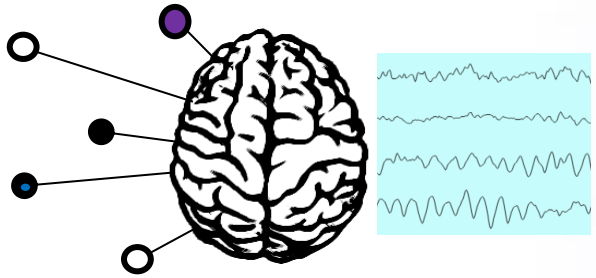
Late-onset epilepsy

Emily L. Johnson, MD MPH



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Disclosure

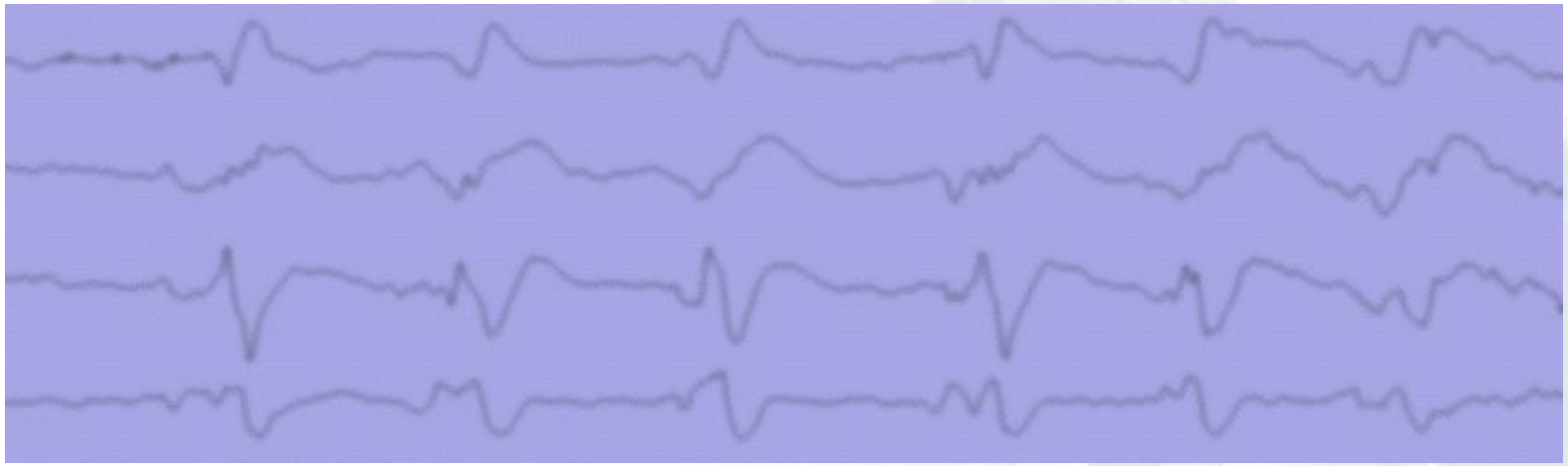
- Nothing to Disclose

Learning Objectives

- Discuss the Epidemiology of late-onset epilepsy.
- Describe the causes of cognitive changes due to epilepsy.
- List current treatments used for epilepsy.

Outline

- Epidemiology
- Causes
- Outcomes
- Work in progress



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Epilepsy

- Recurrent, unprovoked seizures
- Starts in childhood
- Likely grow out of it
- Usually genetic

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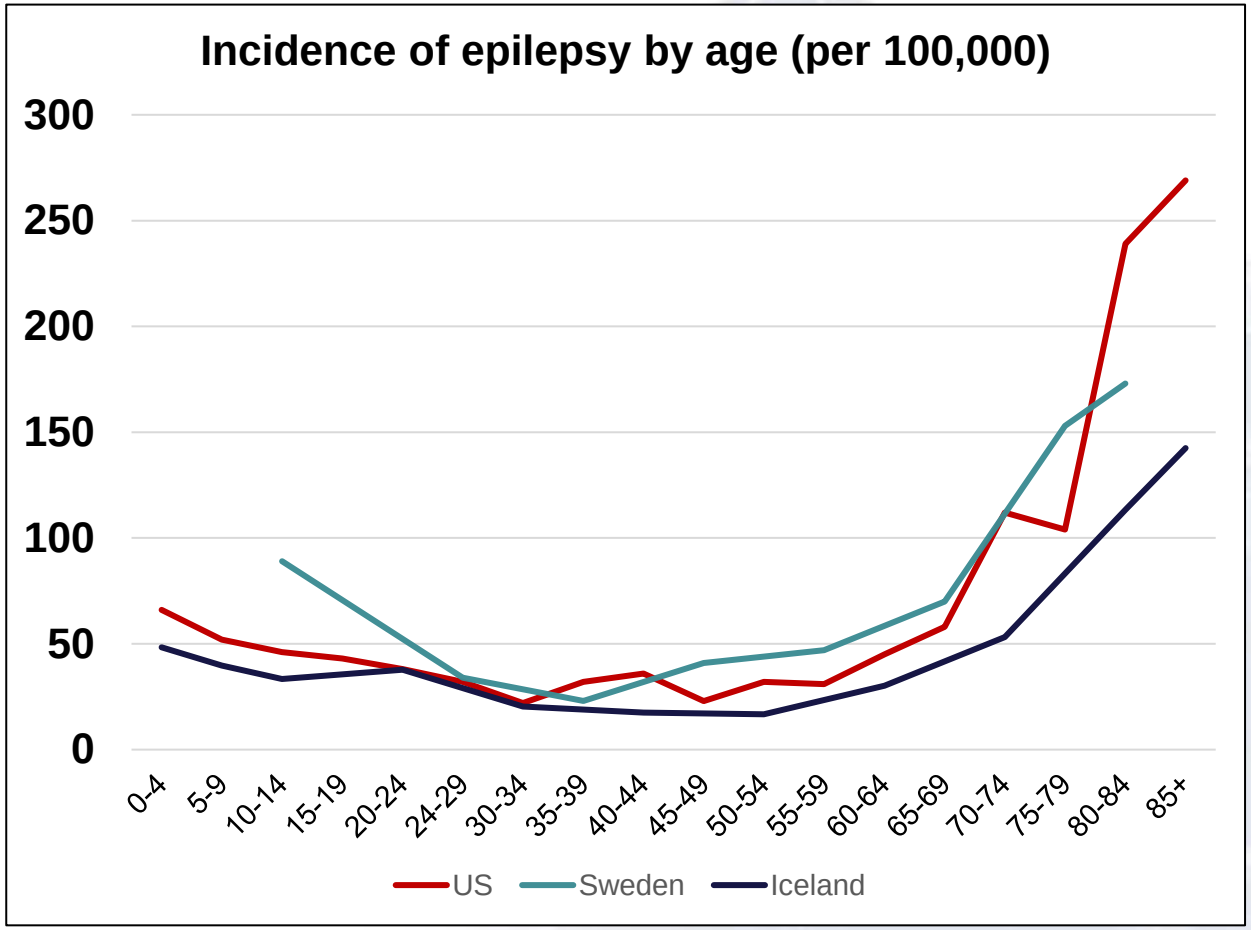
Epidemiology of late-onset epilepsy

Incident epilepsy:

- Bimodal distribution

- ~227,154 new cases annually in ≥65 population in US (393/100,000)



Adapted from Cloyd 2006 Warner 2024

“WHY DO I HAVE SEIZURES?”

I never had seizures as a child!

