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Epilepsy in Adults

Risk factors, Etiologies and Disease progression

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Disclosures

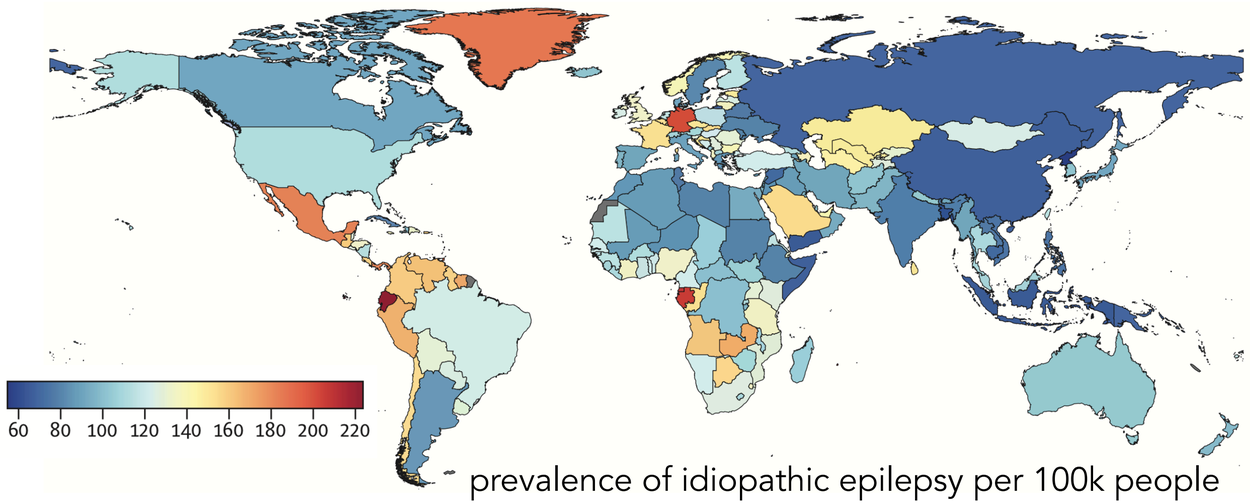
- No conflicts of interest with regard to this presentation

Overview

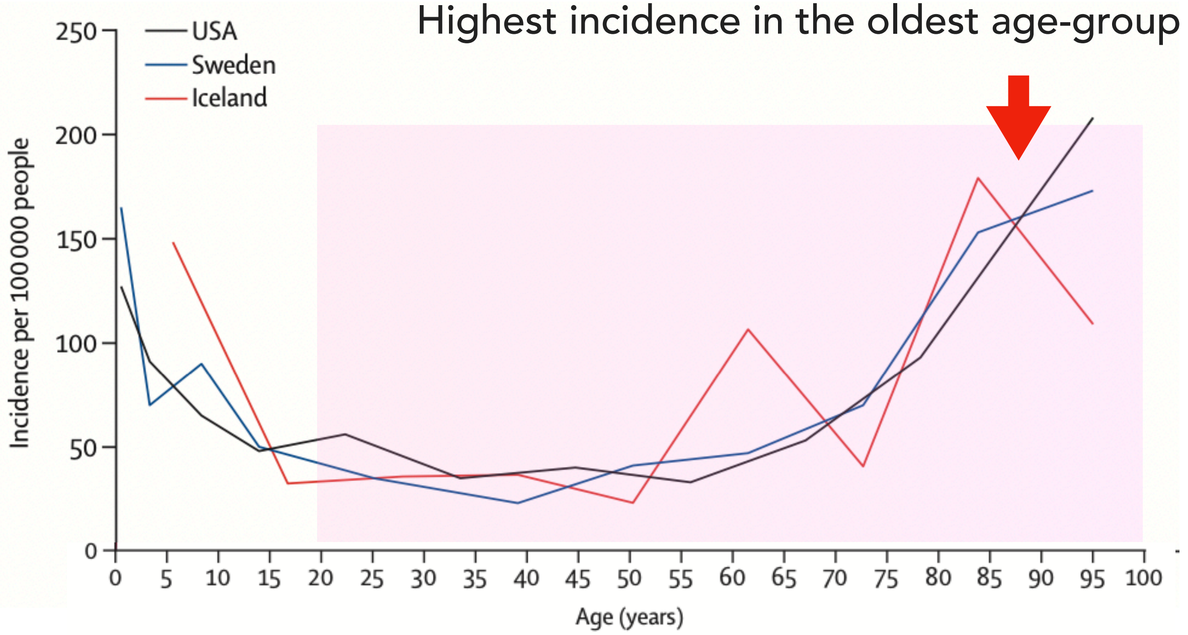
- Key facts about epilepsy
- Risk factors & Etiologies of new-onset epilepsy in adults
- Natural history of epilepsy
  - Single unprovoked seizure
  - Epilepsy

The scale of the "problem"

- Epilepsy is a chronic disease of the brain that affects people of **all ages**
- 51.7 million people with epilepsy (PWE) worldwide, prevalence 6.6/1000
- 80% of PWE live in low-to-middle income countries
- Thailand, in 2021, ~492000 PWE

