng et al.(2010)[42]	Jilin	2008	310402	rural	NS	ILAE 1981	all	3.94	NS	22.55
Li et al(2012)[43]	Hebei	2008-2010	20138	rural	WHO&ICBEGR SQ	common-2	all	6.85	4.9	26.9
Pi et al.(2012)[44]	Hunan	2010	32059	urban/rural	WHO&ICBEGR SQ	ILAE 1993	all	4.5	2.8	NS
Li et al.(2014)[45]	Gansu	2010-2011	2533500	rural	SQ	common-1	convulsive	1.59	NS	NS
Song et al.(2012)[46]	Shandong	2011	850900	rural	SQ	common-1	convulsive	0.75	0.23	4.94
Guo et al.(2014)[18]	Shandong	2011	251492	urban/rural	WHO&ICBEGR SQ	NS	all	t-1.33 r-1.39 u-1.20	NS	18.69
Current study-second survey	Shanghai/Ningxia/Shanxi	2012-2013	16873	rural	WHO&ICBEGR SQ	ILAE1993	all	3.97	NS	NS

NS: not stated; WHO: World Health Organization; ILAE: International League against Epilepsy; ICBERG: International Community-based Epilepsy Research Group; SQ: screening questionnaire; t, total; r, rural; u, urban; y: year.

Active prevalence in the table is defined as a person with epilepsy who has had at least two unprovoked seizures on different days in the previous year, regardless of antiepileptic drug (AED) treatment.

Common-1: The diagnosis of epilepsy: 1) the condition must be characterized by two or more unprovoked epileptic seizures; 2) individuals with febrile seizures were excluded.

Common-2: The diagnosis of epilepsy: 1) the condition must be characterized by two or more unprovoked epileptic seizures; 2) individuals with febrile seizures or seizures related to certain acute cerebral disorders or acute metabolic disorders or to withdrawal of alcohol or drugs were excluded.

Without recorded mass in- and out-migration or major demographic alteration in the population structure, life-time prevalence is determined by the rate at which new cases arise and the rate at which existing cases die.[1] The "Global Campaign against Epilepsy demonstration project" was launched in China in 2000. Over more than a decade, this project was effective and made a difference to epilepsy care in China, especially in rural areas.[15] As well as benefits brought by economic growth, swift urbanization and healthcare improvement, some well-documented risk factors, such as consanguineous marriage, febrile seizures, prenatal and perinatal central nervous system deficits and infections, may have decreased in China.[19–21] These could account for a decrease in the incidence of epilepsy.

As shown in the incidence-prevalence-mortality model in Figure 3, irrespective of mortality, life-time prevalence should increase with age, or remain unchanged if the incidence is zero (Figure 3A). When the death rate is higher than the incidence rate, the prevalence rate decreases (Figure 3B). The discrepancy in prevalence rates at different time points in the same areas highlights the importance of taking premature mortality into account. Generally, epilepsy mortality rates are considered to be 1.3 to 9.3 fold higher than in the general population and this could be even higher in poor-settings.[22–24] Anecdotal evidence from high-income countries suggests that a potential reason for few older people with a life history of epilepsy being seen in epilepsy clinics is premature death,[5] although cerebrovascular disease and trauma are potential risk factors in older adults.[25,26] It has been suggested that a higher mortality rate in low-and middle- income countries may explain the discrepancy between high incidence and relatively low prevalence.[5,27] A small study in rural Laos, with an estimated prevalence of 7.7‰, found that almost one in nine people with epilepsy died within a short period.[28] In China, a cohort study reported that around one fifth died over a 12 years period.[29] Long-term follow-up of cohorts found premature mortality was higher in people with epilepsy than in the general population and much higher in young people.[30,31] Sudden unexpected death in epilepsy, an important cause of premature mortality in people with epilepsy, was estimated to have higher incidence in China than in high-income countries.[32] We hypothesize that the decreasing life-time prevalence we found is attributed to a combination of a lower incidence rate and higher premature mortality. Effective ways should be implemented to reduce premature mortality.