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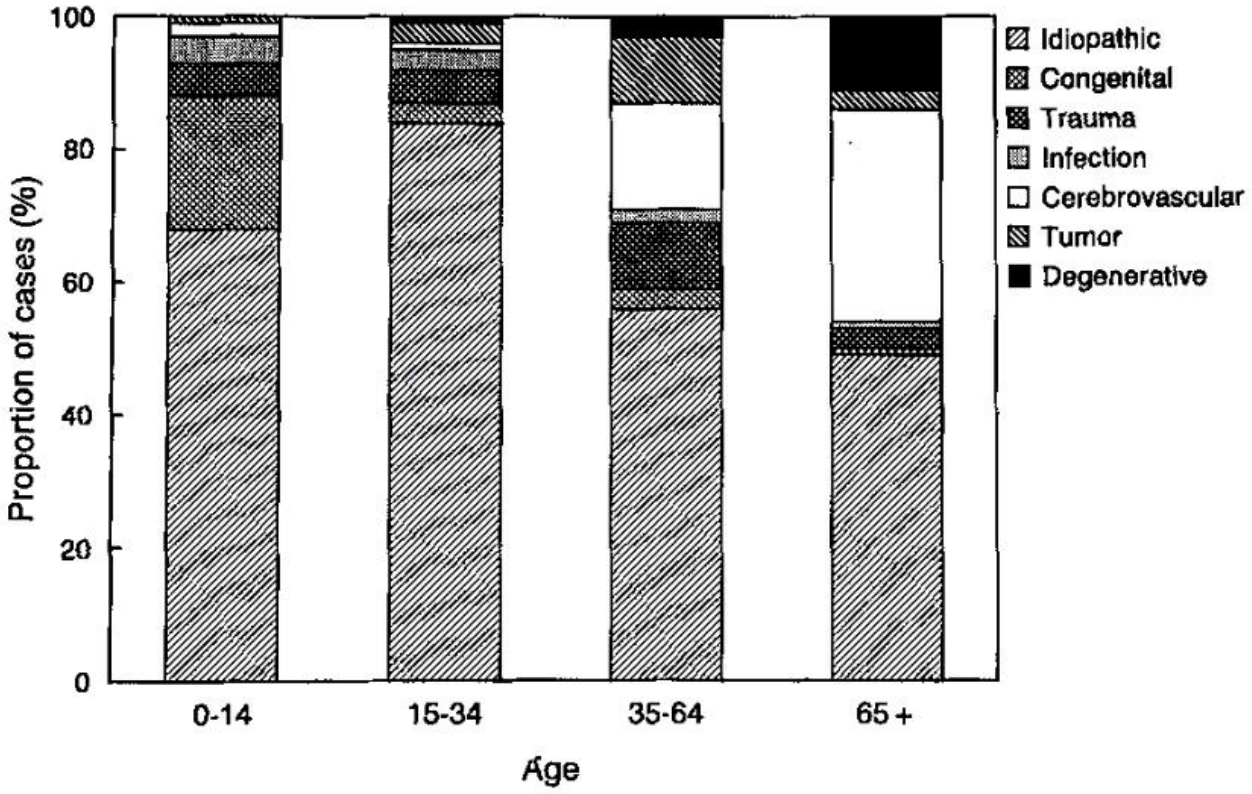
Causes of epilepsy throughout life: Rochester Epidemiology Project



All cases of incident epilepsy in Rochester, MN 1935-1984

≥ 65: 50% unknown
Cerebrovascular
Degenerative

Hauser et al, Epilepsia 1993

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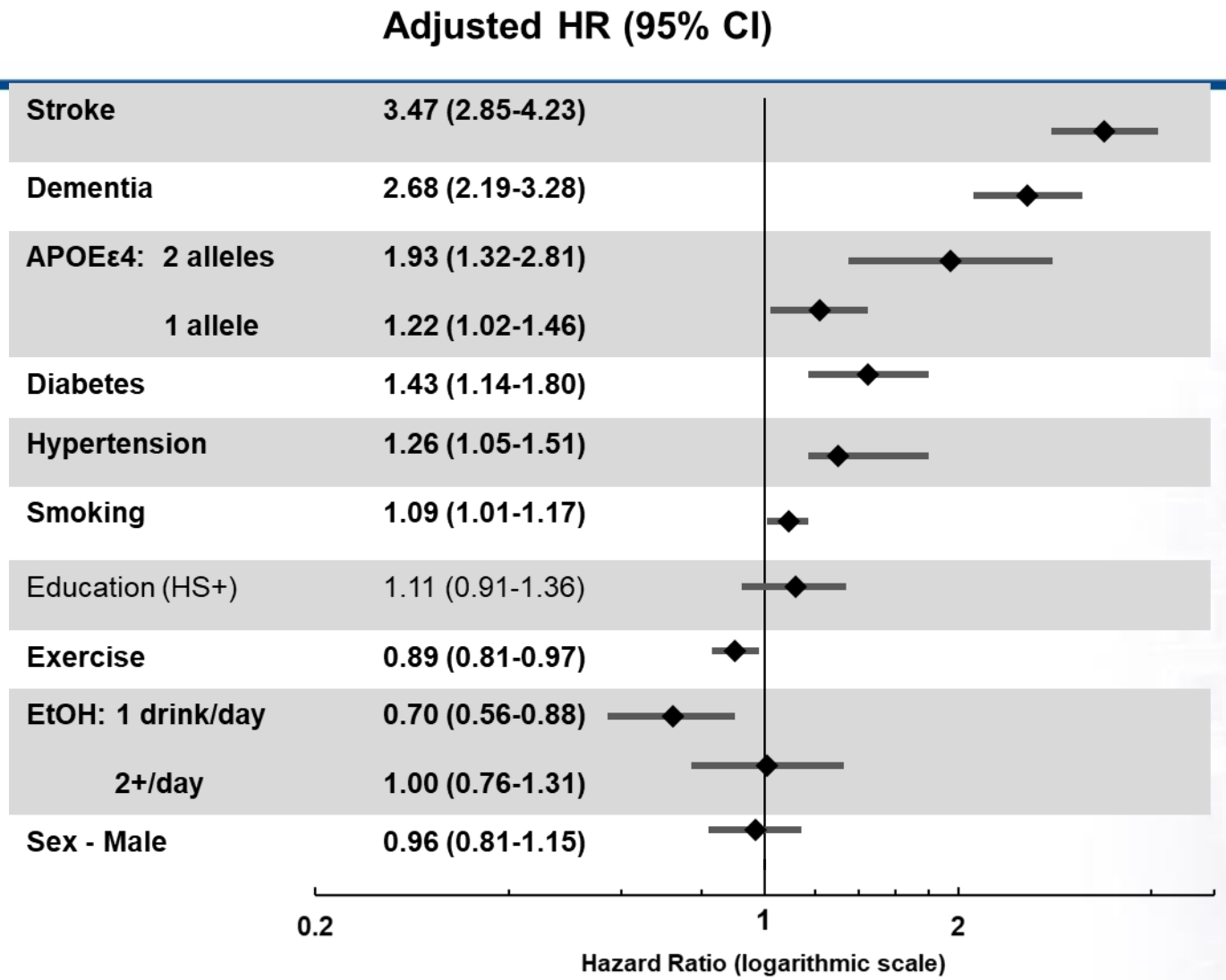
Midlife risk factors for LOE