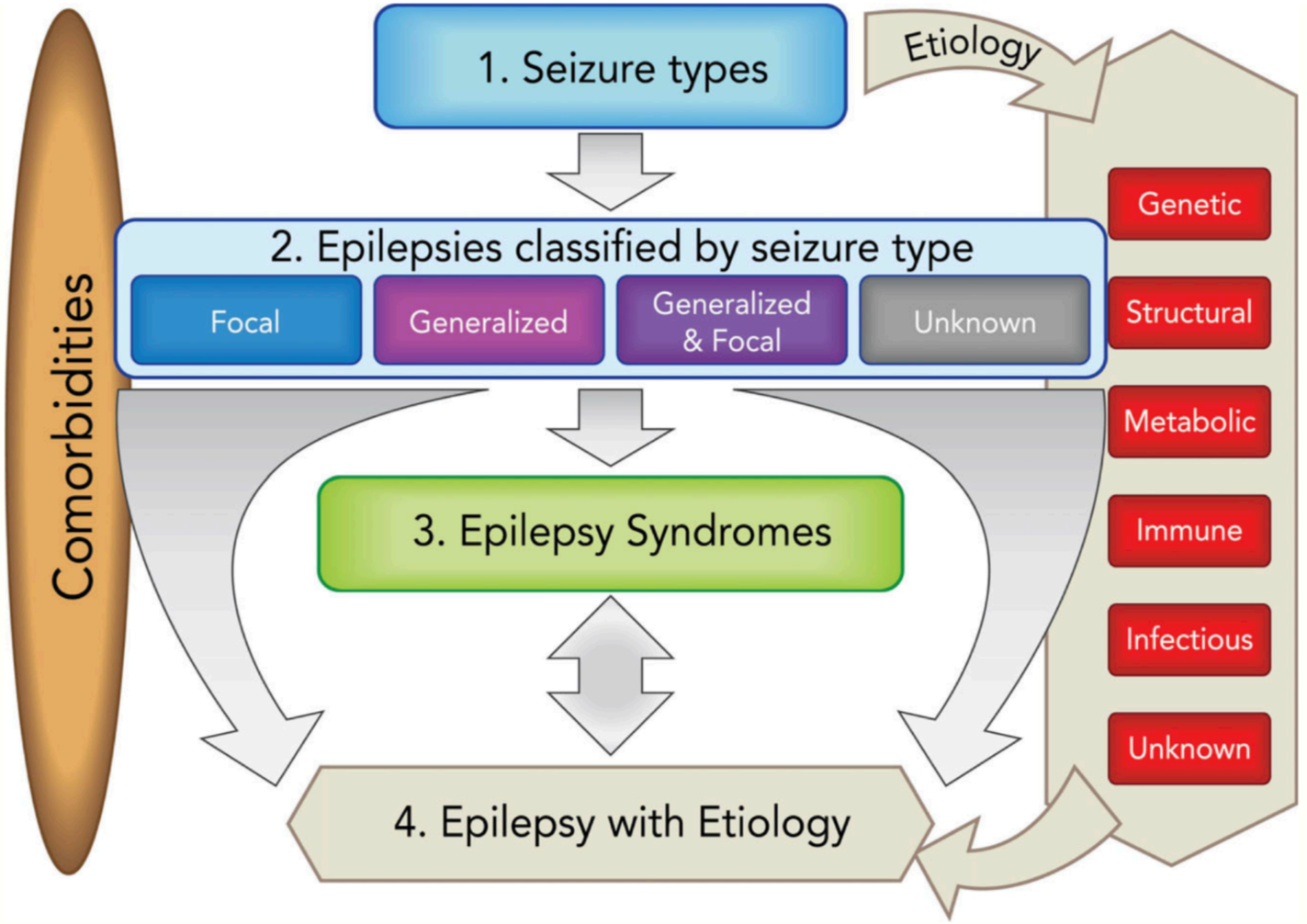


prevalence of idiopathic epilepsy per 100k people



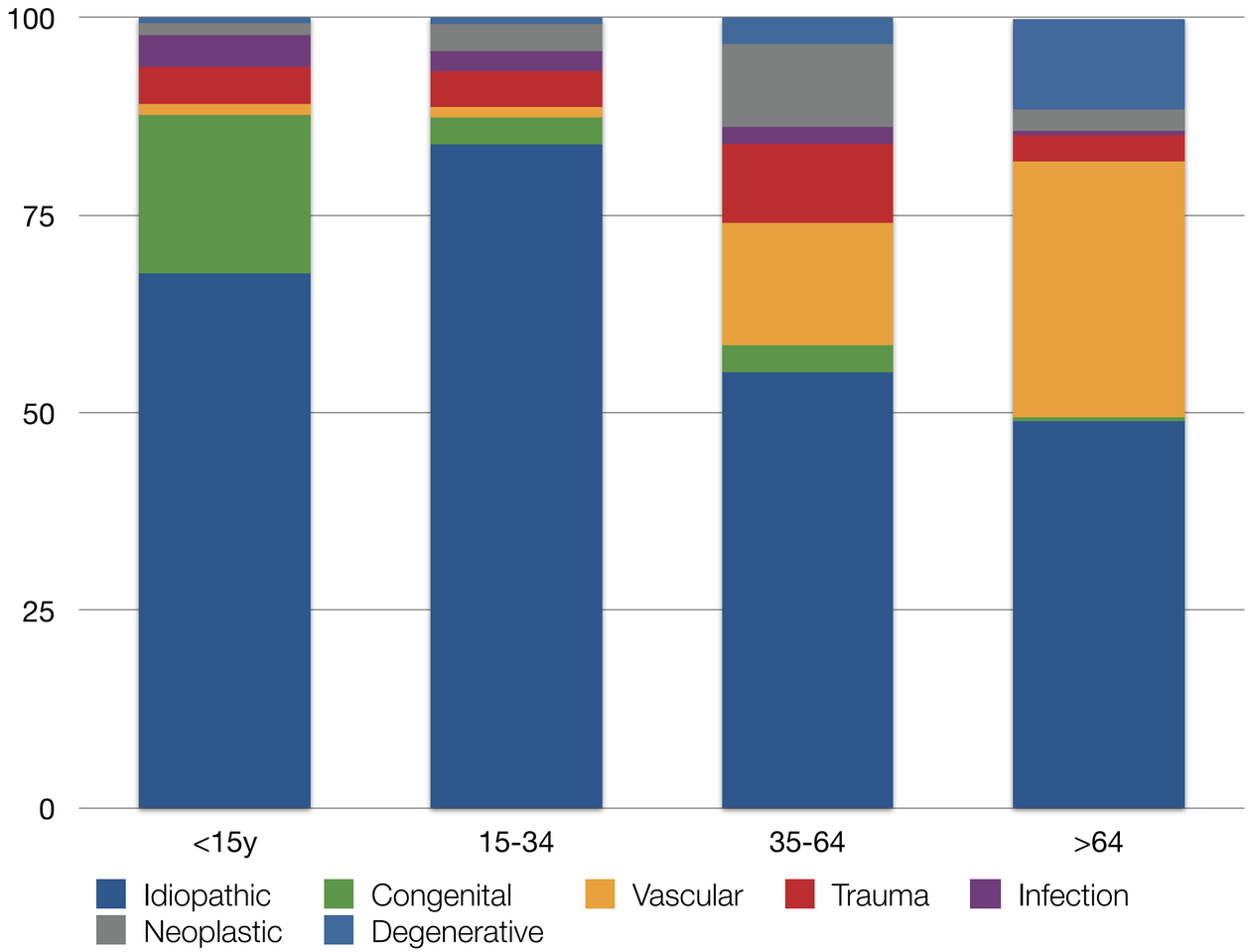
Thurman et al. *Epilepsia* 2017; Sen et al. *Lancet* 2020; https://www.who.int accessed on June 2024; GBD Epilepsy Collaborators. *Lancet Public Health* 2025

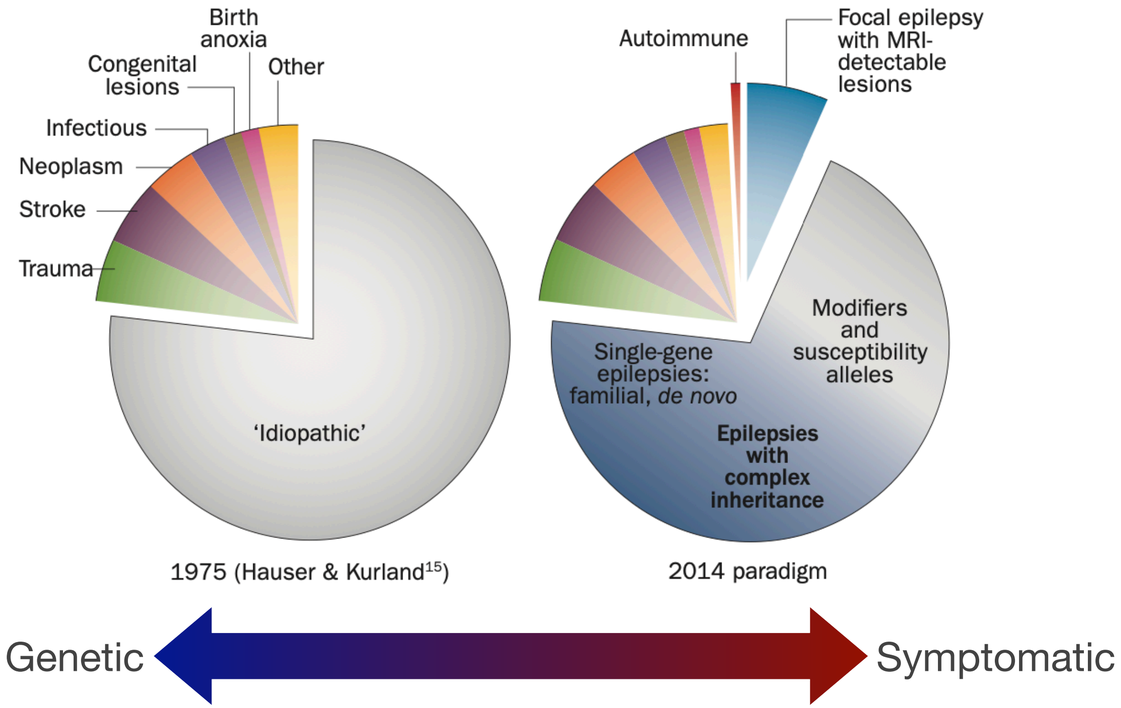
Highlights the importance of considering etiology



Scheffer IE, et al. *Epilepsia Open* 2016

Epilepsy refers to a clinical phenomenon rather than a single disease entity





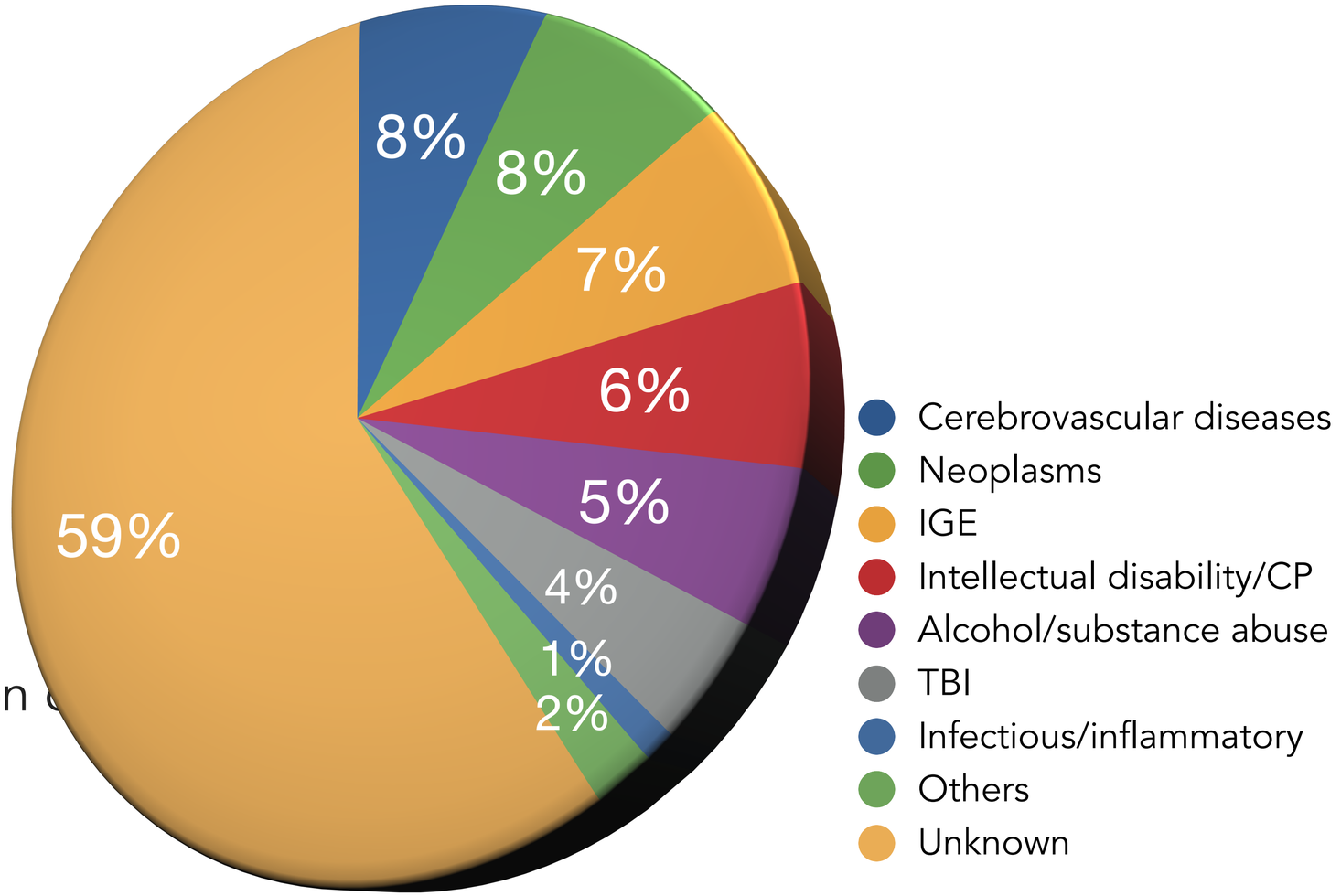
Hauser et al. *Epilepsia* 1992; Thomas & Berkovic. *Nat Rev Neurol* 2014