Our study has limitations. Firstly, although highly specific and sensitive screening tools and strict diagnostic procedures were used, epilepsy is a condition with a long history of stigma and discrimination influencing individuals' attitude toward disclosure of a diagnosis, so epilepsy prevalence might have been underestimated. Using an identical survey protocol, in the same general survey areas, however, and with no evidence of increasing concealment, we found a difference in the two surveys. Secondly, compared to the 2000-2002 survey, the sample size of the 2010-2013 survey was smaller; it was, however, large enough to obtain an adequate cross-sectional prevalence based on the sample size calculation. Thirdly, data in the surveys may not fully reflect the overall Chinese situation. Nevertheless, our target areas represented rural and urban areas of China. Fourthly, there is incomplete overlap of the surveyed population at the two time points. The target survey populations are, however, in adjacent areas receiving the same level of care and having subjects with similar social and demographic changes over the time period. Lastly, the lack of datasets of concurrent active prevalence, incidence, mortality and treatment gap hinder us from analyzing the change in the full epilepsy burden in China.

Our findings differ from the recognized upward trend in life-time epilepsy prevalence. Epilepsy seems to be decreasing in China, but we suspect it may be related to decreased incidence and increased premature mortality. High-quality, large-sample, multi-center epidemiological surveys collecting concurrent data on incidence, prevalence, mortality in low- and middle- income countries are warranted to confirm a change in the epilepsy burden.

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Contributors DD, ZH, SCL and JWS conceptualized and designed the study. GXZ, QZ, TPW, YHC and WZW organized and conducted the survey. MJW analyzed data. MJW, DD and JWS drafted the manuscript. All authors were involved in the interpretation of data, critically reviewed the manuscript, and approved the final version.

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Patient consent Obtained

Ethics approval The 2000-2002 survey was approved by the Medical Ethics Committee of Beijing Neurosurgical Institute, Beijing, China. The 2012-2013 survey was approved by the Medical Ethics Committee of Huashan Hospital, Fudan University, Shanghai, China.

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REFERENCES

1 Ngugi AK, Bottomley C, Kleinschmidt I, *et al.* Estimation of the burden of active and life-time epilepsy: A meta-analytic approach: Estimation of the Burden of Epilepsy. *Epilepsia* 2010; **51**: 883–90.

2 Scott RA, Lhatoo SD, Sander JW. The treatment of epilepsy in developing countries: where do we go from here? *Bull World Health Organ* 2001; **79**: 344–51.

3 Wang WZ, Wu JZ, Wang DS, *et al.* The prevalence and treatment gap in epilepsy in China: an ILAE/IBE/WHO study. *Neurology* 2003; **60**: 1544–5.

4 Song P, Liu Y, Yu X, *et al.* Prevalence of epilepsy in China between 1990 and 2015: A systematic review and meta-analysis. *J Glob Health* 2017; **7**: 020706.

5 Bell GS, Neligan A, Sander JW. An unknown quantity-The worldwide prevalence of epilepsy. *Epilepsia* 2014; **55**: 958–62.

6 Trinka E, Kwan P, Lee B, *et al.* Epilepsy in Asia: Disease burden, management barriers, and challenges. *Epilepsia* 2018; published online June 28. DOI:10.1111/epi.14458.

7 Placencia M, Sander JW, Shorvon SD, *et al.* Validation of a screening questionnaire for the detection of epileptic seizures in epidemiological studies. *Brain* 1992; **115 (Pt 3)**: 783–94.

8 Thurman DJ, Beghi E, Begley CE, *et al.* Standards for epidemiologic studies and surveillance of epilepsy: Standards for Epidemiologic Studies and Surveillance of Epilepsy. *Epilepsia* 2011; **52**: 2–26.

9 Guidelines for Epidemiologic Studies on Epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. *Epilepsia* 1993; **34**: 592–6.