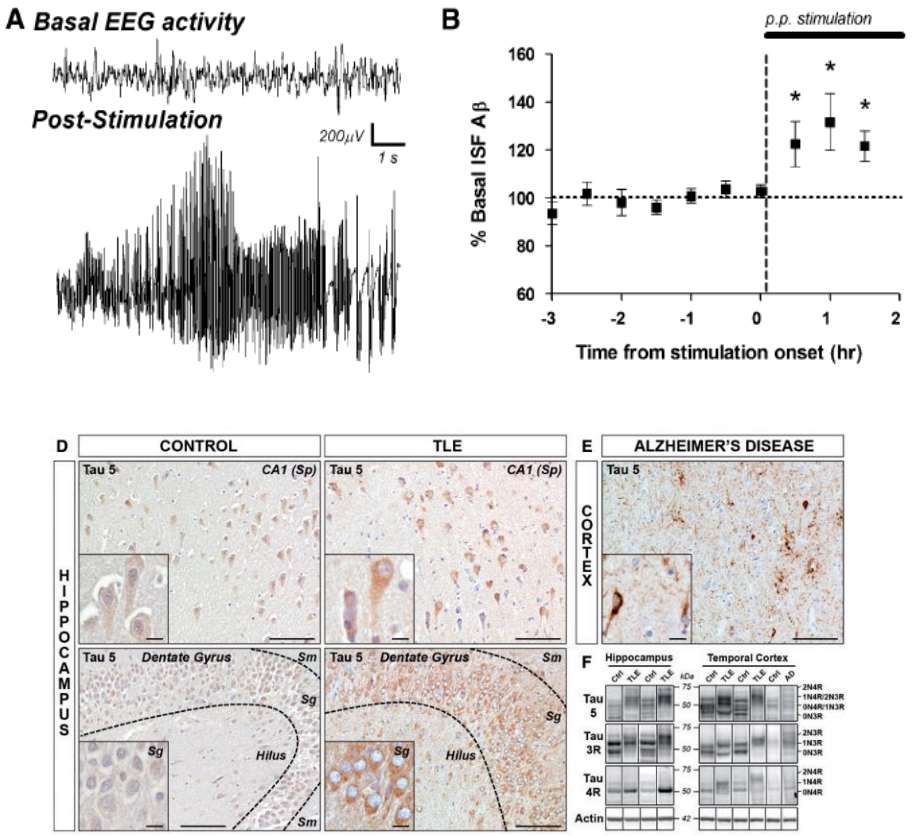


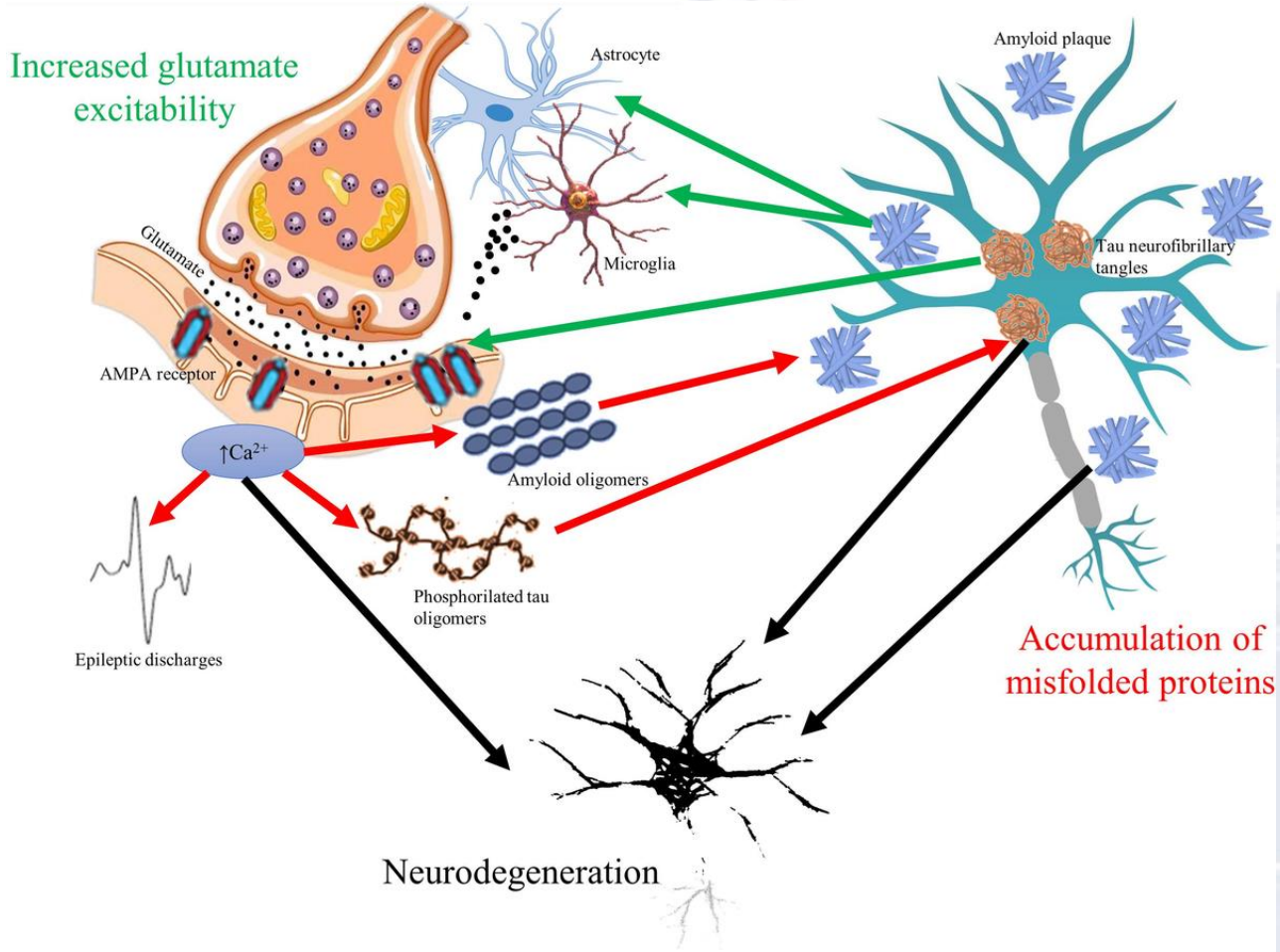
All risk factors included in same model; adjusted for center-race and age

16,792 participants
4 sites
30+ years

Johnson et al, JAMA Neurology 2018

Bidirectional relationship with amyloid, tau





Hovarth 2020

Gourmaud et al, Brain 2020

Cirrito 2005 Neuron

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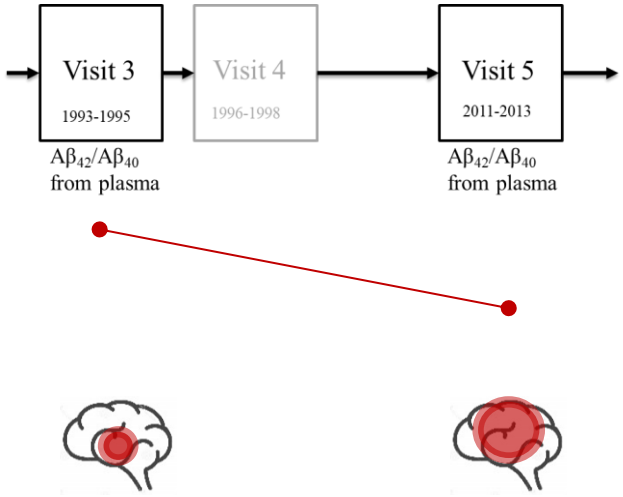
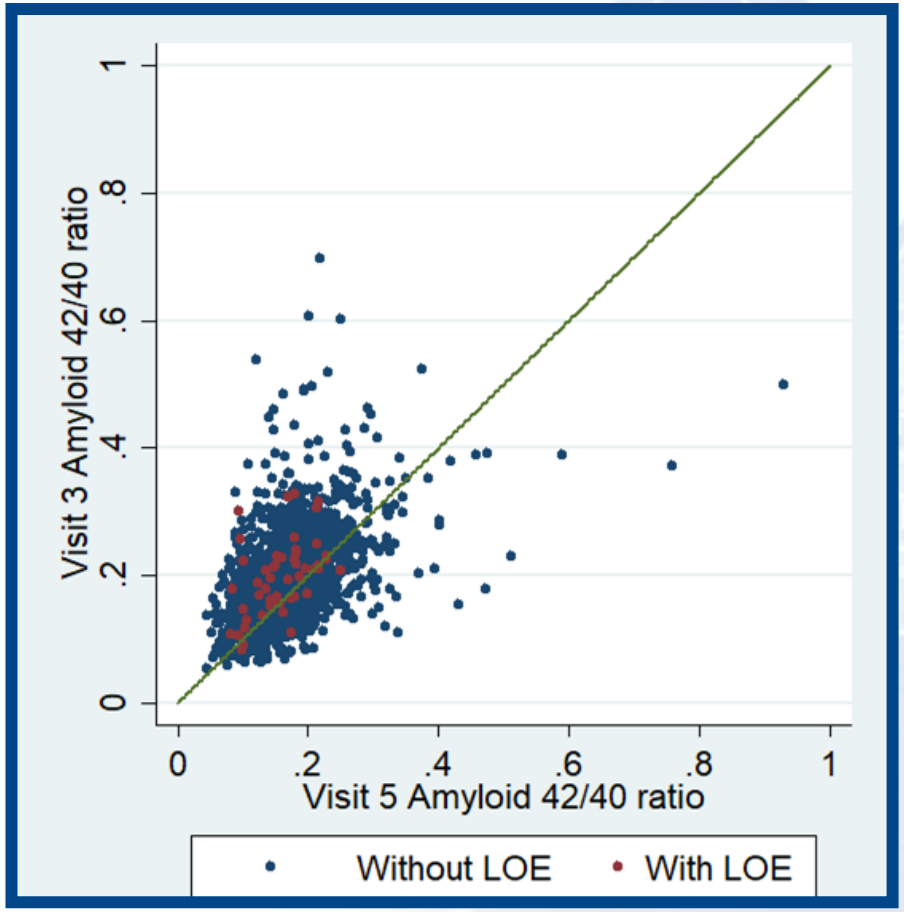
Plasma Aβ and LOE

