EPILESSIA
Epidemiologia e inquadramento diagnostico

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Disclosures

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- Speaker for UCB-Pharma

Outline

- Definitions and worldwide epidemiology of epilepsy
- Epilepsy and comorbidity
- Epilepsy & Alzheimer disease
- Early epilepsy and cognitive dysfunction
- Epilepsy and cognition: association and causation
- Problems and future directions

Epilepsy & Cognitive Deficits

- **Static factors**:
  - Developmental or acquired cerebral lesions
- **Dynamic factors**:
  - Active epilepsy
  - Antiepileptic drugs
  - Psychiatric comorbidities

Witt & Helmstaedter, Seizure 2015; 26:75

Factors Affecting Cognition Before, During & After Epilepsy

	Prior to epilepsy onset	At epilepsy onset	Controlled epilepsy (100% seizure control)	Cured epilepsy (seizure free, AEDs withdrawn)	Chronic refractory epilepsy
Cerebral lesions					
Covert epileptic dysfunction					
Overt epileptic seizures					
Antiepileptic treatment					
Behavioral/ psychiatric problems					

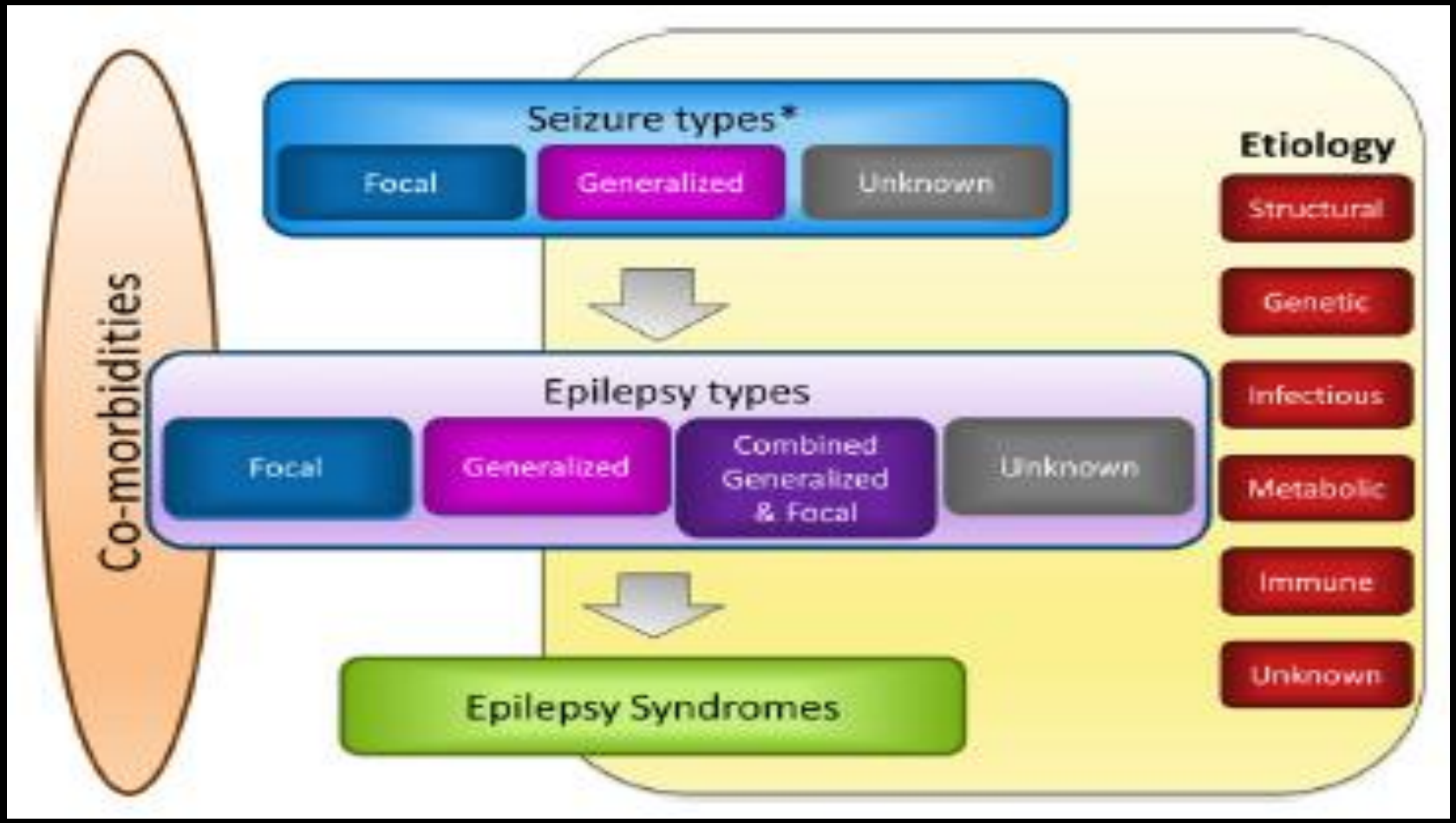
Witt & Helmstaedter, Seizure 2015; 26:75

New ILAE Definition of Epilepsy

- 1. At least two unprovoked (or reflex) seizures occurring more than 24 hours apart;
- 2. **One unprovoked (or reflex) seizure and a probability for further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years**;
- 3. Diagnosis of an epilepsy syndrome.