Brief Communication

Risk factors associated with new-onset epilepsy in young adults: Population-based study

- Stroke and neoplasm are the most common risk factors
- IGE, 13-28% begin at age ≥20y
- Intellectual disability, 30% ≥20y
- Alcohol/substance abuse
- Traumatic brain injury
- Rare degenerative, malformation c
  cortical development

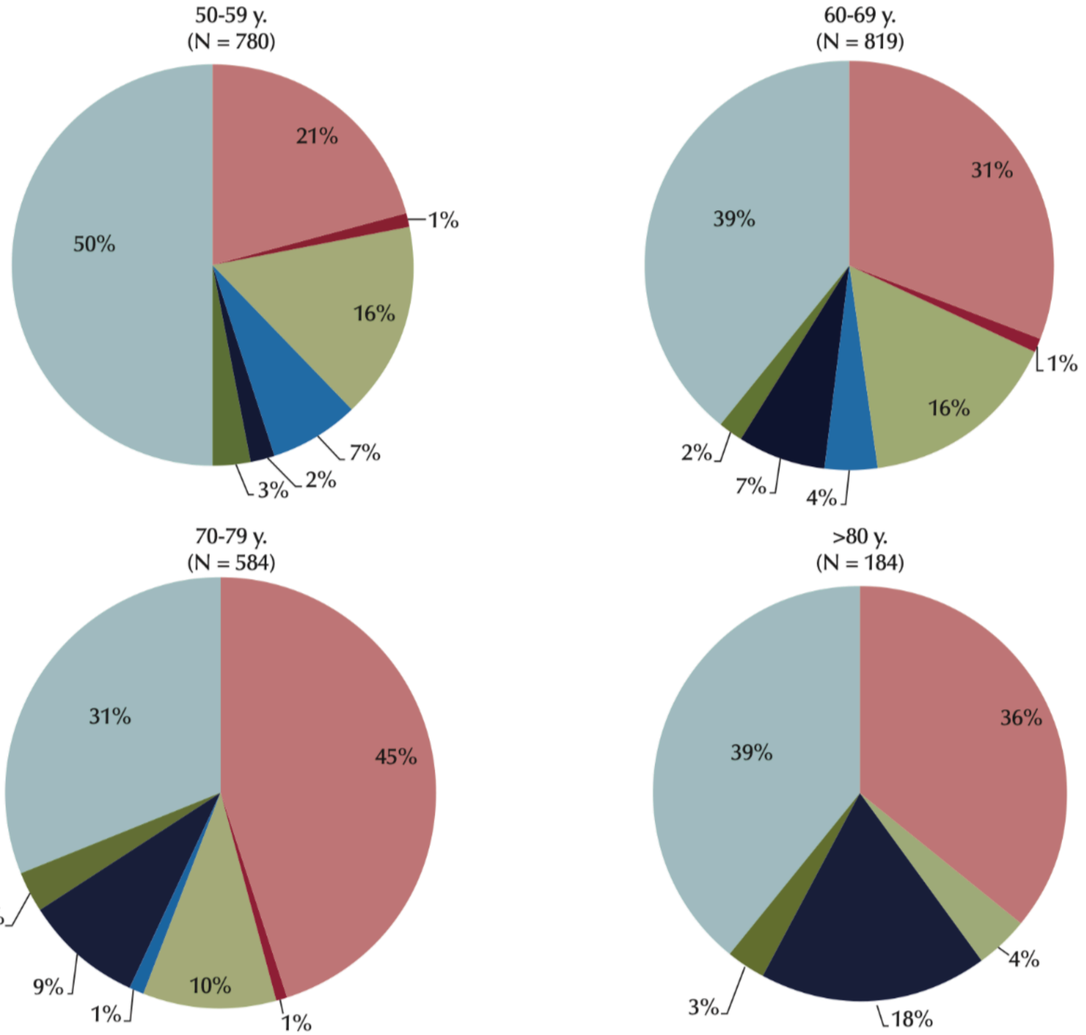
Adults 20-49 YOA with new-onset epilepsy
North Macedonia, 2015-2018
1691 patients



Babunovska M, et al. *Epilepsy Behav* 2021

Prevalence of various risk factors associated with new-onset epilepsy after the age of 50: a retrospective population-based study

Adults >50 YOA with new-onset epilepsy
North Macedonia, 2015-2018
2367 patients



- Stroke is the most common risk factor
- Prevalence gradually increased in subsequent age groups
- Second most frequent risk factor
  - <70-79y: Neoplasm
  - >80y: Dementia

Cvetkovska E, et al. *Epileptic Disord* 2022

Midlife vascular & lifestyle factors - associated with late-onset epilepsy

Atherosclerosis Risk in Communities (ARIC) study
Multicenter from 4 US communities
10420 participants (596 LOE)
Risk factors at age 45-64y
Epilepsy starting ≥60 YOA

Increased risk of LOE

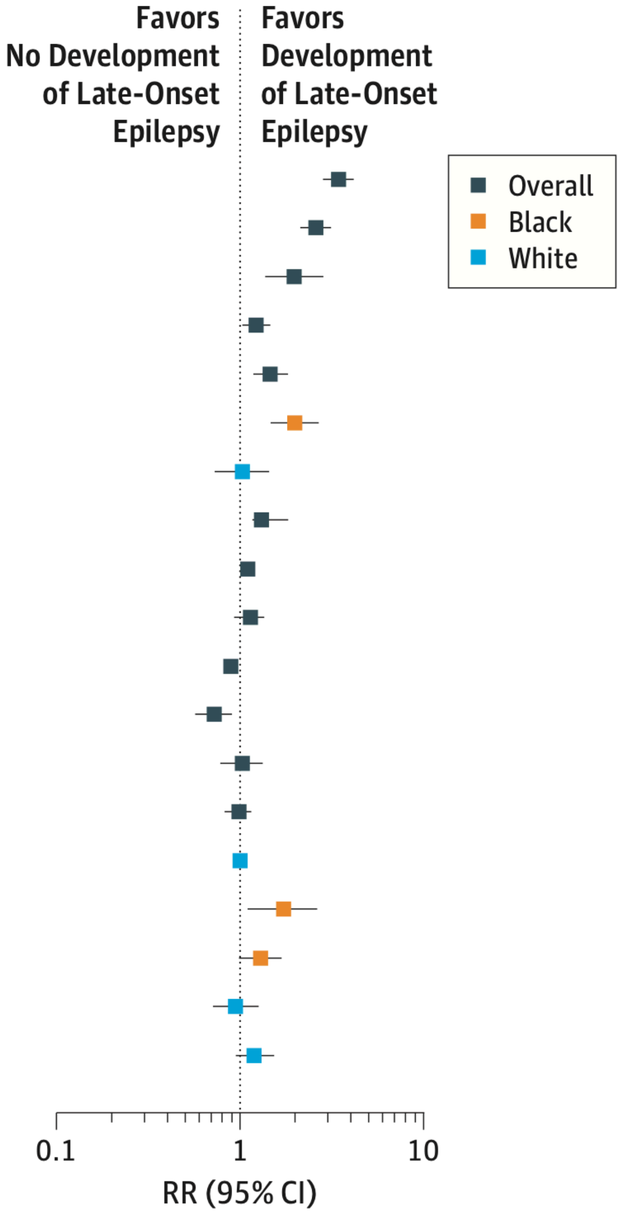
- HTN, DM, smoking
- APOE ε4
- Incident stroke and dementia