- Greater decrease in $A\beta_{42}/A\beta_{40}$ ratio is associated with LOE





Johnson et al, Neurology 2023

Cohort Harmonization

- ARIC, CHS, MESA, NOMAS, and WHICAP cohorts
  - 28,291 participants (294,575 years of follow up)
  - 998 cases of LOE (3.4 per 1000 person-years)
  - Age, smoking, HTN, DM, CKD, stroke, heart disease, APOE4 alleles associated with LOE

ARIC CHS MESA NOMAS

Choi et al, under review

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“EPILEPSY IS JUST SEIZURES, RIGHT?”

Why is Mom or Dad forgetful – is it the Keppra?

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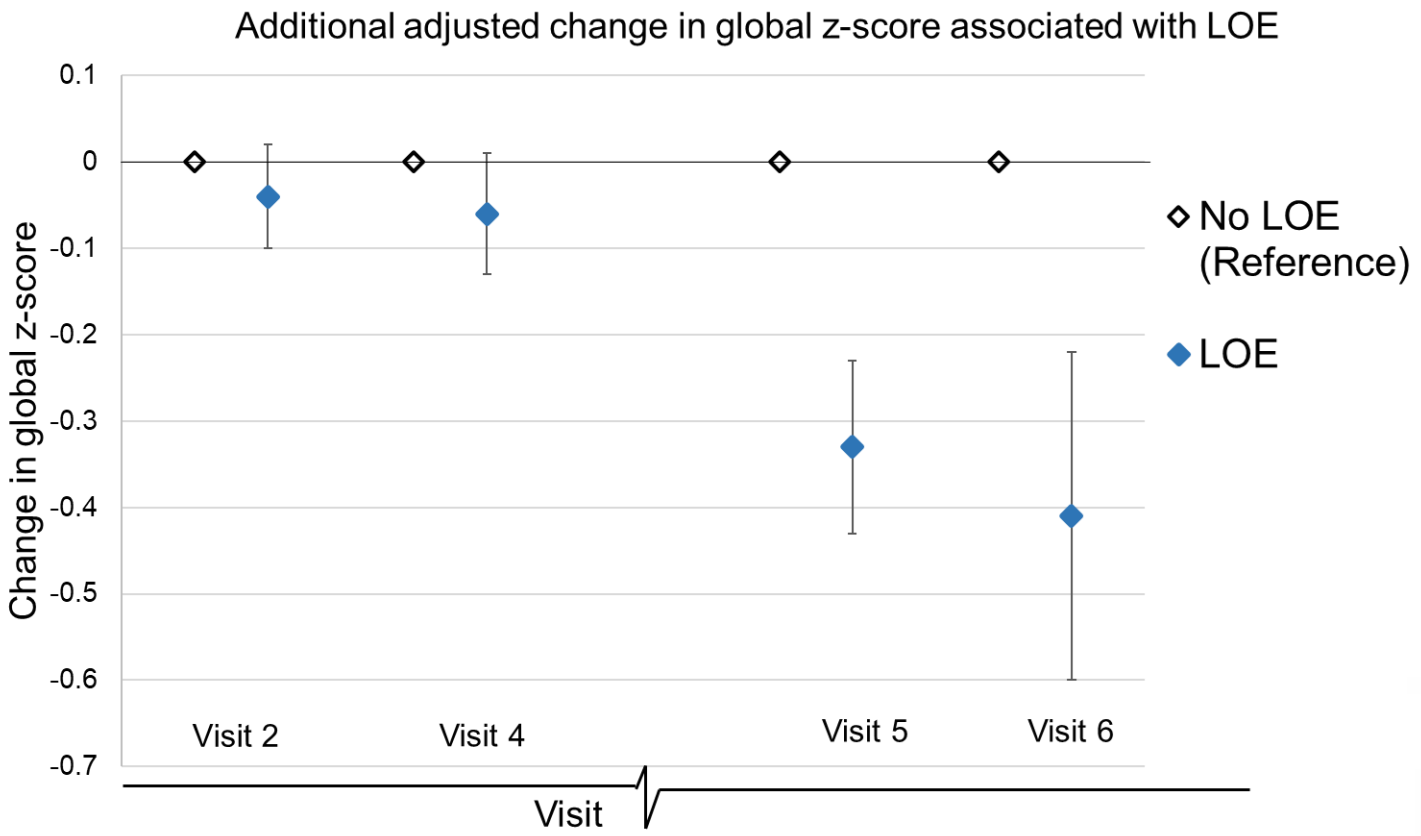
25-year cognitive change in persons with LOE



- Comparable to additional 6.5 year age-difference at baseline
- Change with diabetes: -0.19 z-score= over 25 years

Johnson et al, Epilepsia 2020

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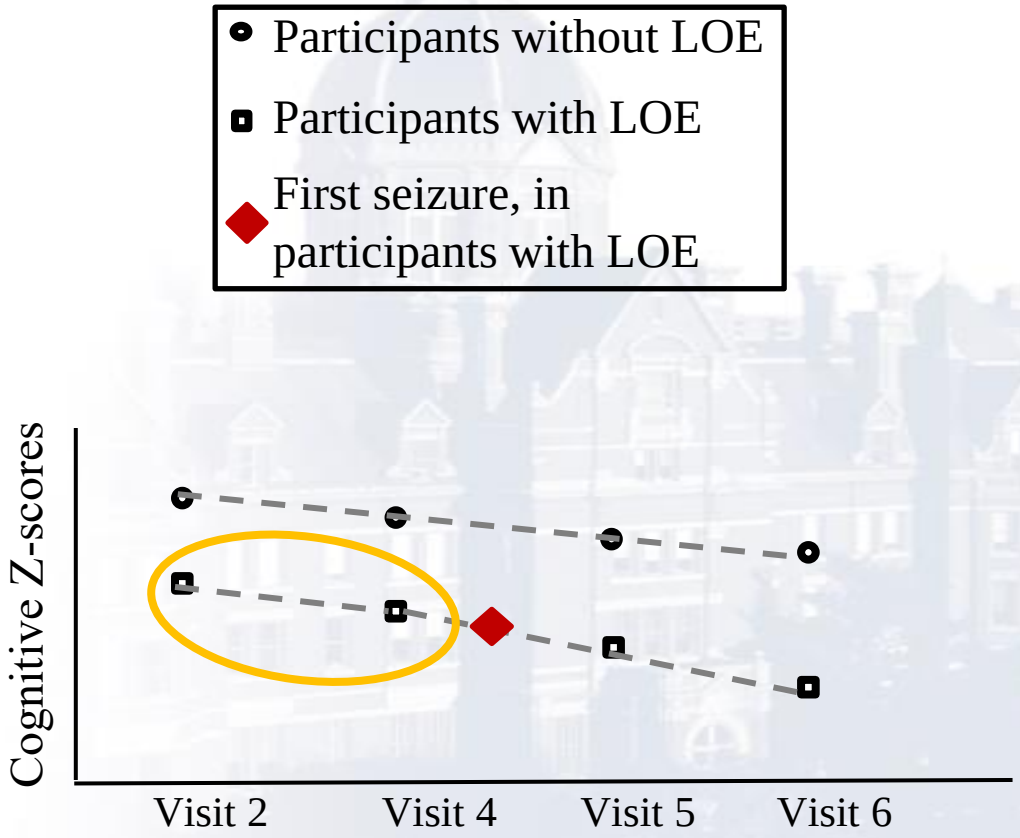
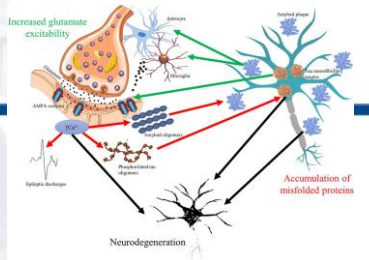
25-year change in cognition