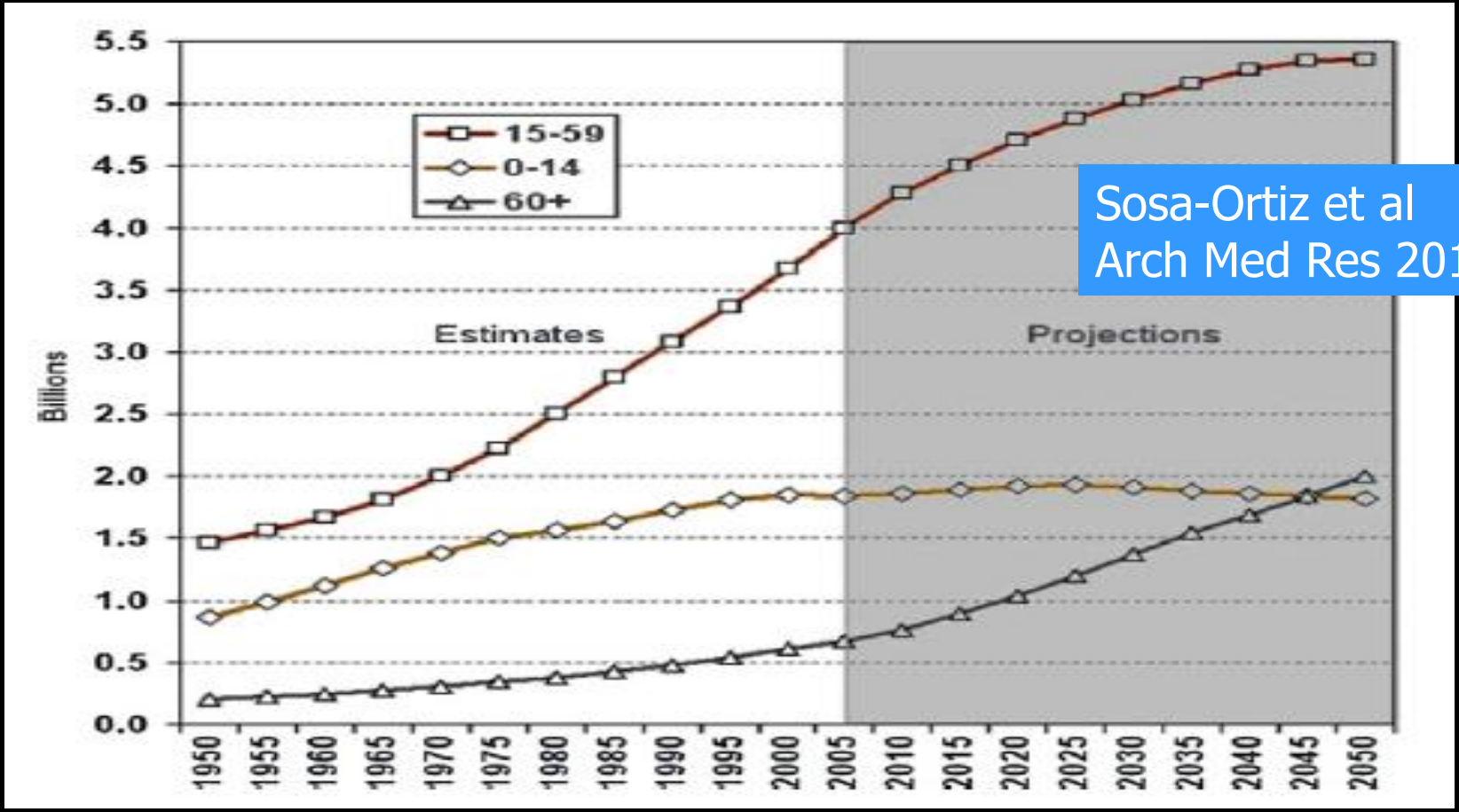
Fisher et al. Epilepsia 2014 ; 55: 475

Framework of the Classification of the Epilepsies

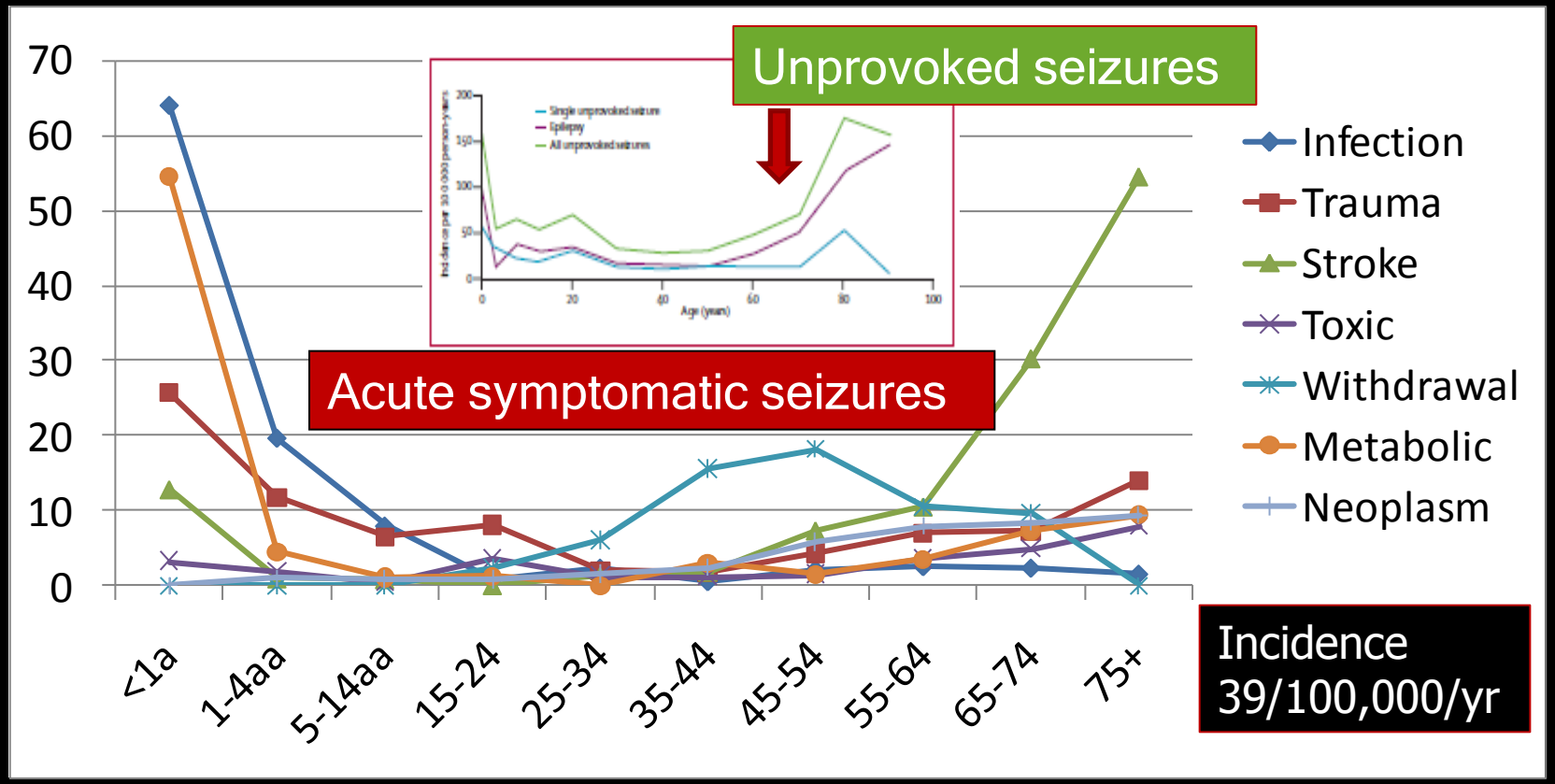


Scheffer et al, Epilepsia 2017

Trends in the World Population by Age Groups

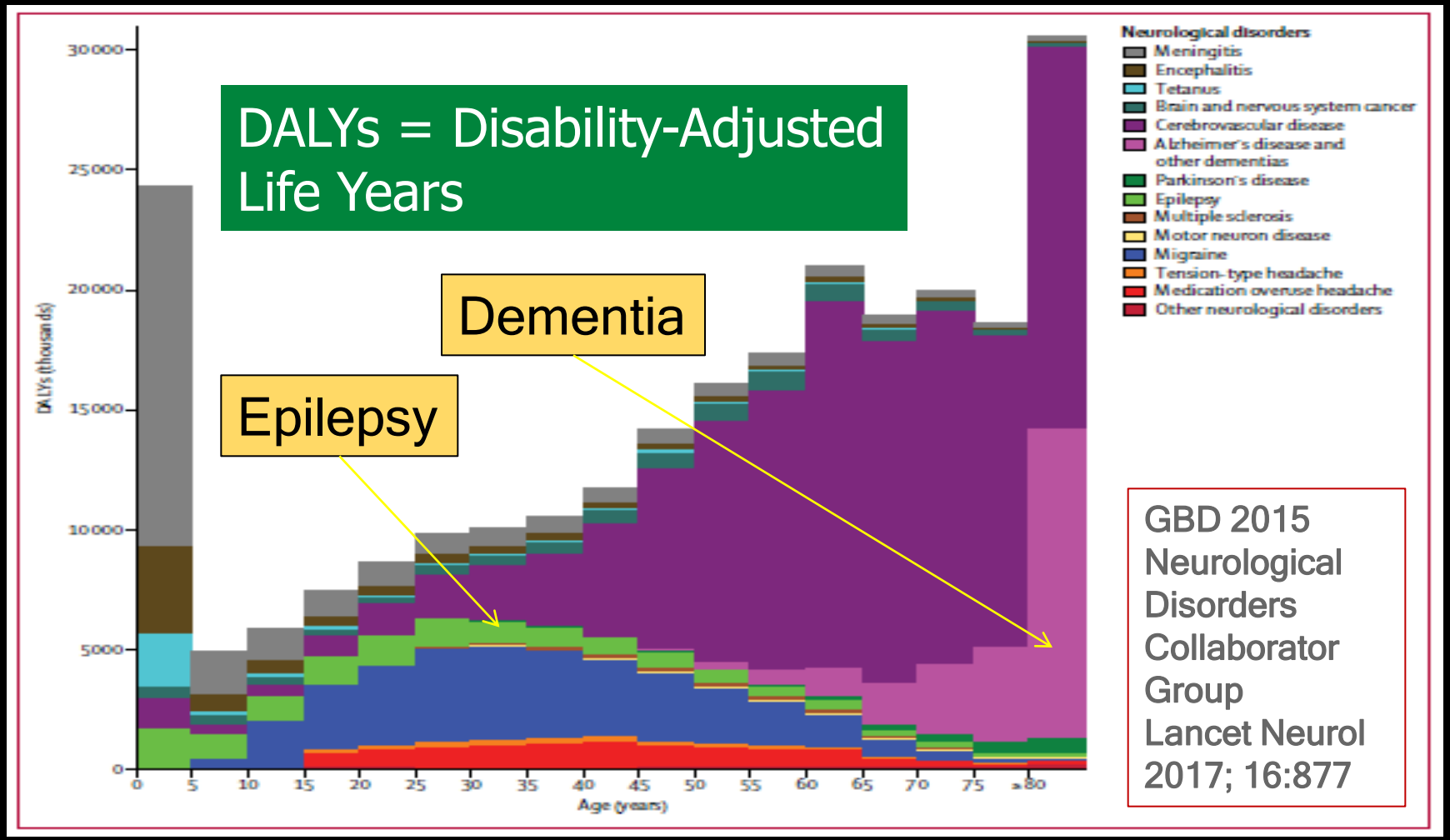


Incidence (per 100,000 per year) of Acute Symtomatic Seizures & Unprovoked Seizures by Age & Etiology