Lower risk of LOE

- Exercise
- Moderate alcohol intake

Risk Factor	Race/ Ethnicity	HR (95% CI)
Stroke	All	3.47 (2.85-4.23)
Dementia	All	2.68 (2.19-3.28)
APOE ε4: 2 alleles	All	1.93 (1.32-2.81)
1 allele	All	1.22 (1.02-1.46)
Diabetes[a]	All	1.43 (1.14-1.80)
	Black	2.04 (1.47-2.84)
	White	1.04 (0.74-1.45)
Hypertension	All	1.26 (1.05-1.51)
Smoking	All	1.09 (1.01-1.17)
Education (≥HS)	All	1.11 (0.91-1.36)
Exercise	All	0.89 (0.81-0.97)
Alcohol use: 1 drink/d	All	0.70 (0.56-0.88)
≥2/d	All	1.00 (0.76-1.31)
Male	All	0.96 (0.81-1.15)
Field center-race	NC-white	1 [Reference]
	NC-black	1.75 (1.12-2.75)
	MS-white	1.41 (1.07-1.85)
	MN-black	1.07 (0.81-1.41)
	MD-white	1.33 (1.04-1.70)

[a] Interaction with race, $P < .05$



Johnson EL, et al. *JAMA Neurol* 2018

Overview

- Key facts about epilepsy
- Risk factors & Etiologies of new-onset epilepsy in adults
- Natural history of epilepsy
  - Single unprovoked seizure
  - Epilepsy: overall prognosis, pattern of treatment response, intractable epilepsy, after treatment withdrawal, untreated epilepsy

First unprovoked seizure has higher risk of subsequent seizure

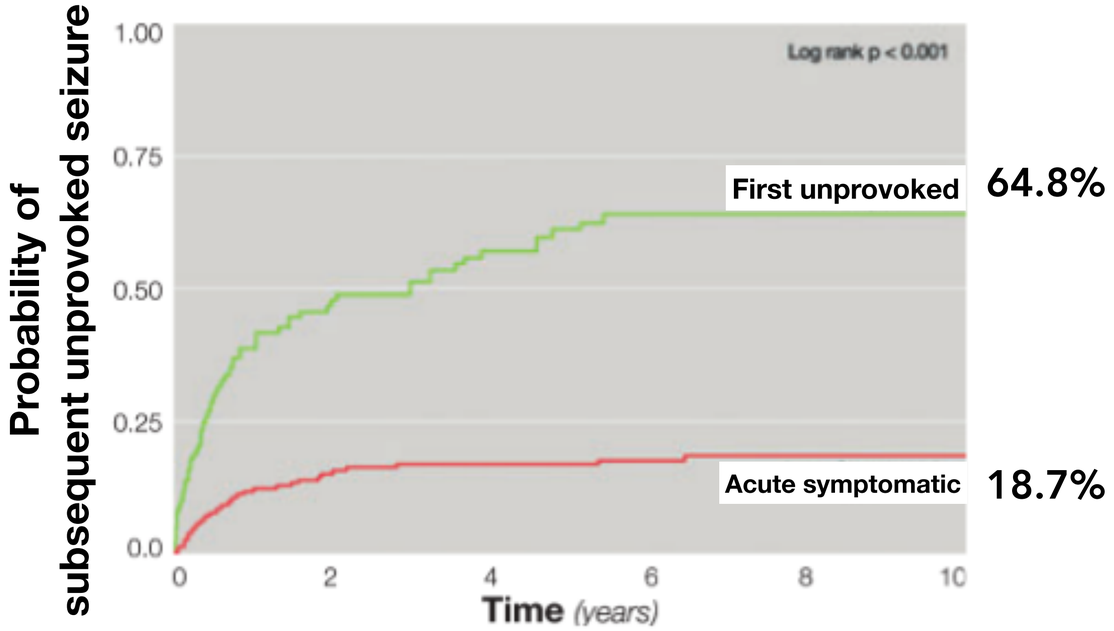
Epilepsia, 50(5):1102–1108, 2009
doi: 10.1111/j.1528-1167.2008.01945.x

FULL-LENGTH ORIGINAL RESEARCH

Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure

***Dale C. Hesdorffer, †Emma K. T. Benn, ‡Gregory D. Cascino, and §¶W. Allen Hauser**

To compare subsequent unprovoked seizure risk
Rochester Epidemiology Project's records-linkage system
First acute symptomatic (n=262) vs.
First unprovoked seizure (CNS infection, stroke, TBI) (n=148)
O: Subsequent unprovoked seizure over next 10y



First unprovoked seizure

- Stroke 71.5%
- TBI 46.6%
- CNS injection 63.5%

Hesdorffer DC, et al. *Epilepsia* 2009

Diagnosis of epilepsy can be applied after single unprovoked seizure

ILAE OFFICIAL REPORT

A practical clinical definition of epilepsy

*Robert S. Fisher, †Carlos Acevedo, ‡Alexis Arzimanoglou, §Alicia Bogacz, ¶J. Helen Cross, #Christian E. Elger, **Jerome Engel Jr, ††Lars Forsgren, ‡‡Jacqueline A. French, §§Mike Glynn, ¶¶Dale C. Hesdorffer, ##B.I. Lee, ***Gary W. Mathern, †††Solomon L. Moshé, ‡‡‡Emilio Perucca, §§§Ingrid E. Scheffer, ¶¶¶Torbjörn Tomson, ###Masako Watanabe, and ****Samuel Wiebe

Epilepsia, 55(4):475–482, 2014
doi: 10.1111/epi.12550

Epilepsy is a disease of the brain defined by any of the following conditions

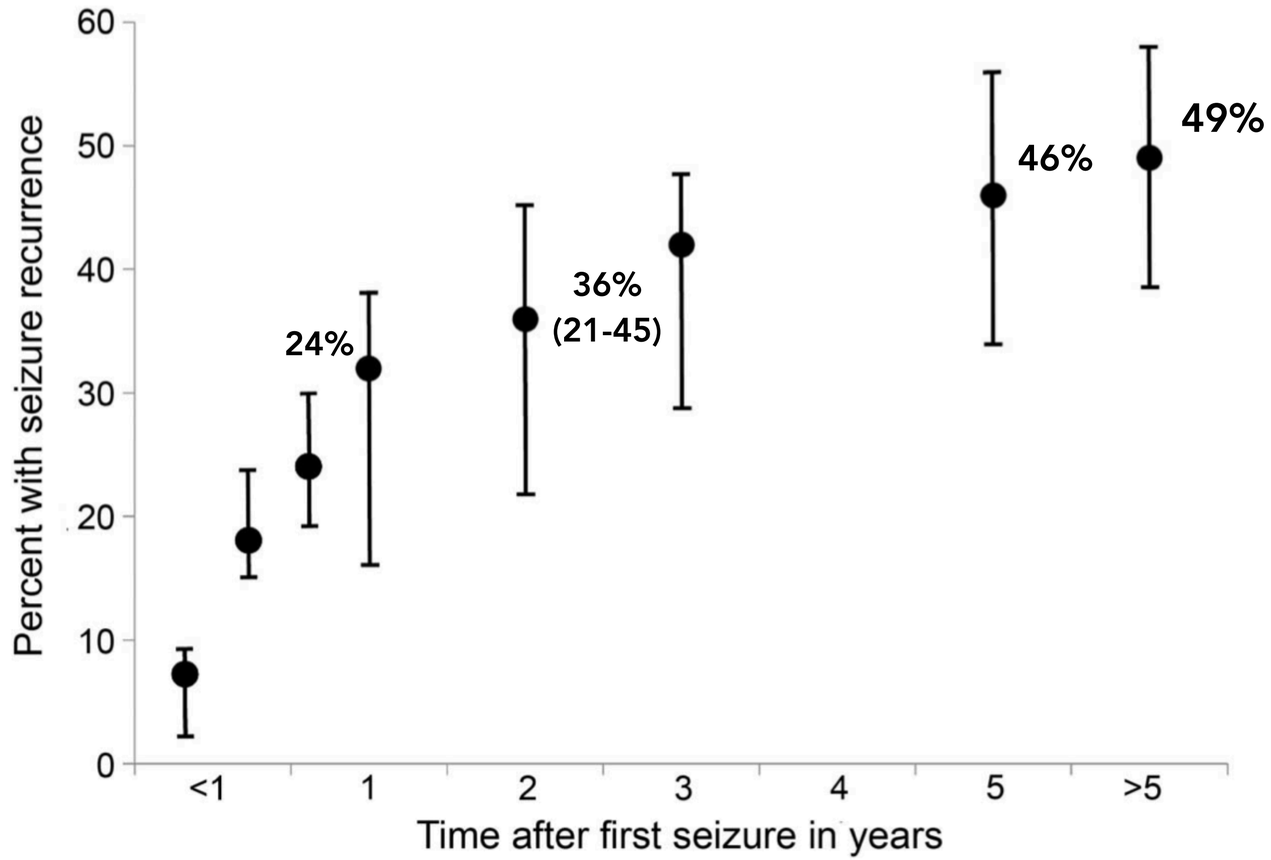
1. ≥ 2 unprovoked seizures occurring >24 h apart
2. <u>One unprovoked seizure</u> & probability of further seizures ≥60% over next 10 y
3. Diagnosis of epilepsy syndrome