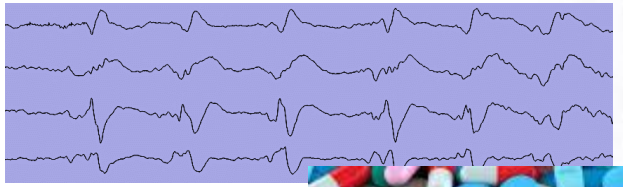
	No LOE	LOE (prior to first seizure only)	95% CI
Global z score	0 (Reference)	**-0.38**	**(-0.62, -0.14)**
DWRT z score	0 (Reference)	**-0.67**	**(-0.98, -0.35)**
DSST z score	0 (Reference)	**-0.19**	**(-0.28, -0.00)**
WFT z score	0 (Reference)	-0.03	(-0.28, 0.21)
DWRT raw score	0 (Reference)	**-1.02**	**(-1.49, -0.54)**
DSST raw score	0 (Reference)	**-2.74**	**(-5.42, -0.06)**
WFT raw score	0 (Reference)	-0.41	(-3.50, 2.67)



Johnson et al, Epilepsia 2020



WHAT CAUSES COGNITIVE DECLINE?



Seizures/epileptiform activity

Medications

Neurodegenerative pathology

ELUCID study: Epilepsy of Late-onset Unknown etiology as a risk factor for Cognitive Impairment and Dementia

CLUE | CONSORTIUM FOR LATE-ONSET UNEXPLAINED EPILEPSY

Alice Lam
Brandon Westover
Rani Sarkis
Leah Blank
Tyler Gaston
Rodrigo Zepeda
Mo Shafi

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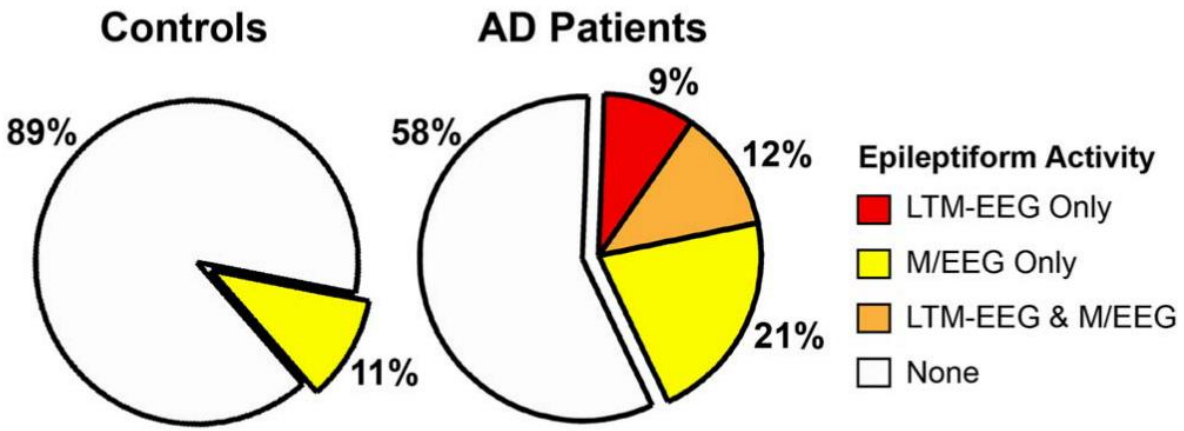
Known dementia and subclinical epileptiform activity

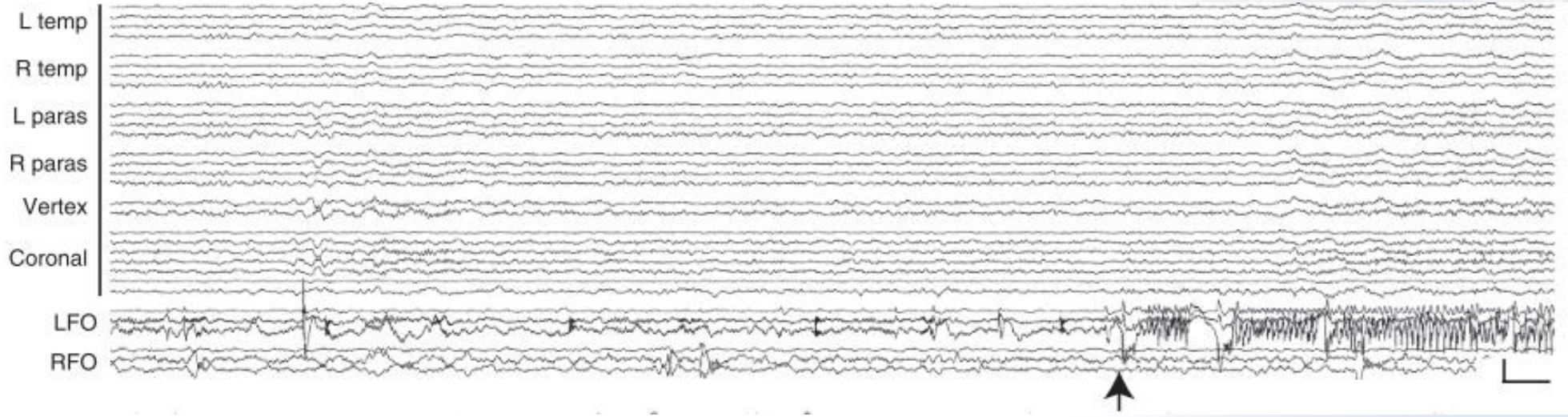
- 42.4% (14/33) patients with AD (without known epilepsy) had subclinical epileptiform activity, compared to 10.5% of cognitively normal controls
- AD Patients with SEA had faster cognitive decline over time than those without SEA



Vossel et al, Ann Neurol 2016

Epileptiform activity in AD may go undetected

- 2 patients with AD and fluctuating cognition monitored with scalp and FO electrodes
- Hippocampal seizures detected on FO were not detected on scalp