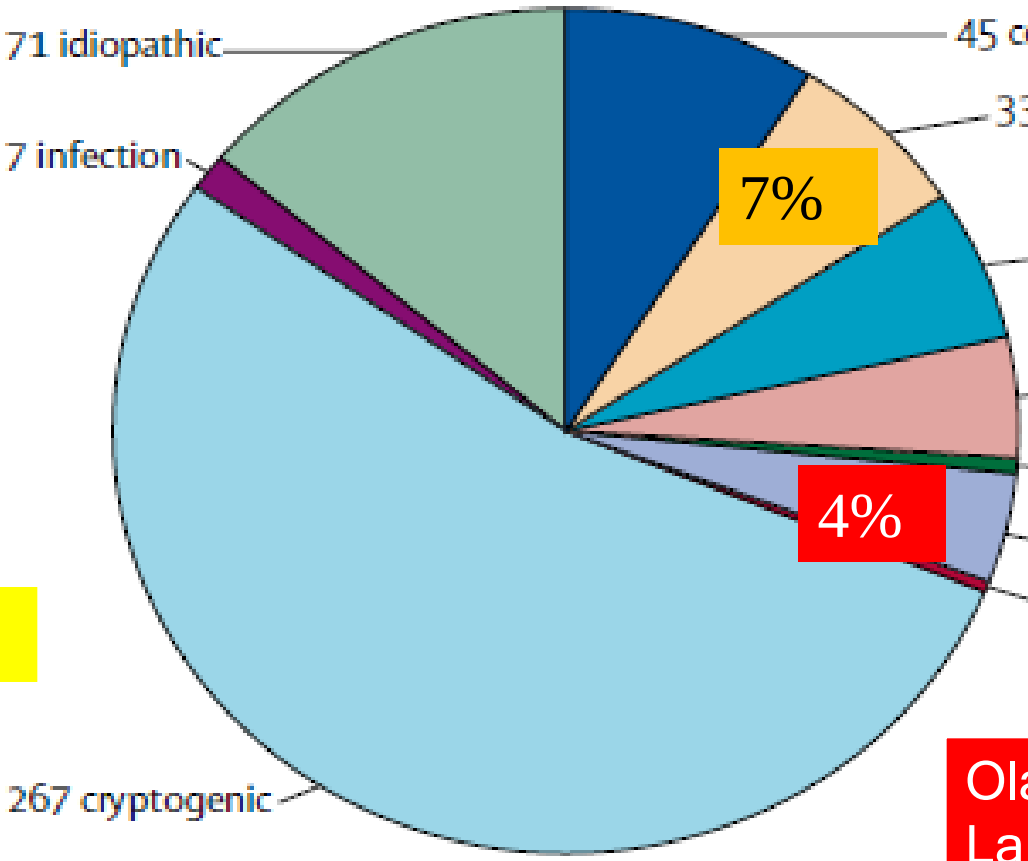


Annegers et al, Epilepsia 1995

Global DALYs by Age & Neurological Disorder



Causes of Unprovokd Seizures

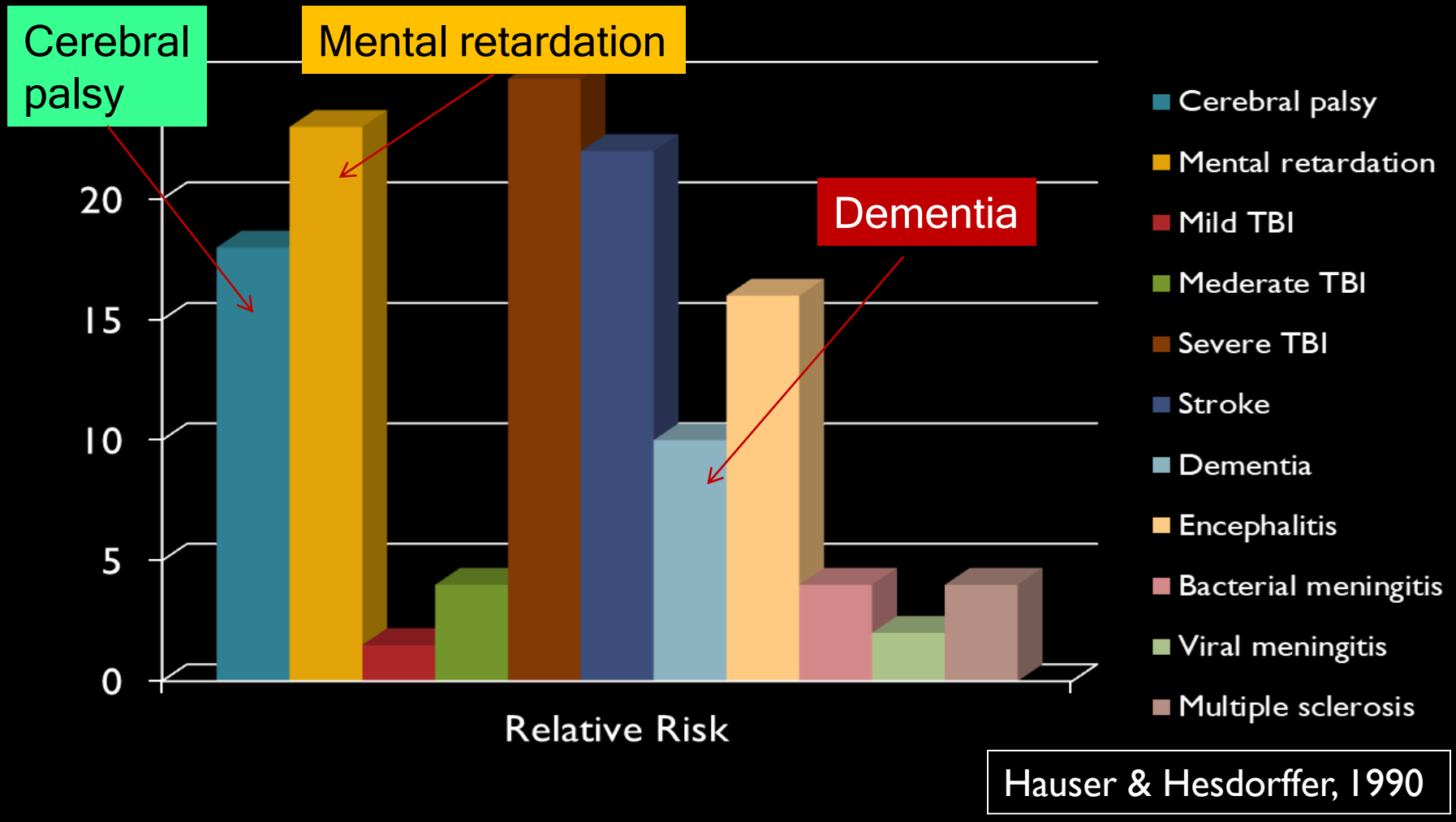


N = 501

Olafsson et al
Lancet Neurol 2005

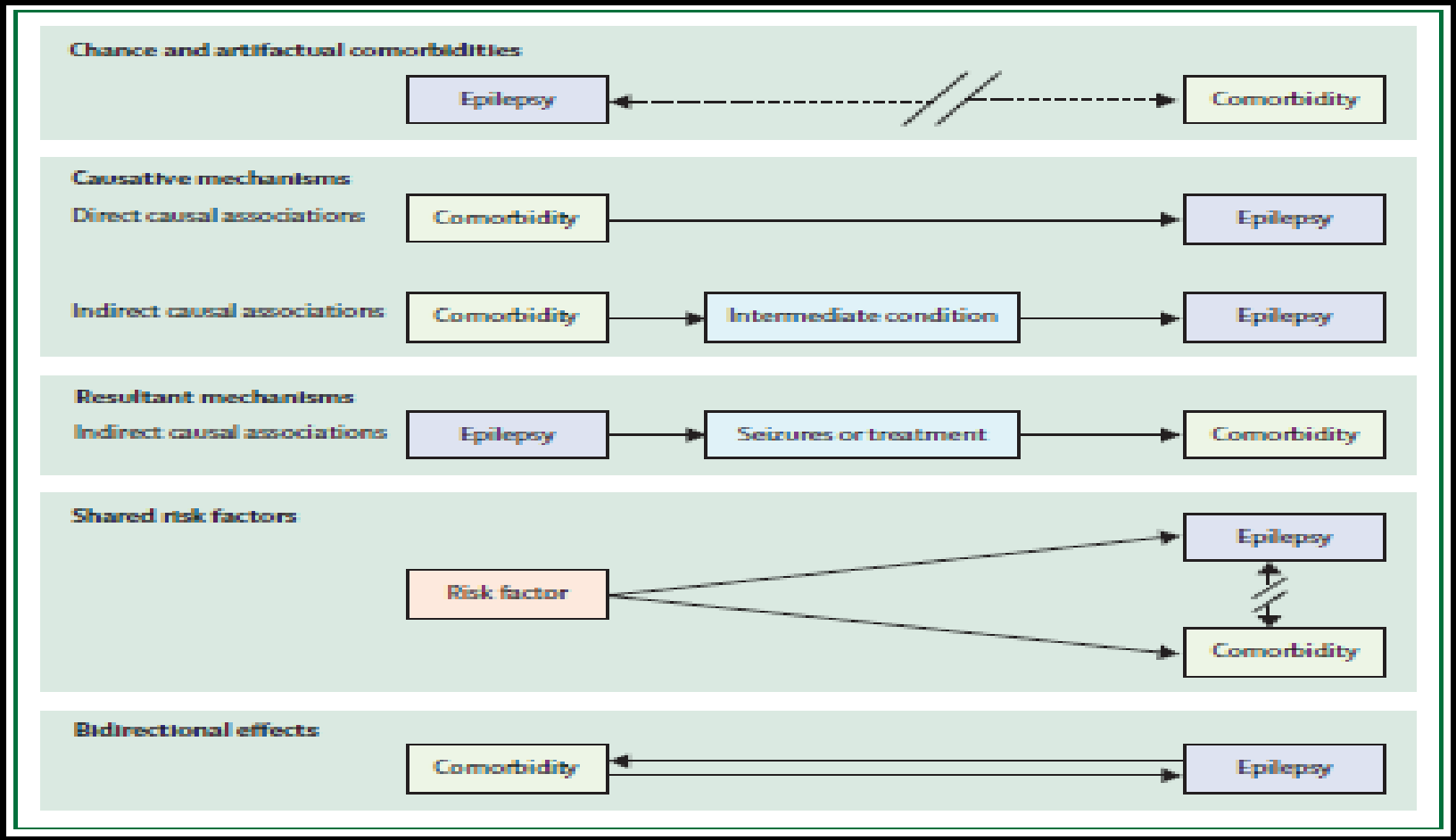
MR = Mental retardation; CP = Cerebral palsy