Resolved: seizure-free for last 10 y, with no ASM for last 5 y

Fisher et al. *Epilepsia* 2014

Adults with unprovoked seizure - recurrence risk is greatest early within the first 2 yr

Figure 1 **Percentages of patients with first seizure experiencing a recurrent seizure over time**



To provide recommendations for adults with an unprovoked first seizure

Systematic review: 47 articles

Krumholz A, et al. *Neurology* 2015

Predictors of recurrent seizure

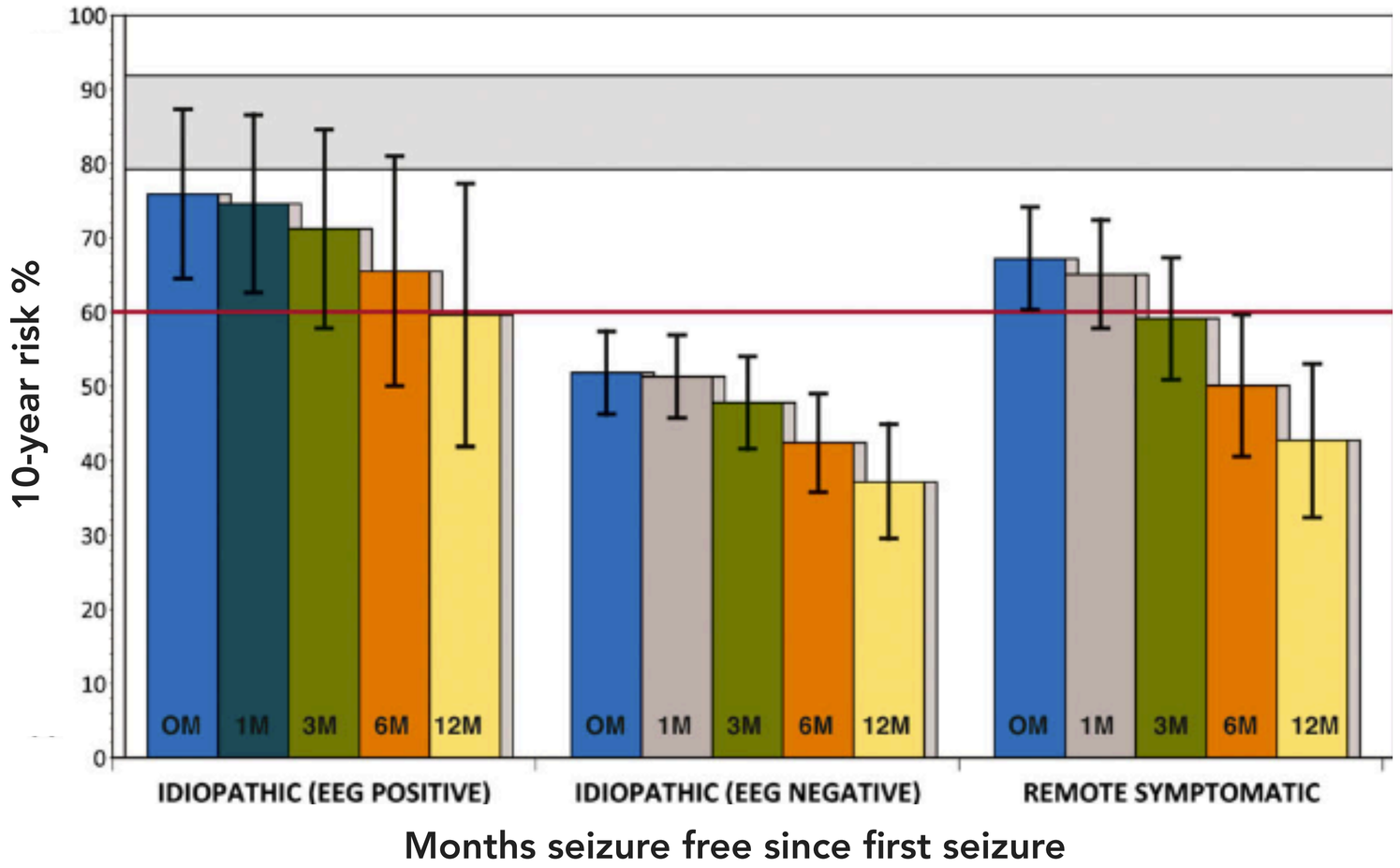
	2y-risk
Idiopathic + normal EEGs	24%
Idiopathic + abnormal EEGs	48%
Remote symptomatic + normal EEGs	48%
Remote symptomatic + abnormal EEGs	65%

	HR
Prior brain insult	2.5 (1.4-4.5)
Abnormal CT/MRI	2.4 (1.1-5.4)
Epileptiform EEG	2.1 (1.1-4.3)
Nocturnal seizure	2.1 (1.0-4.3)

Berg AT & Shinnar S. *Neurology* 1991; Kim LG et al. *Lancet Neurol* 2006; Krumholz A et al. *Neurology* 2015

Risk of recurrence is highly time dependent

798 adults with first-ever first seizure, aged 38 (14-91)
Western Australian first seizure database

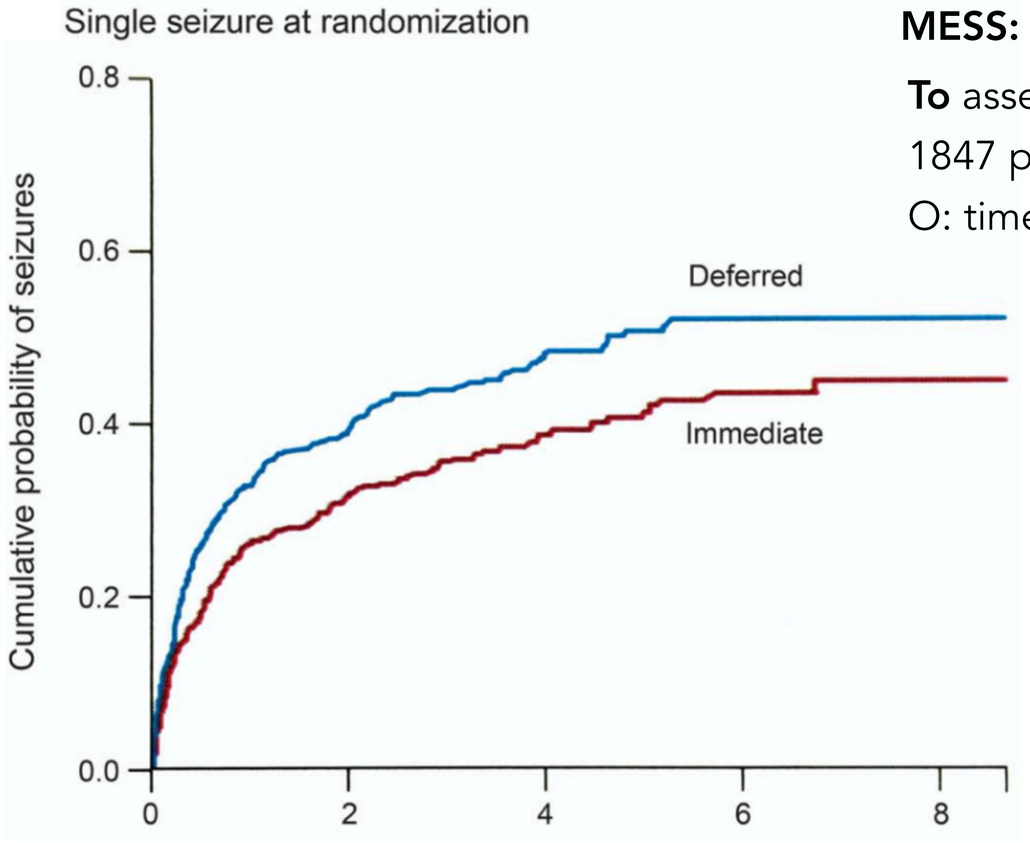


Lawn et al. Epilepsia 2015

Treatment of first seizure

Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial

*A Marson, A Jacoby, A Johnson, L Kim, C Gamble, D Chadwick, on behalf of the Medical Research Council MESS Study Group**



MESS: MRC Multicentre trial for Early Epilepsy and Single Seizures

To assess effect of immediate vs. deferred treatment on outcomes

1847 pt with single and early epilepsy

O: time to first seizure, time to 2y remission, seizures between 1-3y and 3-5y

2-year remission	Immediate Rx	Deferred Rx
2 years	64%	52%
5 years	92%	90%
8 years	95%	96%