Lam et al, Nature Medicine 2016

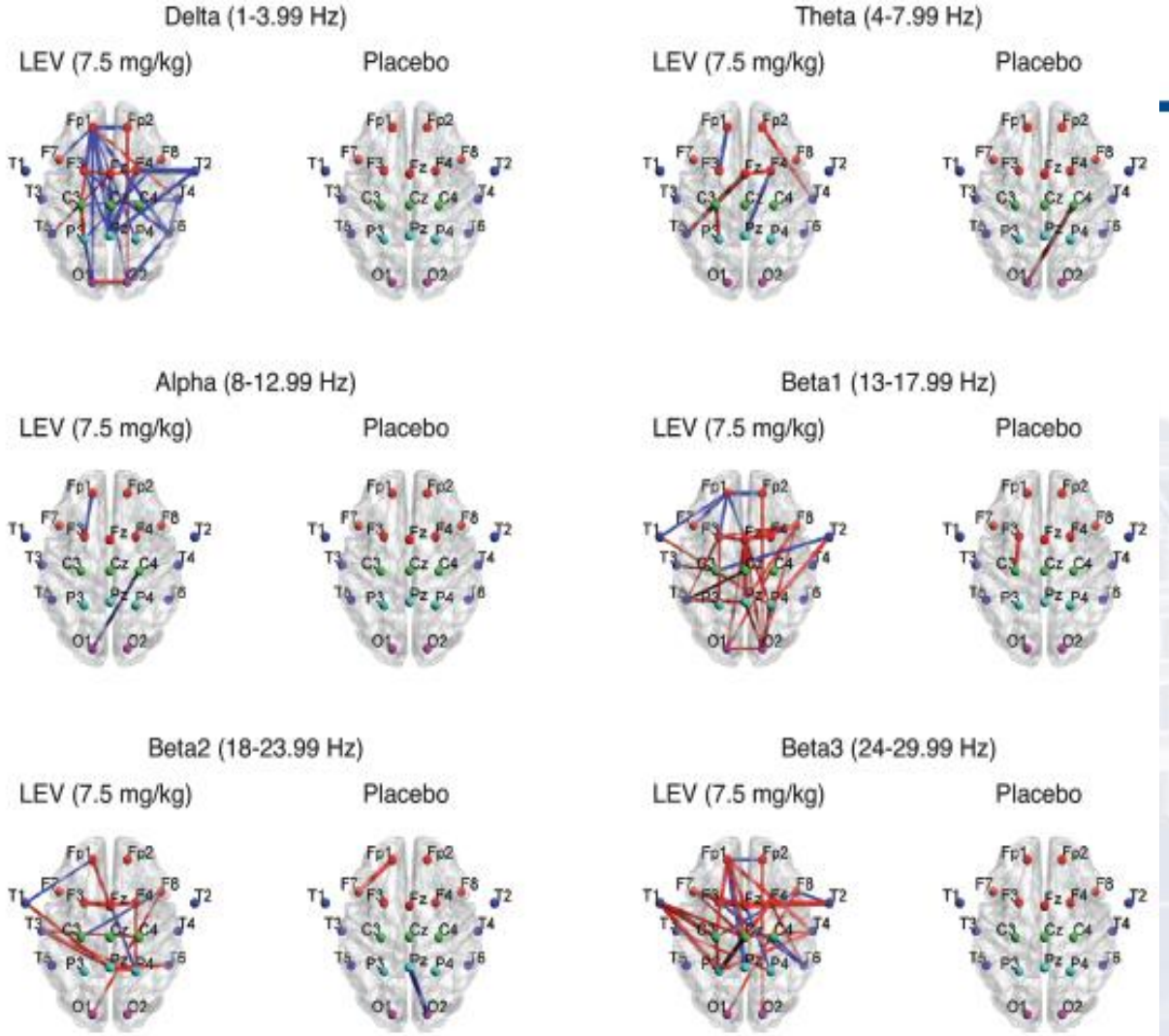
Treating AD with ASDs?

- 17 patients with aMCI and hippocampal hyperactivity on fMRI given LEV 125mg BID (+ control group of 17)
- Memory errors and hippocampal hyperactivation reduced

Bakker et al, Neuron 2012; Bakker et al, Neuroimage Clin 2015

Treating AD with ASDs?

- May “normalize” EEG connectivity
- Clinical trials of low-dose LEV in MCI, AD ongoing



Museaus et al, J Alz Dis 2017

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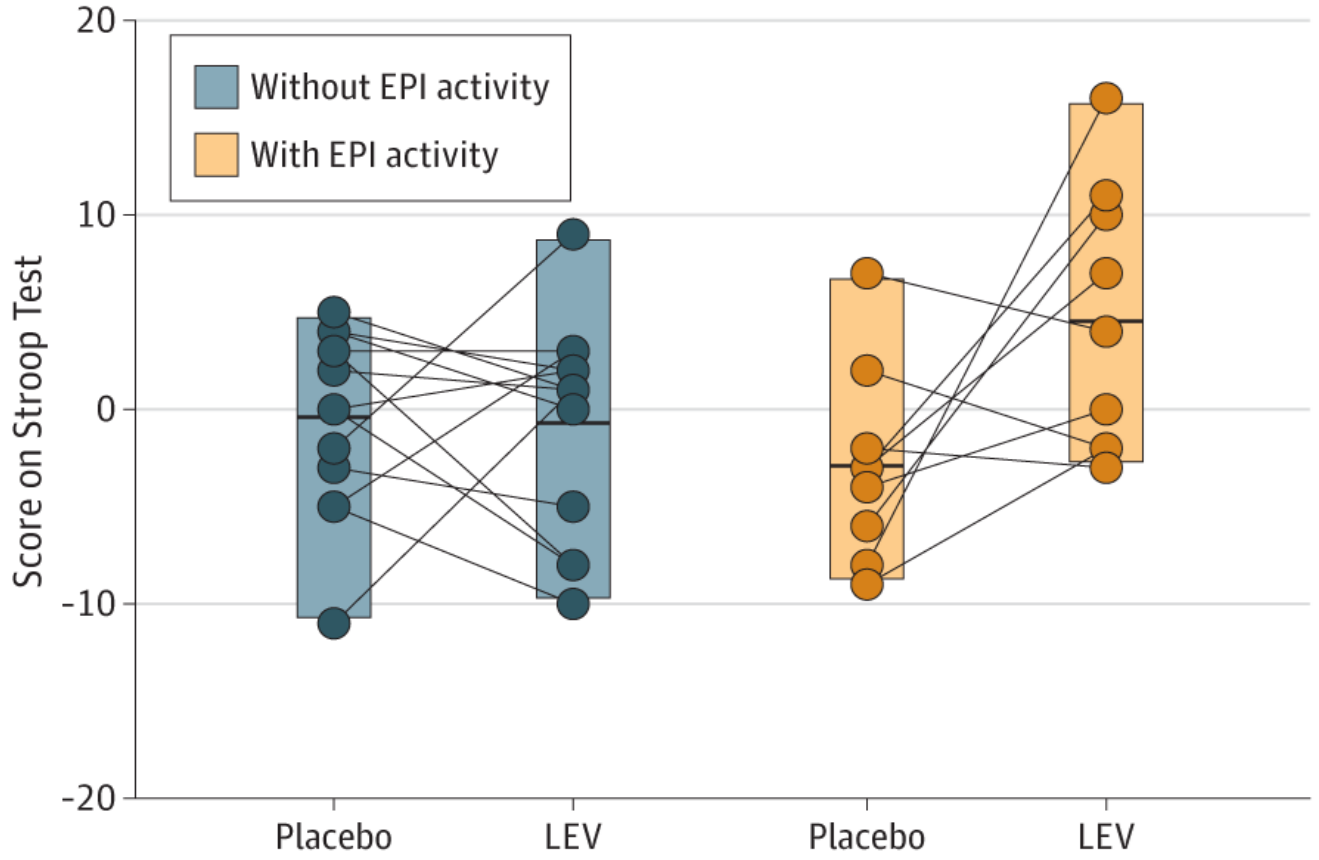
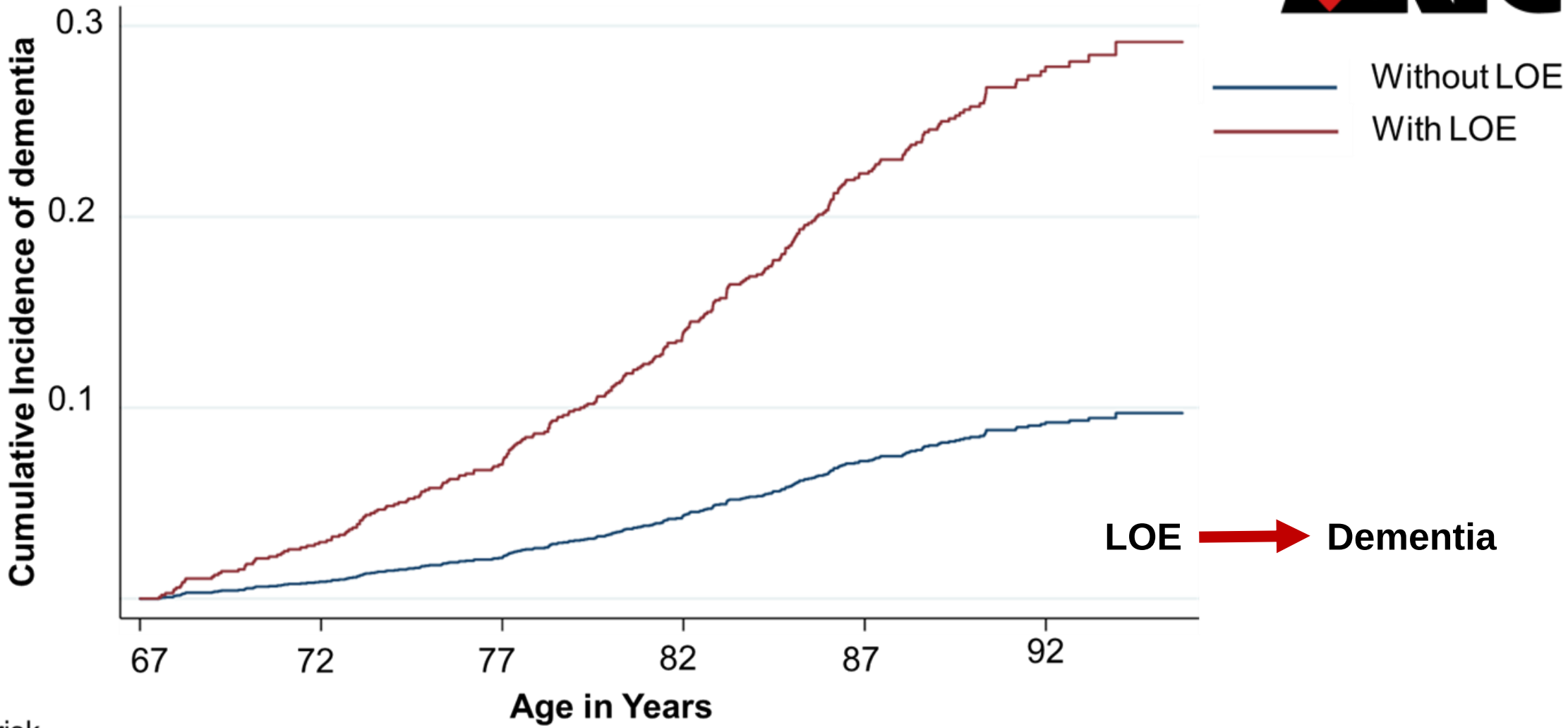
Treating AD with ASDs?