10 Gu L, Liang B, Chen Q, *et al.* Prevalence of epilepsy in the People's Republic of China: A systematic review. *Epilepsy Research* 2013; **105**: 195–205.

11 The national health and family planning commission. China health and family planning statistical yearbook. Beijing: China union medical university press, 2015. (in Chinese)

12 Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med* 1998; **17**: 857–72.

13 Hauser WA, Annegers JF, Kurland LT. Prevalence of Epilepsy in Rochester, Minnesota: 1940–1980. *Epilepsia* 1991; **32**: 429–45.

14 Cockerell OC, Eckle I, Goodridge DM, *et al.* Epilepsy in a population of 6000 re-examined: secular trends in first attendance rates, prevalence, and prognosis. *Journal of Neurology, Neurosurgery & Psychiatry* 1995; **58**: 570–6.

15 Wang W, Wu J, Dai XY, *et al.* Global campaign against epilepsy: assessment of a demonstration project in rural China. *Bulletin of the World Health Organization* 2008; **86**: 964–9.

16 Wu S, Li S, Cheng X, *et al.* Comparative analysis of epilepsy epidemiology in urban and rural areas in five cities. *Chinese Medical Journal* 1991; **71**: 156. (in Chinese)

17 Chang L, Zhang L, Guan Q, *et al.* Epidemiological investigation of epilepsy in urban district of Nanjing. *Journal of Clinical Neurology* 2013; **26**: 341–3. (in Chinese)

18Guo M, Zhang J, Sun Z, et al. Investigation on the Epidemiology of Epliepsy in Shandong Province. *Chin J Clin Neurosci* 2014; **22**: 307–12. (in Chinese)

19 Chawla S, Aneja S, Kashyap R, *et al.* Etiology and clinical predictors of intractable epilepsy. *Pediatr Neurol* 2002; **27**: 186–91.

20 Duncan JS, Sander JW, Sisodiya SM, *et al.* Adult epilepsy. *Lancet* 2006; **367**: 1087–100.

21 Singhi P, Jagirdar S, Khandelwal N, *et al.* Epilepsy in children with cerebral palsy. *J Child Neurol* 2003; **18**: 174–9.

22 Levira F, Thurman DJ, Sander JW, *et al.* Premature mortality of epilepsy in low- and middle-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy. *Epilepsia* 2017; **58**: 6–16.

23 Shackleton DP, Westendorp RGJ, Kasteleijn-Nolst Trenité DGA, *et al.* Survival of Patients with Epilepsy: An Estimate of the Mortality Risk. *Epilepsia* 2002; **43**: 445–50.

24 Thurman DJ, Logroscino G, Beghi E, *et al.* The burden of premature mortality of epilepsy in high-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy. *Epilepsia* 2017; **58**: 17–26.

25 Jungehulsing GJ, Heuschmann PU, Holtkamp M, *et al.* Incidence and predictors of post-stroke epilepsy. *Acta Neurol Scand* 2013; **127**: 427–30.

26 Wilson L, Stewart W, Dams-O'Connor K, *et al.* The chronic and evolving neurological consequences of traumatic brain injury. *Lancet Neurol* 2017; **16**: 813–25.

27 Mac TL, Tran D-S, Quet F, *et al.* Epidemiology, aetiology, and clinical management of epilepsy in Asia: a systematic review. *The Lancet Neurology* 2007; **6**: 533–43.

28 Tran D-S, Zen J, Strobel M, *et al.* The challenge of epilepsy control in deprived settings: low compliance and high fatality rates during a community-based phenobarbital program in rural Laos. *Epilepsia* 2008; **49**: 539–40.

29 Ge Y, Ding D, Yu P, *et al.* Mortality of People with Epilepsy in a Community-based Cohort in Jinshan District, Shanghai: A Follow-up after 12 Years. *Chin J Clin Neurosci*; **23**: 366–71. (in Chinese)

30 Ding D, Wang W, Wu J, *et al.* Premature mortality risk in people with convulsive epilepsy: Long follow-up of a cohort in rural China: *Mortality in People with Epilepsy in China*. *Epilepsia* 2013; **54**: 512–7.