Marson A et al. *Lancet* 2005; Kim LG et al. *Lancet Neurol* 2006; Krumholz A et al. *Neurology* 2015

Overall prognosis of epilepsy is favorable for majority

Remission of Seizures and Relapse in Patients with Epilepsy

*John F. Annegers, †W. Allen Hauser, and *Lila R. Elveback

*Department of Medical Statistics and Epidemiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901; and †Department of Neurology, Columbia University College of Physicians and Surgeons, New York, New York 10032

Medical records linkage system of the Mayo Clinic
Epilepsy in population of Rochester, Minnesota
457 patients
O: seizure-free period of 5 years
f/u: ≥5y (328 followed ≥10y, 141 ≥20y)

Poorer in …
- *Neurologic deficit at birth or mental retardation*
- *Adult-onset epilepsy, focal impaired consciousness sz*

Remission highest in generalized seizures before 10YO

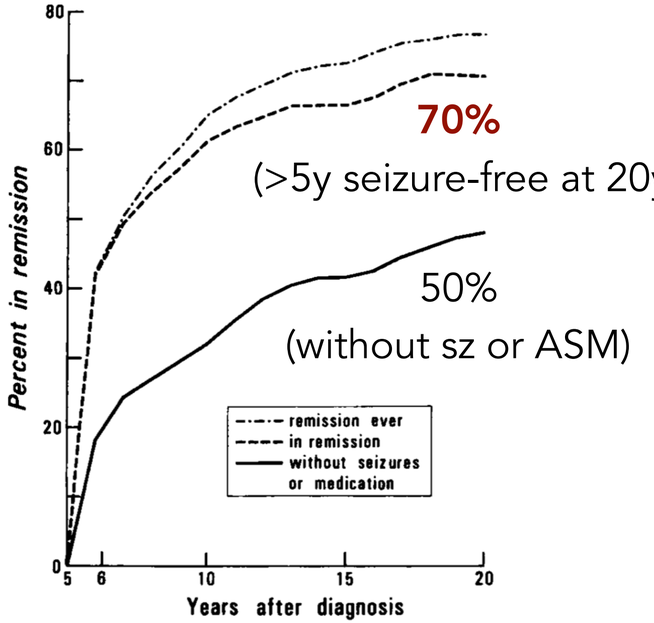


FIG. 1. Remissions among all 457 cases. Remission ever: percentage of patients who achieved remission status. In remission: percentage who have been seizure-free during last 5 years or more. Without seizures or medication: percentage during last 5 years or more.

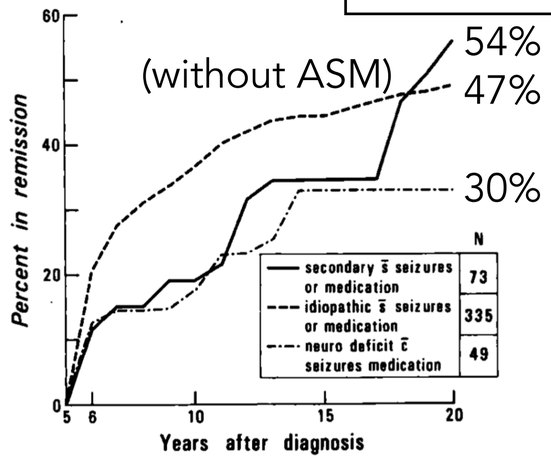


FIG. 3. Percentage in remission, by etiology and medication status.

"Mean annual relapse rate was 1.6%"

Annegers JF, et al. *Epilepsia* 1979

Prognostic predictors of treated epilepsy

Prognostic Predictor	Author, year
Symptomatic aetiology	Bonnett *et al.*, 2014; Wirrell *et al.*, 2012; Sillanpää *et al.*, 2012; Sillanpää and Schmidt, 2009a; Jallon *et al.*, 2003; Berg *et al.*, 2001; Ko and Holmes, 1999; Aikiä *et al.*, 1999; Sillanpää *et al.*, 1998; Annegers *et al.*, 1979
Abnormal intelligence	Sillanpää *et al.*, 2012; Wirrell *et al.*, 2012; Aikiä *et al.*, 1999; Sillanpää, 1993; Camfield *et al.*, 1993; Brorson and Wranne, 1987
Tonic or simple focal seizures	Bonnett *et al.*, 2014; Su *et al.*, 2013; Jonsson and Eeg-Olofsson, 2011; Del Felice *et al.*, 2010; Ko and Holmes, 1999; Shafer *et al.*, 1988
Complex focal or atonic seizures	Aikiä *et al.*, 1999; Sillanpää, 1993
Early childhood age at onset	Wirrell *et al.*, 2012; Sillanpää *et al.*, 2012; Ko and Holmes, 1999; Sillanpää, 1993; Camfield *et al.*, 1993
Prior neonatal seizures	Sillanpää, 1993; Camfield *et al.*, 1993
High seizure frequency prior to treatment	Su *et al.*, 2013; Berg *et al.*, 2001; Camfield *et al.*, 1993
High seizure frequency during early treatment	MacDonald *et al.*, 2000; Arts *et al.*, 1999; Cockerell *et al.*, 1997
Poor early effects of treatment	Bonnett *et al.*, 2014; Sillanpää *et al.*, 2012; Arts *et al.*, 1999; Sillanpää *et al.*, 1998; Annegers *et al.*, 1979
Neurological dysfunction	Annegers *et al.*, 1979
Abnormal interictal EEG	Berg *et al.*, 2014; Su *et al.*, 2013; Wirrell *et al.*, 2012; Berg *et al.*, 2001; Shafer *et al.*, 1988
Time to first remission	Sillanpää *et al.*, 2012; Sillanpää and Schmidt, 2009b

Predictor

- Etiology of epilepsy
- Neurologic deficit/MR
- Early seizure frequency
- Longer time to first remission
- Age: <1y, older age
- Focal seizure, multiple types
- Abnormal EEG

Beghi E et al. *Epileptic Disord* 2015

Prognosis of epilepsy syndrome

Syndrome	Study design	Cases	Follow-up (years)	Sz-free %	Author, year
BECTS	Retrospective cohort	29	12-17	**89**	Callenbach *et al.*, 2010
Panayiotopoulos	Retrospective cohort	93	1-14	**41**	Specchio *et al.*, 2010
CAE	Retrospective cohort	47	12-17	**93**	Callenbach *et al.*, 2009
CAE/JAE	Retrospective cohort	163	3-69	**56 (CAE)** **62 (JAE)**	Trinka *et al.*, 2004
JME	Retrospective cohort	186	1-41	**58**	Martínez et al., 2006
West	Retrospective cohort	214	20-35	**33**	Riikonen, 2001
LGS	Retrospective cohort	107	>3 in 74	**3**	Goldsmith *et al.*, 2000
Dravet	Retrospective cohort & review	24	Up to age 50	**8**	Genton *et al.*, 2011
Landau-Kleffner	Retrospective cohort	9	6-25	**0**	Cockerell *et al.*, 2011
ESES	Prospective cohort	32	>3	**43 (>90% reduction)**	Liukkonen *et al.*, 2010
EGMA	Retrospective cohort	42	40	**62**	Holtkamp et al., 2014

BECTS: benign childhood epilepsy with centrotemporal spikes; CAE: childhood absence epilepsy; JAE: juvenile absence epilepsy; JME: juvenile myoclonic epilepsy; LGS: Lennox-Gastaut syndrome; ESES: encephalopathy with status epilepticus during sleep; EGMA: epilepsy with grand mal on awakening.

Beghi E et al. *Epileptic Disord* 2015

Journey of PWE

paroxysmal events

Diagnostic Workup

Hx, PE, MRI, EEG, CSF

Dx of Epilepsy

Initial monotherapy

Sz remission 50%

2nd drug therapy

Sz remission 9%

Drug resistant epilepsy (DRE)