- Treatment with low-dose LEV improved executive function (only in those with epileptiform activity)



Vossel et al, JAMA Neurology 2021

Cumulative Incidence of Dementia in ARIC Participants with and without Late-onset Epilepsy (LOE)



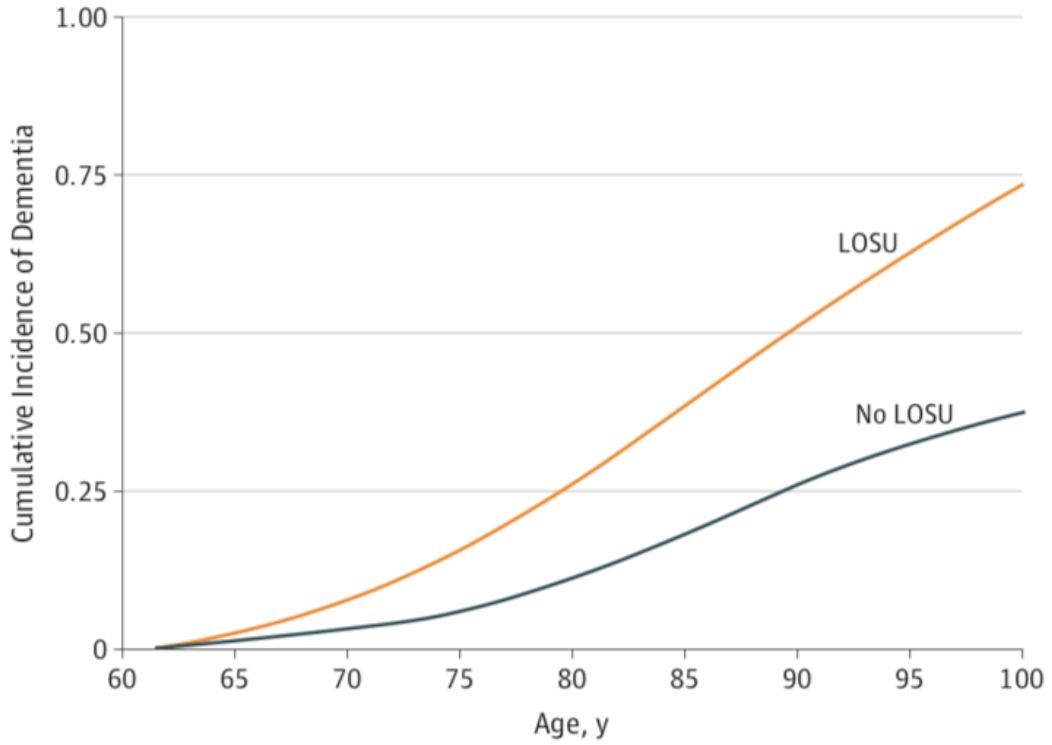
LOE → Dementia

Number at risk						
Without LOE	8362	7536	5369	2903	1121	296
With LOE	671	611	451	239	86	14

Johnson et al, Neurology 2020

LOE and Dementia: Veterans' study

Figure 2. Cumulative Incidence of Dementia Adjusted for Demographic Characteristics and Comorbid Conditions in Patients With and Without Late-Onset Unprovoked Seizures of Unknown Etiology (LOSU)



Adjusted cumulative incidence of dementia is shown for veterans with and without LOSU at baseline accounting for the competing risk of mortality. Age is used as the time scale to indicate age at dementia diagnosis. Models were adjusted for demographic variables, cardiovascular risk factors, depression, and traumatic brain injury.

HR: **1.95** (95% CI 1.67-2.27)