31 Mu J, Liu L, Zhang Q, *et al.* Causes of death among people with convulsive epilepsy in rural West China: A prospective study. *Neurology* 2011; **77**: 132–7.

32 Ge Y, Ding D, Zhang Q, *et al.* Incidence of sudden unexpected death in epilepsy in community-based cohort in China. *Epilepsy & Behavior* 2017; **76**: 76–83.

33 Qin D, Yang B, Li J, *et al.* Epidemiological survey of epilepsy in rural population of Wuyi County, Jiaozuo City, Henan Province. *Henan journal of Practical Nervous Disease* 2001; **4**: 82–3. (in Chinese)

34 Du Y, Chen G, Dai XY, *et al.* Epidemiological survey on epilepsy in rural residents of Ningxia and on tentative effectiveness with single antiepileptic drugs-Luminal. *Journal of Ningxia Medical College* 2002; **24**: 316-318,322. (in Chinese)

35 Xu Z, Wang T, Sun Y, *et al.* Epidemiological survey on epilepsy in rural population of Zezhou shanxi. *Proceeding of Clinical Medicine* 2002; **11**: 811–4. (in Chinese)

36 Wang D, Li G, Ma G, *et al.* Prvalence of epilepsy in Dongning- a rural area of China. *J Apoplexy and Nervous Disease* 2002; **19**: 159–61. (in Chinese)

37 Zhang H, Yuan C, Xu J, *et al.* Study on the management current status of prevention and treatment for epilepsy in Touqiao rural area in Yangzhou city. *Journal of Clinical Medicine in Practice* 2005; **9**: 75-76,78. (in Chinese)

38 Ding D, Lv G, Huang M, *et al.* A Sampled Epidemiological Survey of Epilepsy in Shanghai Rural Area. *Chin J of Clin Neurosci* 2004; **122**: 122–4. (in Chinese)

39 Huang Y, Du H, Yang S, *et al.* Investigation on epilepsy epidemiology and drug therapy in Qingtongxia area of Ningxia. *Shaanxi Medical Journal* 2008; **37**: 1068–70. (in Chinese)

40 Ren H, Yu Z, Chang L, *et al.* Epidemiological survey on epilepsy in Jinuo ethnic minority group in Yunnan Province. *Journal of international neurology and neurosurgery* 2002; **34**: 10–2. (in Chinese)

41 Yu Z, Tang Y, Wang W, *et al.* Epidemiological survey on epilepsy in Kawa ethnic minority group in Yunnan province. *Chin J Epidemiol* 2009; **30**: 95–6. (in Chinese)

42 Meng H, Li N, Cui L, *et al.* A survey on the epidemiology of epilepsy in partial rural areas of Jilin Province. *Journal of Apoplexy and Nervous Diseases* 2010; **27**: 1108–10. (in Chinese)

43 Li X, Yang Y, Wei Z, *et al.* Epidemiological investigation of epilepsy in Chengde area. *Hebei Medicine* 2012; **18**: 1676–8. (in Chinese)

44 Pi X, Cui L, Liu A, *et al.* Investigation of prevalence, clinical characteristics and management of epilepsy in Yueyang city of China by a door-to-door survey. *Epilepsy Research* 2012; **101**: 129–34.

45 Li K, Jiang X, Wu Z, *et al.* Analysis on the Epidemiology of Convulsibility Epilepsy in Rural Areas of Gansu Province. *Chinese Primary Health Care* 2014; **28**: 62-63,66. (in Chinese)

46 Song H, Du S, Wang Y, *et al.* Epidemiology investigation of convulsive epilepsy in Gaomi City of Shandong. *Journal of Psychiatry* 2012; **25**: 106–8. (in Chinese)