Relative Risk of Epilepsy by Putative Cause



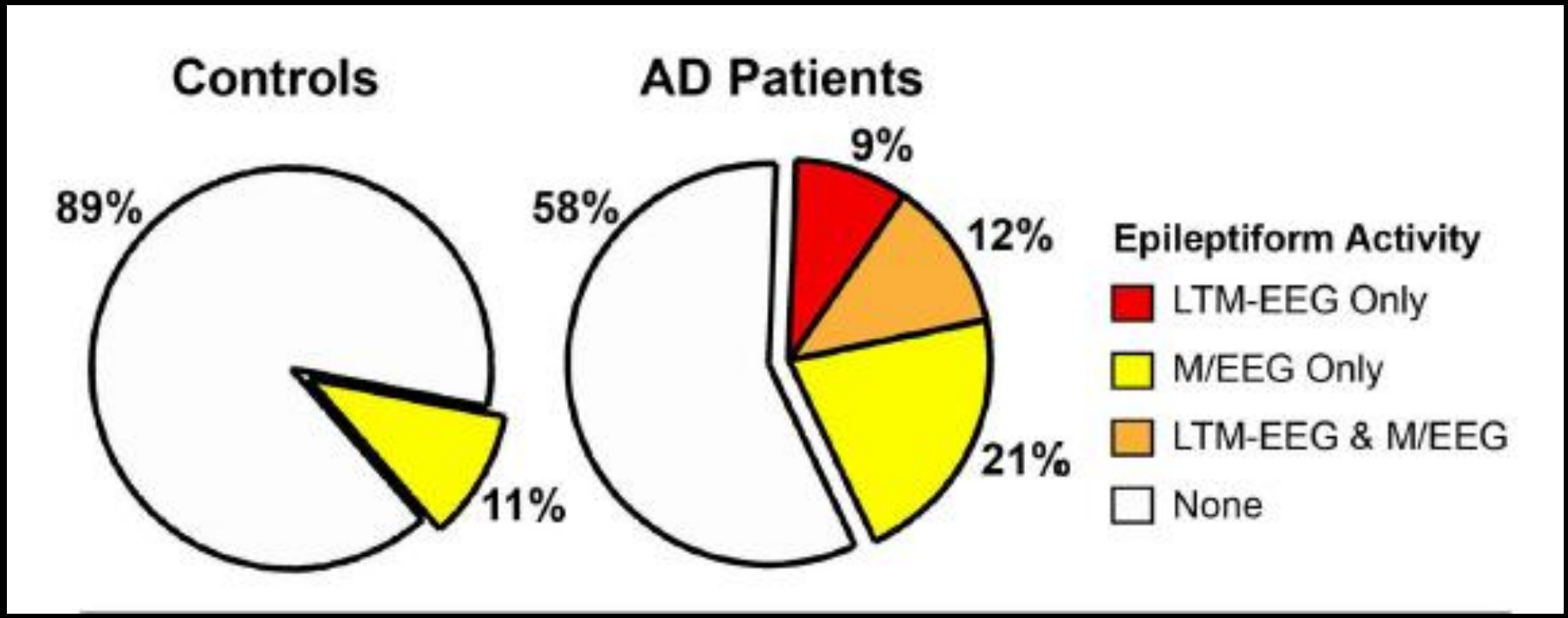
Hauser & Hesdorffer, 1990

Mechanisms of Association Between Epilepsy & Comorbidities



Keezer et al, Lancet Neurol 2016; 15: 106

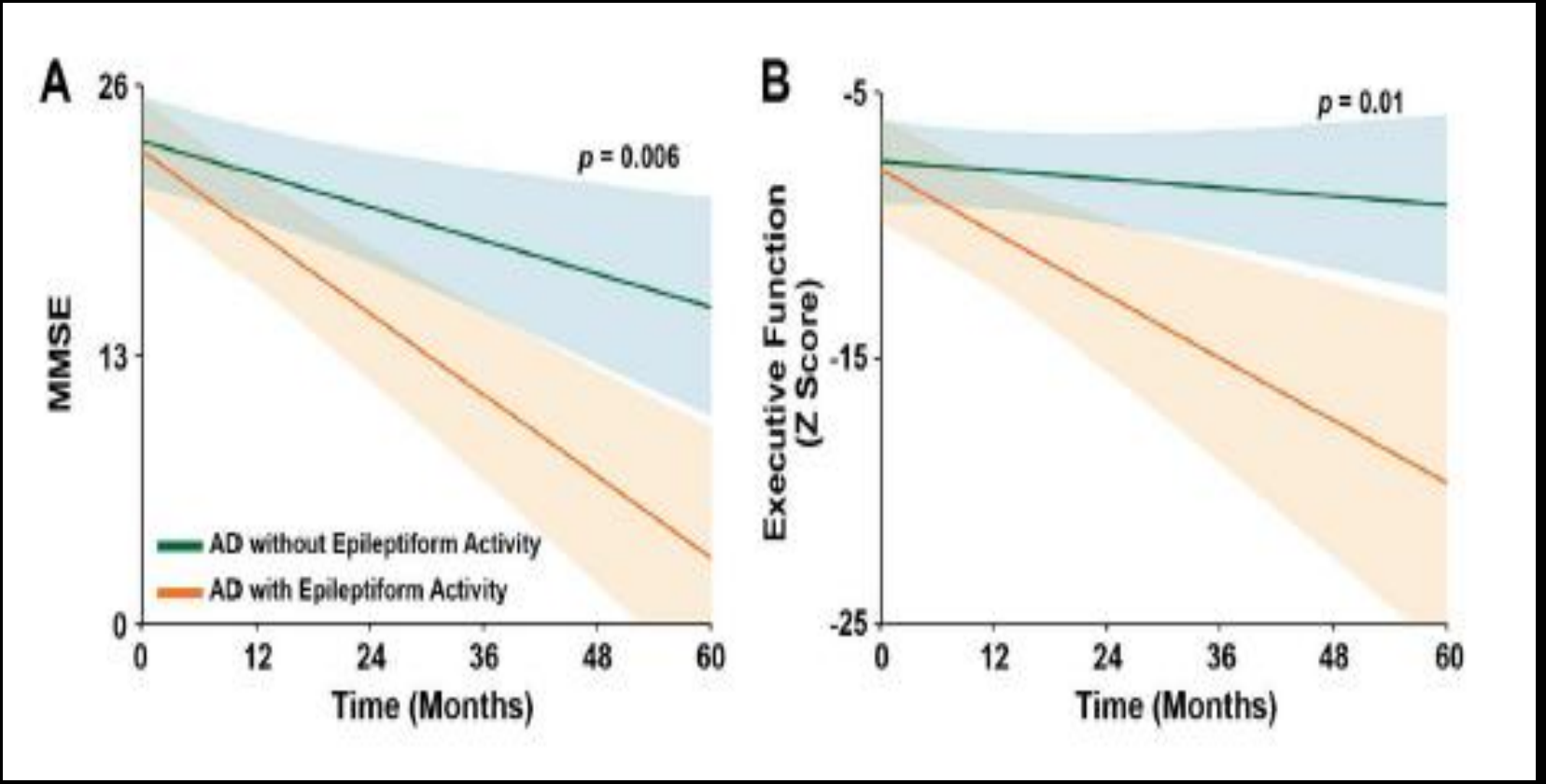
Subclinical Epileptiform Activity in Patients With Alzheimer Disease & Controls



LTM = Long-term monitoring
M/EEG = Magnetoencephalography

Vossel et al, Ann Neurol 2016; 80:858

Subclinical Epileptiform Activity & Longitudinal Change in Cognition in Alzheimer Disease



Vossel et al, Ann Neurol 2016; 80:858

Epilepsy & Psychiatric Comorbidity

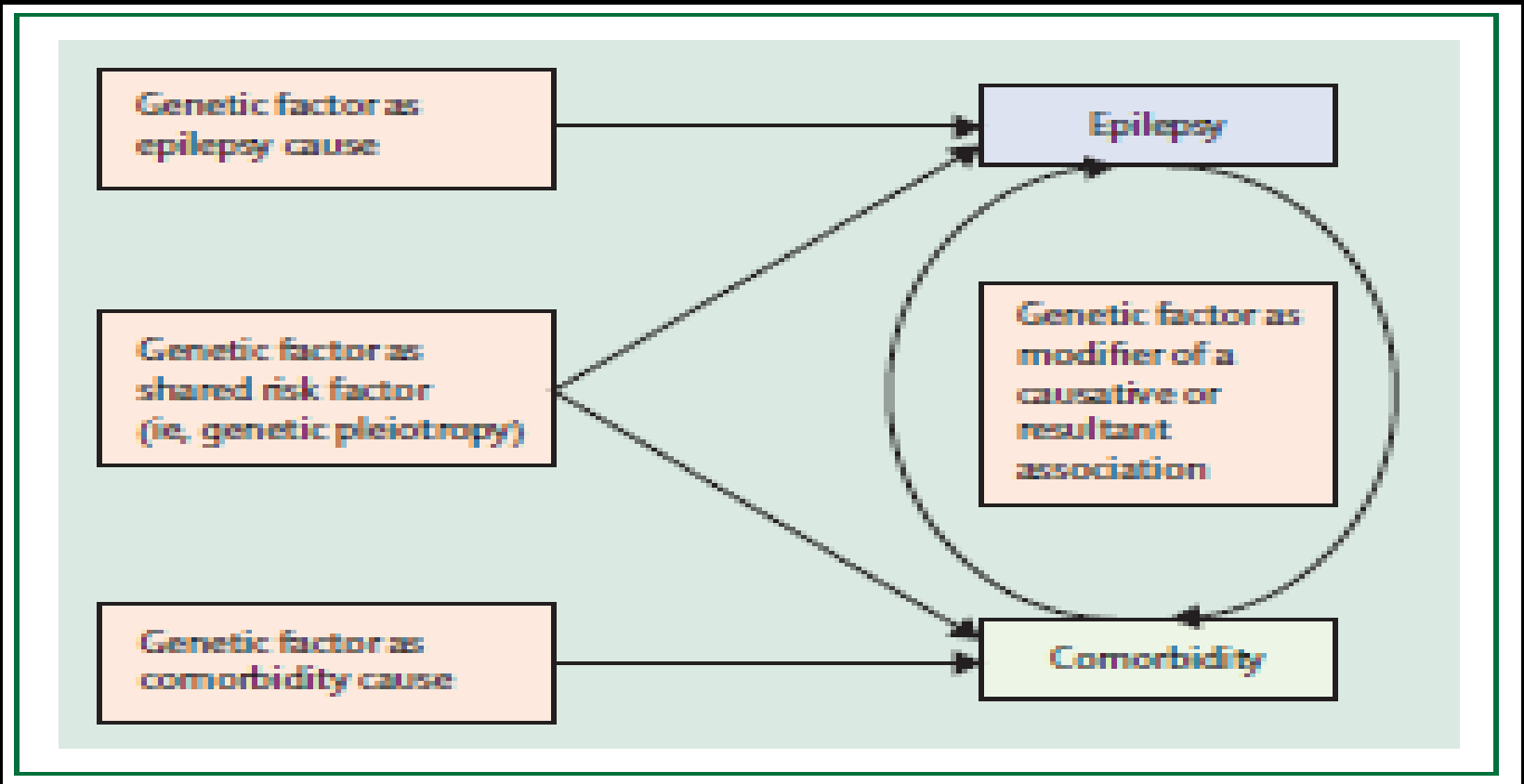
	Controls	Epilepsy
Major depressive disorder	10·7 (10·2–11·2)	17·4 (10·0–24·9)
Mood disorder	13·2 (12·7–13·7)	24·4 (16·0–32·8)
Anxiety disorder	11·2 (10·8–11·7)	22·8 (14·8–30·9)
Mood disorder, anxiety disorder, or dysthymia	19·6 (19·0–20·2)	34·2 (25·0–43·3)
Panic disorder or agoraphobia	3·6 (3·3–3·9)	6·6 (2·9–10·3)
Suicidal ideation	13·3 (12·8–13·8)	25·0 (17·4–32·5)
Any mental health disorder	20·7 (19·5–20·7)	35·5 (25·9–44·0)

Figures quoted as prevalence (95% CI). Patients without epilepsy (n=36727); patients with epilepsy (n=253). Adapted with permission from Blackwell Publishing.[14]

Table: Lifetime prevalence of psychiatric comorbidity in patients with epilepsy compared with the general population