LOE → **Dementia**

Keret et al, JAMA Neurology 2020

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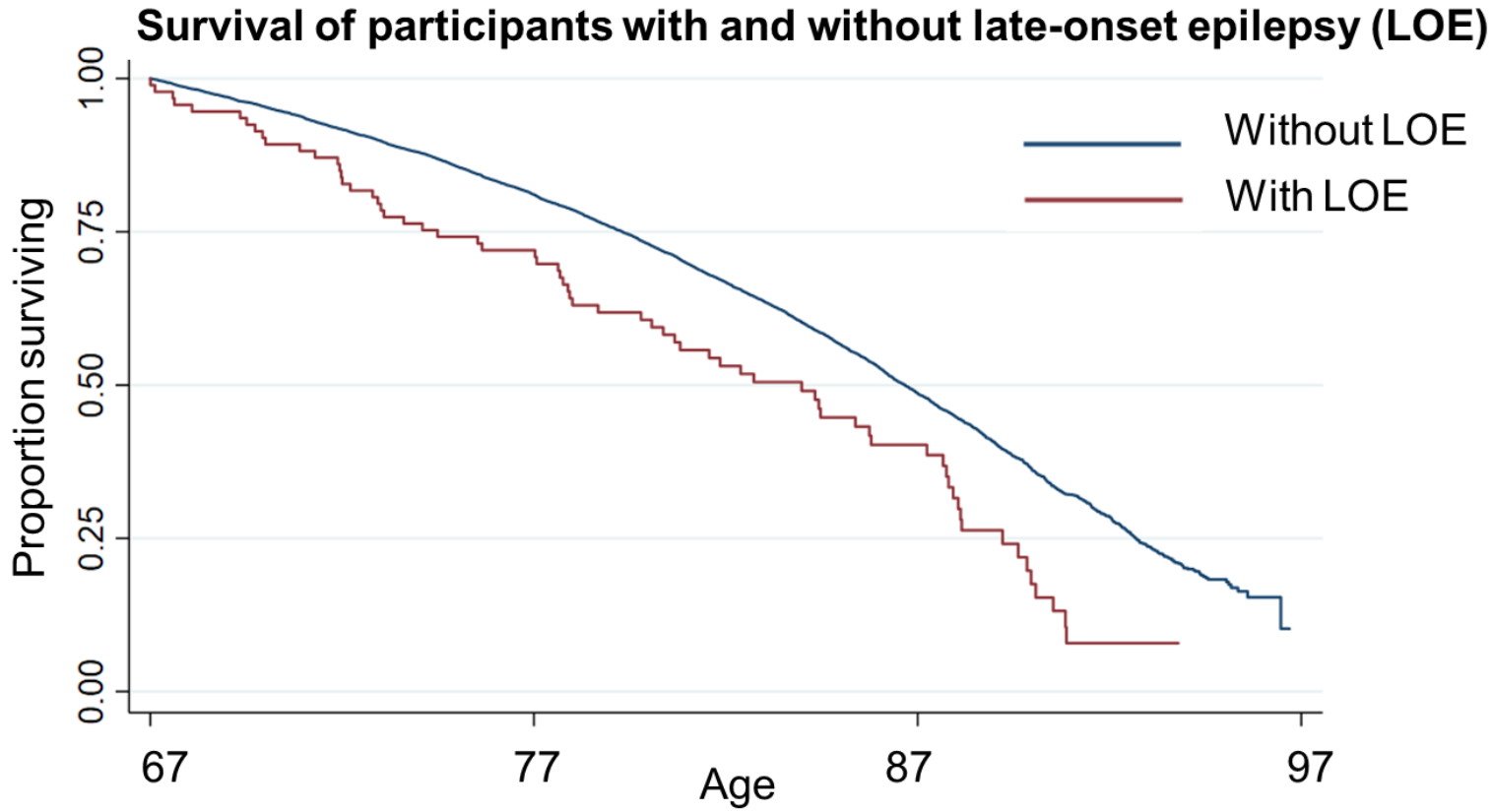
Mortality in LOE



Johnson et al, Neurology 2021

TREATING LOE

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Evaluation

- EEG
- MRI / *MRA?*
- Risk factor screening
  - Similar to TIA
- Cognitive screening
- OSA screening?
- Counselling

Medical treatment

- Special considerations:
  - Pharmacokinetics; renal, hepatic dysfunction
  - Susceptibility to adverse effects
  - Interactions with other medications
  - Cost

Kirmani et al, Curr Treat Op Neurol 2014

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Medical treatment

- 5 RCT of monotherapy in LOE
- Pairwise comparisons of lacosamide, lamotrigine, levetiracetam, valproic acid, and carbamazepine from RCT show no differences in efficacy
- Carbamazepine (IR and ER) had higher risk of discontinuation due to adverse effects
- Highest chance of seizure-freedom at 12 months: levetiracetam, lamotrigine, lacosamide

Lattanzi et al, Epilepsia 2019

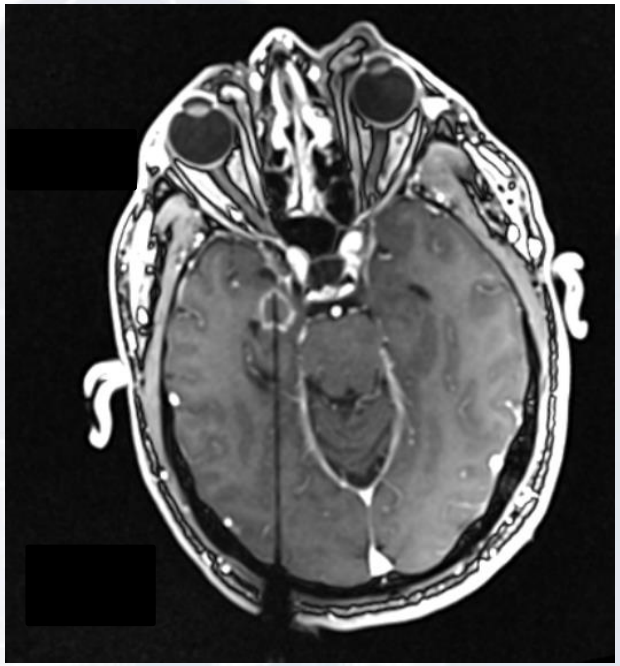
Surgery?

- Older patients less likely to undergo surgery
- Early studies: older patients less likely to be seizure-free; higher risk of complications
- Recent studies: no difference in outcomes (carefully selected older patients)

Sirven et al, Neurol 2000
Srikijvilaikul et al, Seizure 2011
Anderson et al, Epi Res 2013
Bialik et al, Seizure 2014
Punia et al, Epi Behav 2017

Surgery?

- Laser ablation = less invasive, may be option for those not otherwise considered surgical candidates; similar seizure control to younger patients



Waseem et al, Epi Behav 2015

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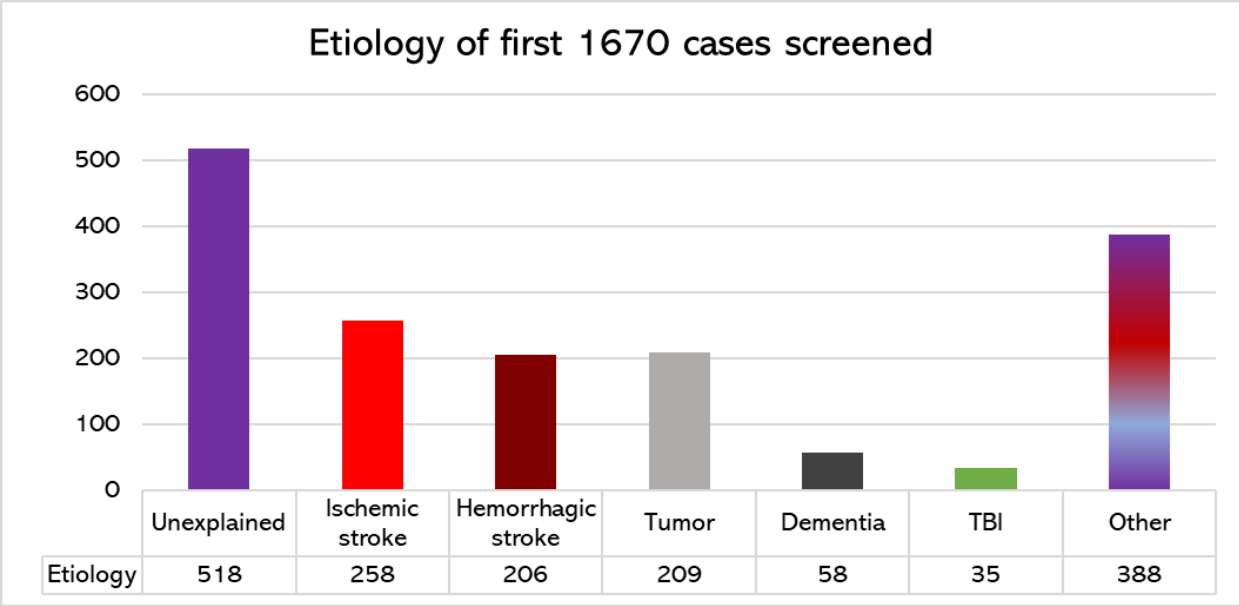
Dietary treatment?

- Ketogenic and Modified Atkins diets are effective in children, adolescents, adults
  - Adults up to age 86 in studies
- Cardiovascular outcomes
- Now being studied for MCI and dementia

Cervenka et al, Epi Behav 2016
McDonald et al, Epi Behav 2018
Brandt et al, J Alz Dis 2019

Current/Future work

- ELUCID: comprehensive cognitive, MRI, EEG, biomarkers at baseline, and longitudinal cognitive assessments
  - 70/600 enrolled across 7 sites
- Social Determinants of Health, epigenetics, and epilepsy risk factors



THANK YOU

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