surgically remediable epilepsy

not-surgically remediable epilepsy

Sz remission 60-80%

Surgery

continue drug trials

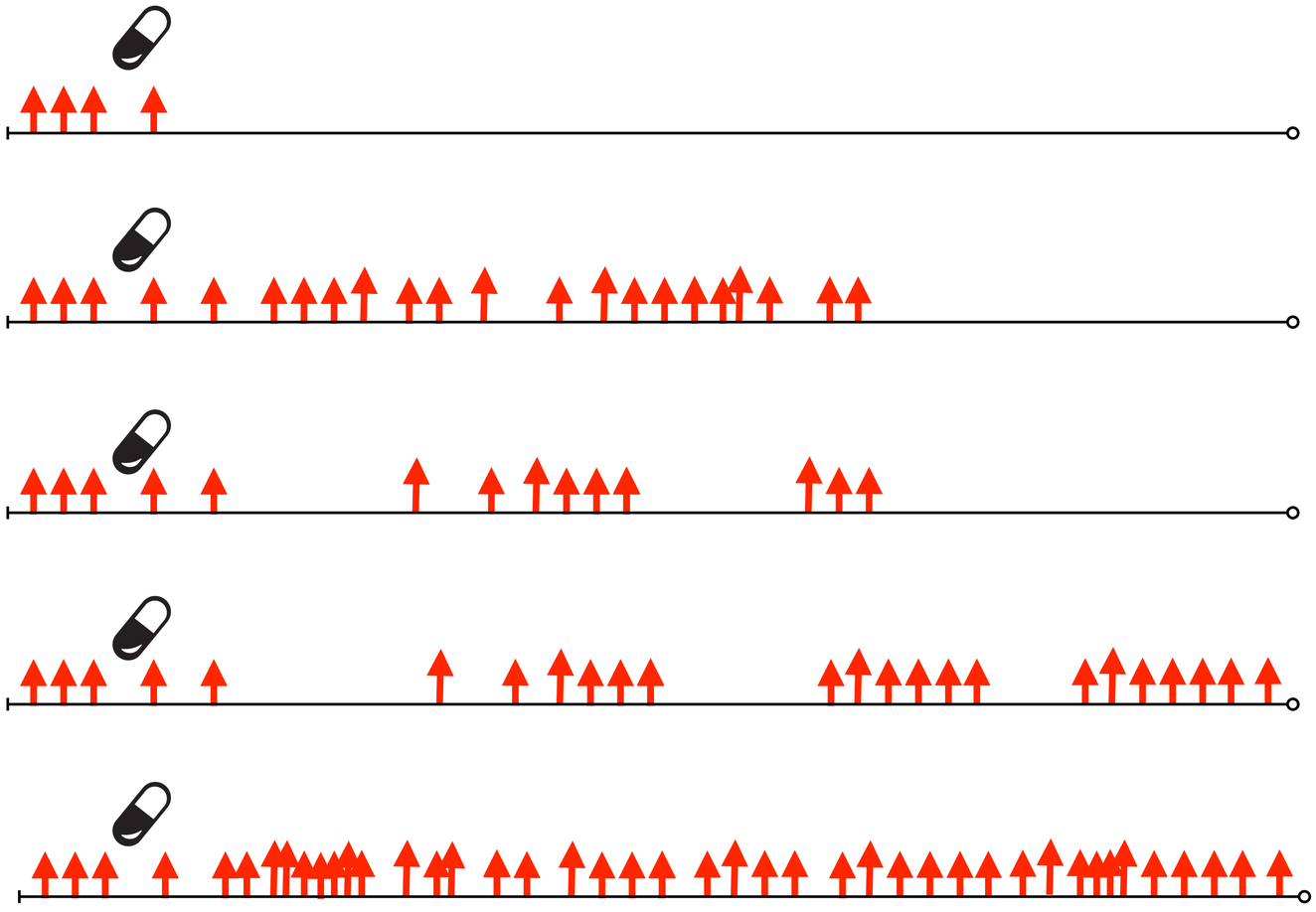
Sz remission 5-30%

Other alternative therapy

VNS, ketogenic diet, etc.

Around **70%** of patients will become seizure free with ASMs

Patterns of treatment response



A. Early remission, sustained without relapsed
(smooth-sailing epilepsy)

B. Early pharmaco-resistance,
achieved sustained remission without relapsed

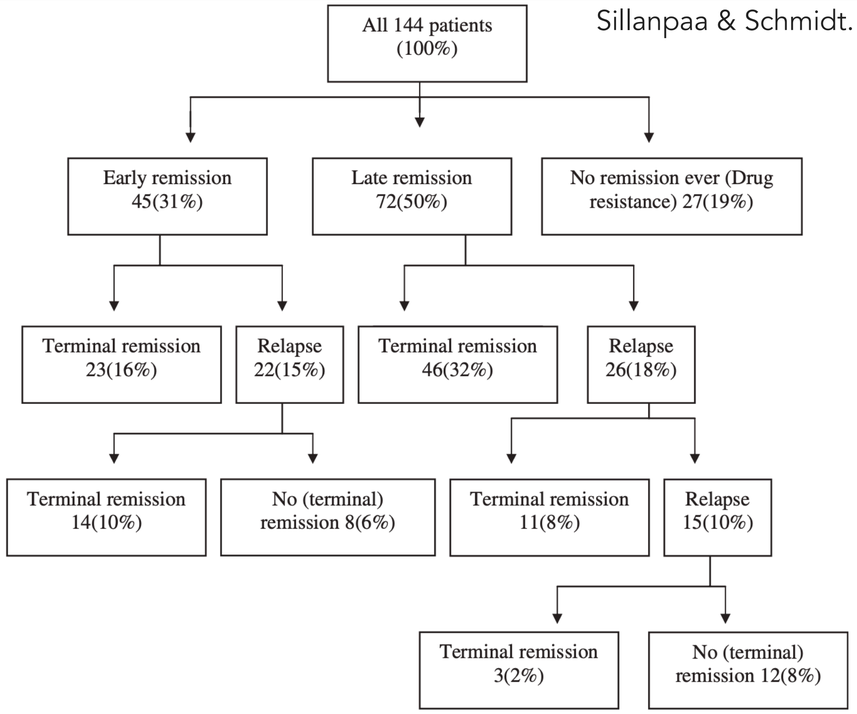
C. Remitting-relapsing course
C1: terminal remission
C2: no terminal remission

D. No remission period ever

Active epilepsy is a dynamic process

University of Turku Central Hospital, Finland
≤15y (childhood-onset epilepsy)
follow-up 37y (11-42)
remission: seizure-free period of ≥5 consecutive years

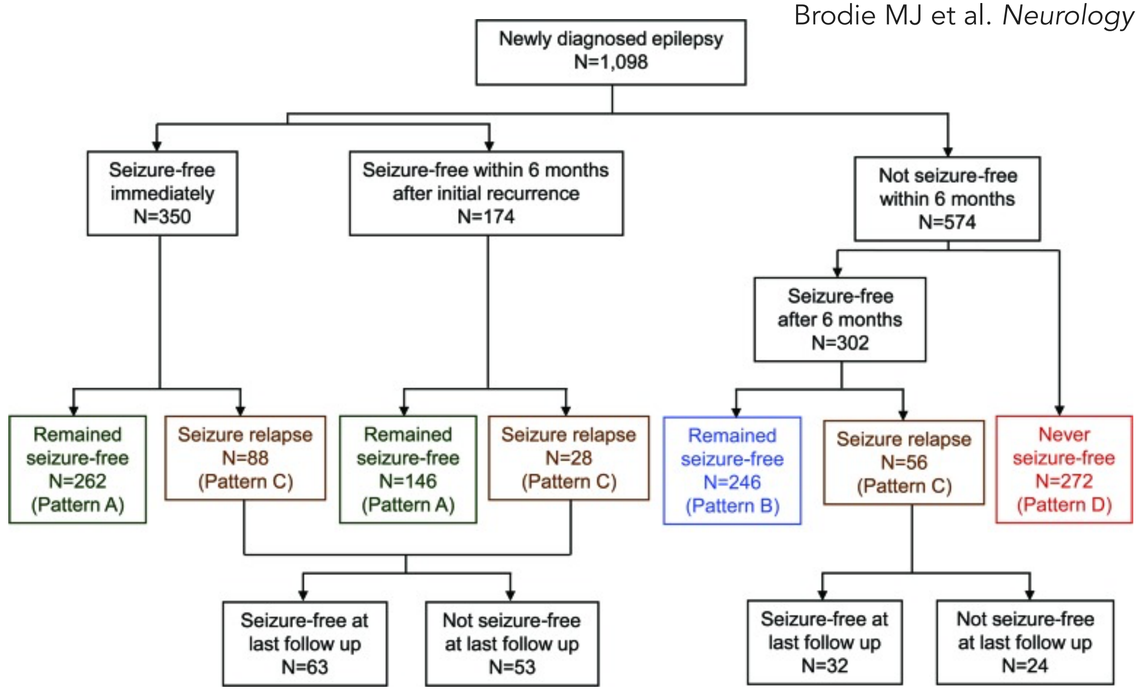
Sillanpaa & Schmidt. *Brain* 2006



A: 23/144 (16%)
B: 46/144 (32%)
C: 48/144 (33%); C1 20%, C2 13%
D: 27/144 (19%)

Western Infirmary in Glasgow, Scotland
32y (9-93)
follow-up 7.5y (4.7-12.0)
seizure-free: seizure-free period of a year of more

Brodie MJ et al. *Neurology* 2012



A: 408/1098 (37%)
B: 246/1098 (22%)
C: 172/1098 (16%); C1 9%, C2 7%
D: 272/1098 (25%)

Prognosis of intractable epilepsy

Likelihood of Seizure Remission in an Adult Population with Refractory Epilepsy

Brian C. Callaghan, MD,[1] Kishlay Anand, MD,[1] Dale Hesdorffer, PhD,[2] W. Allen Hauser, MD,[2] and Jacqueline A. French, MD[2]