Tellez-Zenteno et al, Epilepsia 2007

Genetics, Epilepsy & Comorbidities



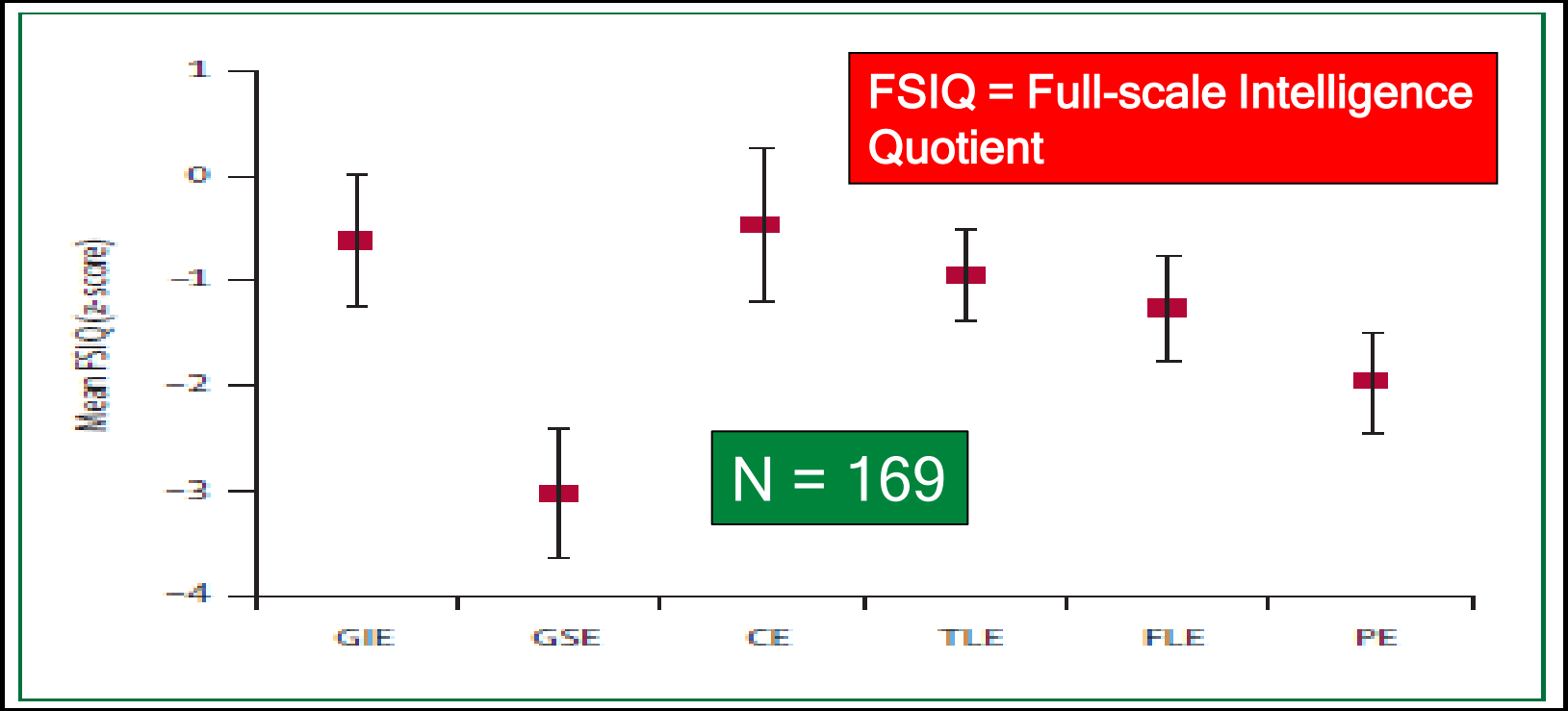
Keezer et al, Lancet Neurol 2016; 15: 106

Studies in Untreated Newly Diagnosed Epilepsy

Author, yr	Epilepsy type	N	Pre-treatm impairm
Kalviainen, 1992	Cryptogenic	74	26-39%
Helmstaedter, 1993	Symptomatic & Idiopathic	16	3/10 measures
Aika, 1995	Cryptogenic	56	14-75%
Prevey, 1998	Symptomatic	201	17/18 measures
Ogunrin, 2000	Focal or generalized	60	7/8 measures
Pulliainen, 2000	Focal or generalized	52	5/20 measures
Aika, 2001	Left temporal lobe	39	44-92%
Wesnes, 2009	Focal or generalized	570	Present (NS)
Taylor, 2010	Non-lesional foc/gen	155	1-18% (6/14 measures)
Witt, 2012	Sympt/Crypt/Idiop	247	48-49%
Witt, 2014	Sympt/Crypt	257	58%

Witt, 2015

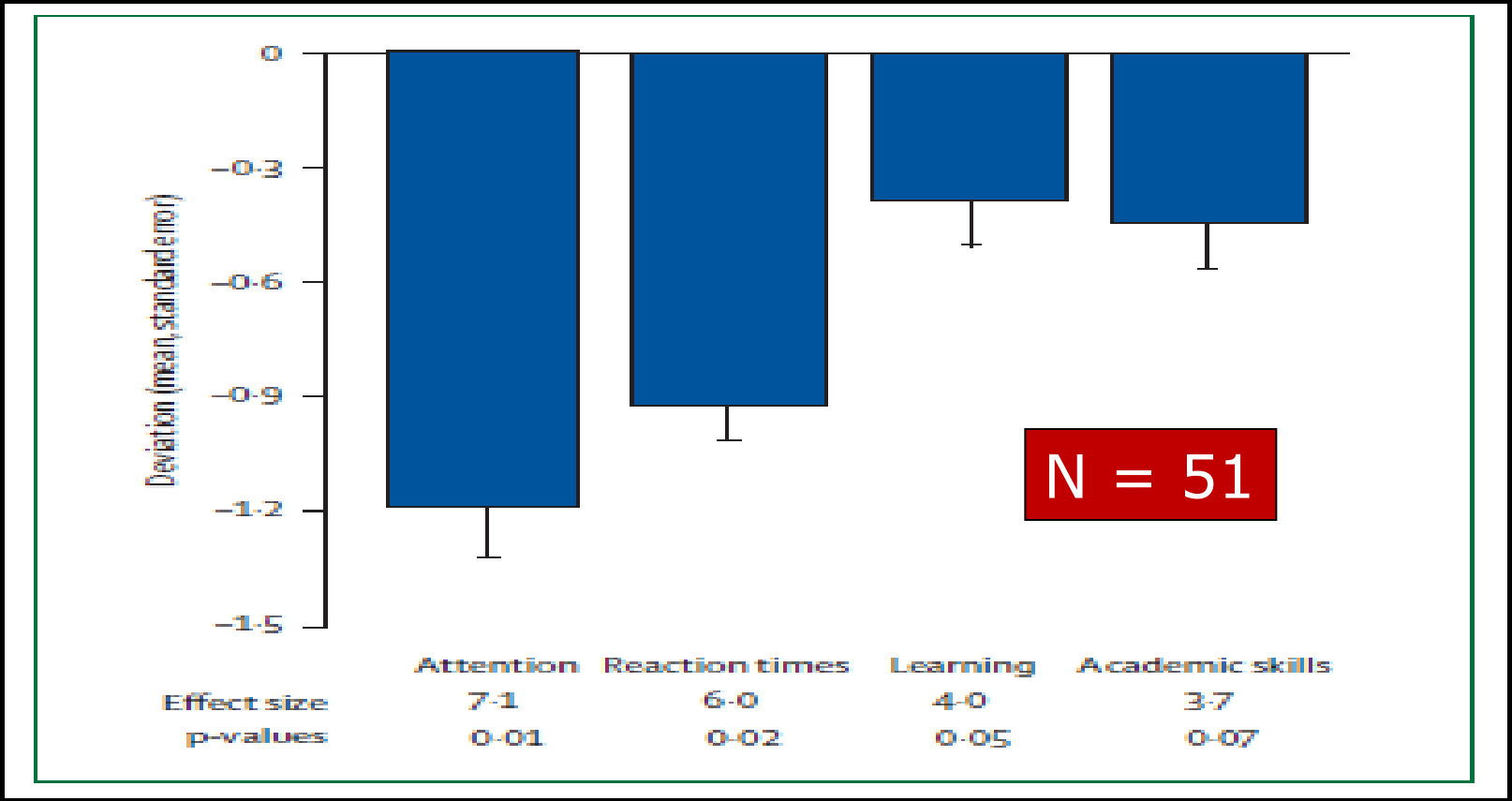
Intelligence Across Epilepsy Syndromes



GIE = General Idiop Epil; GSE = General Sympt Epil; CE = Central Epil
TLE = Temp Lobe Epil
FLE = Front Lobe Epil
PE = Non-loc Part Epil

Nolan et al, Epilepsy Res 2003; 53:139

Adjusted Cognitive Performance in Children with Newly Diagnosed Epilepsy



Oostrom et al, Pediatrics 2003; 112: 1338

Epidemiological Evidence for a Causal Relationship - I

- **Strength**: The larger the association, the more likely that it is causal.
- **Consistency**: Consistent findings are observed by different persons in different places with different samples.
- **Specificity**: The more specific an association, the bigger the probability of a causal relationship.
- **Temporality**: The effect has to occur after the cause.

Sir Austin Bradford Hill, 1965

Epidemiological Evidence for a Causal Relationship - II

- **Biological gradient**: Greater exposure should generally lead to greater incidence of the effect.
- **Plausibility**: Plausible mechanism between cause and effect.
- **Coherence**: Coherence between epidemiological and laboratory findings increases the likelihood of an effect.
- **Experiment**: "Occasionally it is possible to appeal to experimental evidence".
- **Analogy**: The effect of similar factors may be considered

Sir Austin Bradford Hill, 1965

Factors Affecting Cognition in Epilepsy

- Genetic background
- Abnormalities of brain structure
- Early developmental history
- Presence of comorbidities
- Age at seizure onset
- Disease severity and treatment

Problems Related to the Present Knowledge on Epilepsy & Cognition

- Cognitive phenotype has a multifactorial origin
- The role of genetic factors is still ill-defined
- The new classifications of seizures and epilepsies are not modeled to shape cognition
- Available neurocognitive tests are defective for epidemiological purposes

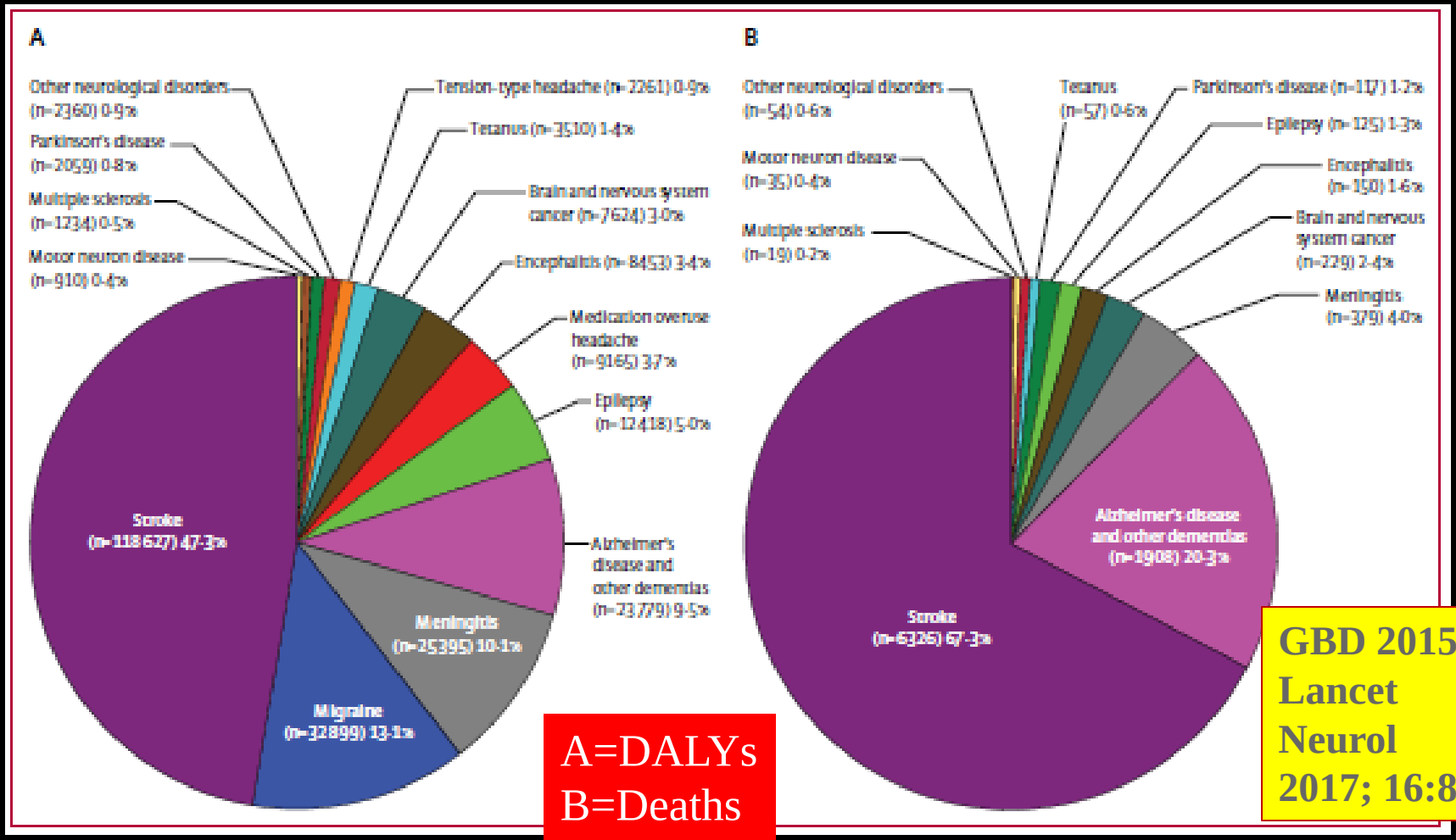
Conclusions

- The burden of epilepsy is increasing due to growth and aging of the world population
- Static & dynamic cognitive impairment are frequent occurrences in people with epilepsy
- Several genetic and environmental factors affect cognition in epilepsy
- The association between epilepsy and cognitive impairment is bidirectional

Future Directions

- Identification of new phenotypes based on cognition and behavior
- Selection of the most appropriate neuropsychological measures
- Assessment of a complete neuropsychological profile of the main epilepsy syndromes
- Identification of neuropsychological markers of epilepsy and its complications