To determine likelihood of remission in refractory epilepsy

246 patients who have DRE

DRE: failure of ≥2 ASM + seizure frequency ≥1/mo

40y (12-83), 59% female

Epilepsy duration: mean 25y

Outcome: 6-mo remission

f/u: median 3.1y

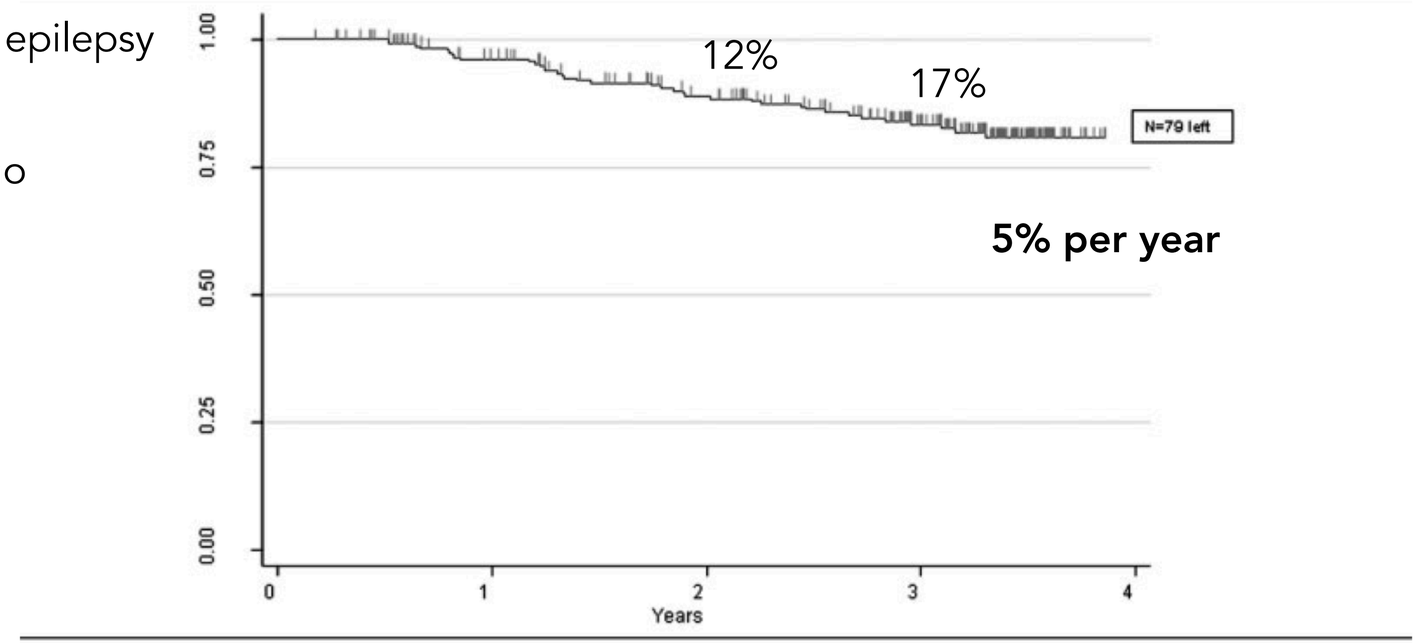


Fig 1. Cumulative probability of remission in the 246 drug refractory epilepsy patients. Cumulative probability of remission for the 37 in remission is 19.3% (95% confidence interval, 14.1–25.9%).

Still hope of seizure control even in patient not responded to multiple ASMs

Callaghan BC et al. *Ann Neurol* 2007

Prognosis after treatment withdrawal

Withdraw ASMs are at higher risk of relapse

Relapse rate was highest in first 12 mo (esp. in first 6 mo)

Recurrence can occur in those continuing therapy

Probability of seizure-free

- Children: 66-96% at 1y, 61-91% at 2y
- **Adults**: 39-74% at 1y, 35-57% at 2y

Risk factors:

- adolescent-onset
- focal seizures
- neurologic deficit/MR
- EEG at withdrawal (children)
- specific syndrome

330 patients, seizure free for ≥2y, on monotherapy

87% aged >15y

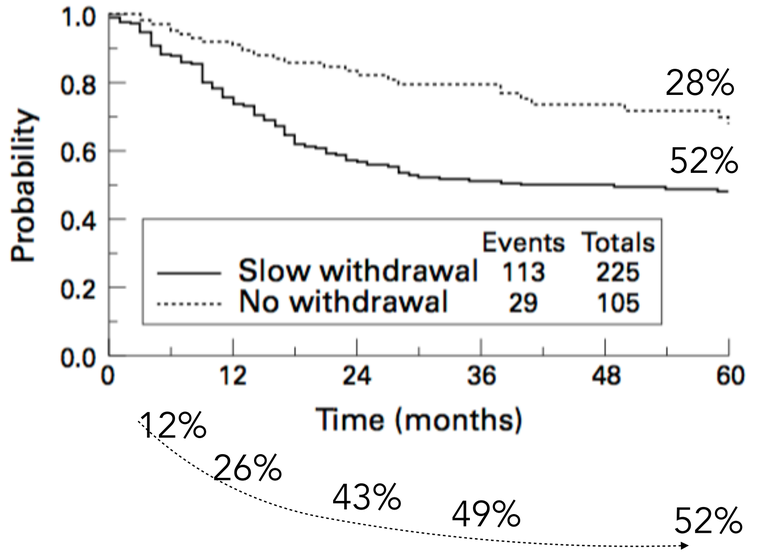


Table 2 Factors influencing the risk of seizure relapse in the multivariate model*

Factor	Hazard ratio	95% CI
Drug withdrawal:		
Yes	2.9	1.8–4.6
No	1	
Duration of active disease:		
2	1	0.3–1.0
3–5	1.6	0.6–3.7
6–10	2.3	1.0–5.3
>10	1	
No of years of remission at study entry:		
2	2.6	1.5–4.8
3–5	1.6	1.0–2.6
>5	1	
Abnormal psychiatric examination:		
Yes	2.1	1.3–3.6
No	1	
Epilepsy syndrome:		
Partial	1.1	0.8–1.6
Generalised	1	

*Other factors included in the model were age, sex, and education.

Specchio LM et al. *J Neurol Neurosurg Psychiatry* 2002; Specchio & Beghi. *CNS Drugs* 2004

Prognosis of untreated epilepsy

Journal of Neurology, Neurosurgery, and Psychiatry 1994;57:320–325

The characteristics of epilepsy in a largely untreated population in rural Ecuador

M Placencia, J W A S Sander, M Roman, A Madera, F Crespo, S Cascante, S D Shorvon

house-to-house survey in rural area of northern Ecuador

1,029 epileptic seizure

Table 2 Treatment state for identified cases

	Active	*Inactive*	*Total*	
On treatment at time of the survey	121	NA	121	12%
Treatment only in the past	125	140	265	
Ever on treatment	246	140	386	37%
Never on treatment	329	314	643	
Total	575	454	1029	

NA = not applicable.

Results

Table 1 shows the age and sex distributions of the surveyed population and of the 1029 cases with a history of seizures. The lifetime prevalence of epileptic seizures was estimated to lie between 12·2/1000 and 19·5/1000 and the prevalence of the active condition between 6·7/1000 and 8·0/1000. The lower figures represent the 881 cases considered as definite and the higher figure is an adjusted figure, calculated by the addition of a further 378 cases estimated from the various quality control steps.[18] The annual incidence rates were similarly estimated to be between 122/100 000 and 190/1000 000. These figures are fully discussed elsewhere.[18]

Spontaneous remission can be achieved even in those untreated

Mortality in epilepsy

- Standardized mortality ratio (SMR): 2.2-2.6
- Etiologies of mortality:
  1. Deaths due to epilepsy
  2. Related to the cause of epilepsy
  3. Unrelated to epilepsy
- Risk: symptomatic epilepsy, neurologic deficit/ learning difficulties, GTC, myoclonic seizure, severity of epilepsy

Unrelated deaths
Neoplasms outside the central nervous system
Ischaemic heart disease
Pneumonia
Others

Related to underlying disease
Brain tumours
Cerebrovascular disease
Cerebral infection-abscesses and encephalitis
Inherited disorders, e.g. Batten's disease

Epilepsy-related deaths
Suicides 5x, severe epilepsy, TLE
Treatment-related deaths
Idiosyncratic drug reactions
Medication adverse effects
Seizure-related deaths
Status epilepticus up to 12.5%
Trauma, burns, drowning 1.2-6.5%
Asphyxiation, aspiration
Aspiration pneumonia after a seizure
Sudden unexpected death in epilepsy 2-18%

Ficker DM. *Epilepsia* 2000; Gaitatzis A & Sander J W. *Epileptic Disord* 2004

Conclusions

- Stroke & brain neoplasm - most prevalent risk factor associated with new-onset epilepsy in adults
- Dementia is the second most common risk factor in pts older than 70 years
- Identification of epilepsy etiology:
  - implications for management
  - prognostic information
- Overall prognosis of epilepsy in adults is favorable in majority

ขอบคุณครับ

สมัครเป็นสมาชิกครอบครัว Neuro CMU
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