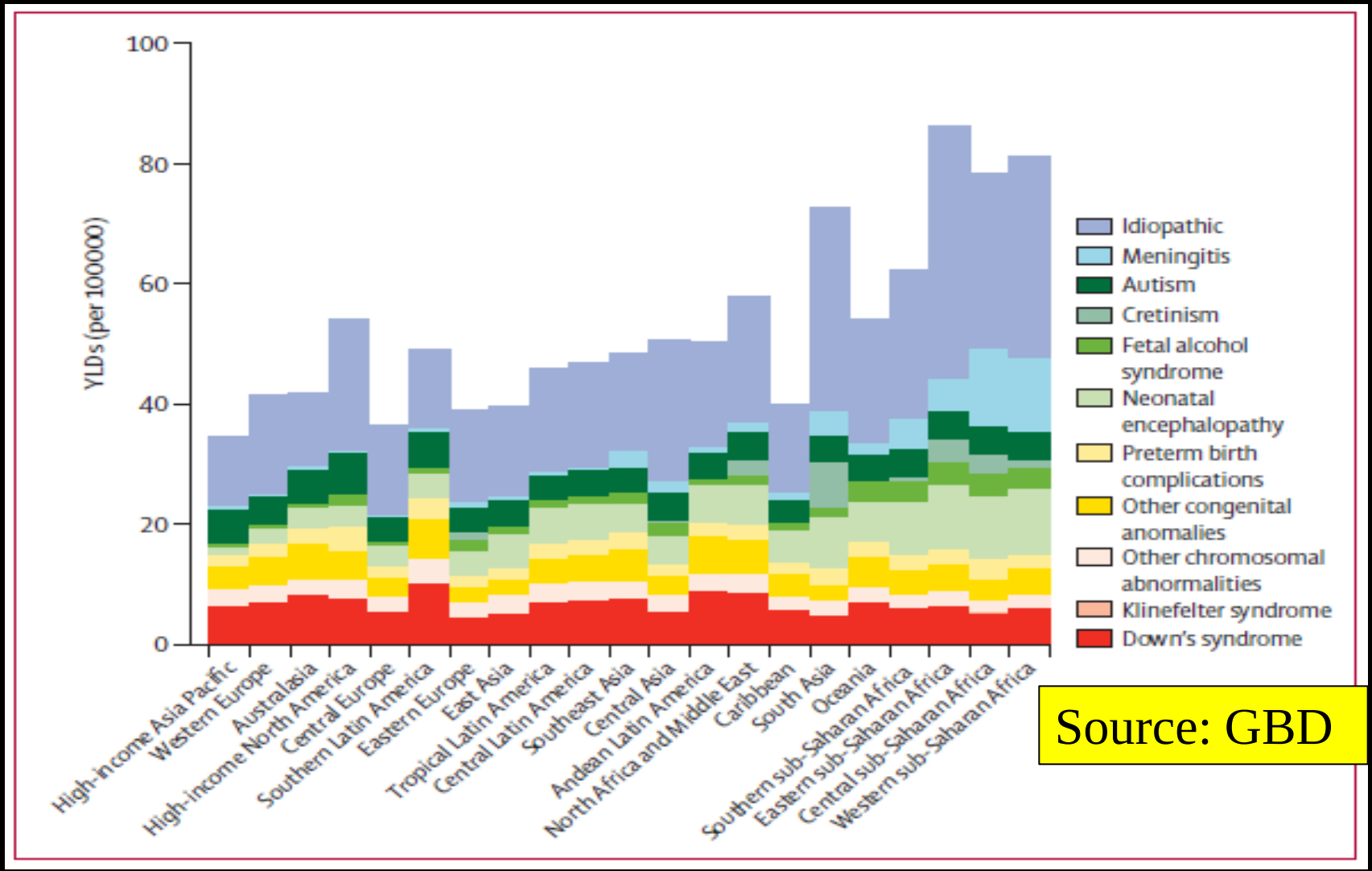
Overall Burden from Neurological Disorders 2015



A=DALYs
B=Deaths

GBD 2015 Lancet Neurol 2017; 16:877

YLDs for Intellectual Disabilities by Cause



Source: GBD

Risk Factor (Definition)

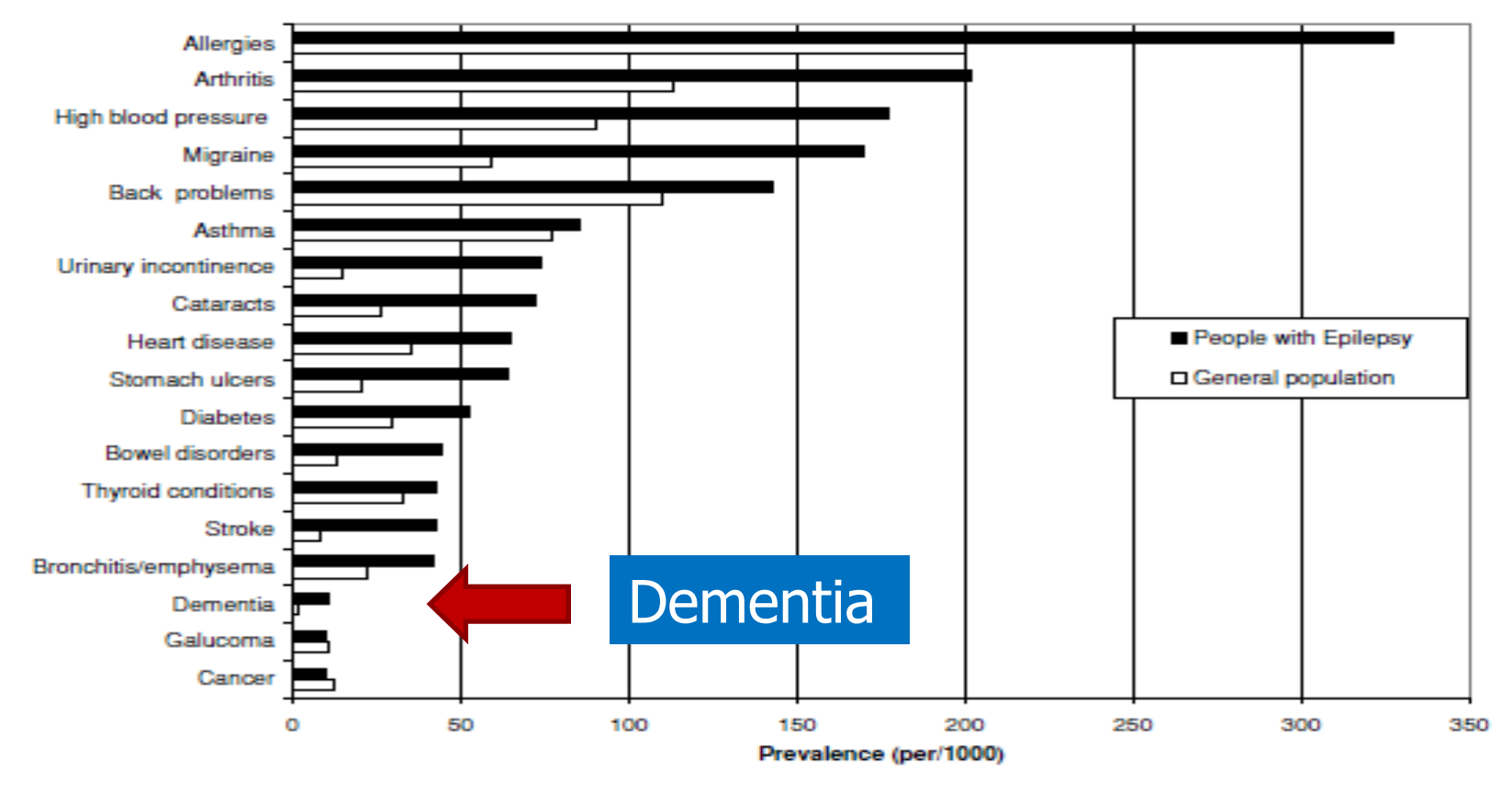
- A risk factor is something that increases risk or susceptibility (Webster Medical Dictionary)
- A risk factor is any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease (WHO)
- Risk factors or determinants are correlational and not necessarily causal, because correlation does not prove causation (Wikipedia)

Prevalence of Somatic Conditions in People With and Without Epilepsy

Comorbidity	Prevalence ratio	% in Epilepsy vs. general population
Any dementia	4.35-6-3	15.7 vs. 2.4; 9.4 vs. 2.2
Alzheimer disease	8.05	-
Parkinson disease	3.2	-
Migraine	1.4-2.6	-
Chronic fatigue	4.1	-
All stroke	3.9-7.0	-
Hemorrhagic stroke	10.6	
Ischemic stroke	7.5	
TIA	4.9	-

Gaitatzis et al, Epilepsia 2012: 53: 1282

Prevalence of Somatic Conditions in People With and Without Epilepsy



Tellez-Zenteno et al, Epilepsia 2005; 46: 1955

Chance & Artifactual Comorbidities

- **Chance**: A circumstance in which prevalence or incidence of a condition is as frequent in epilepsy as in the general population
- **Artifactual**: A circumstance in which the association can be explained by selection or information bias

Examples of Mechanisms of Association

- **Causative**: CNS tumors, stroke, traumatic brain injury, neurodegenerative disorders, arrhythmias (antiepileptic drugs)
- **Shared risk factors**: Vascular (heart disease), cortical hyperexcitability (migraine), GAD antibodies (diabetes), environmental & living conditions (asthma)

Epilepsy & Somatic Comorbidity