

# Alzheimer's Disease





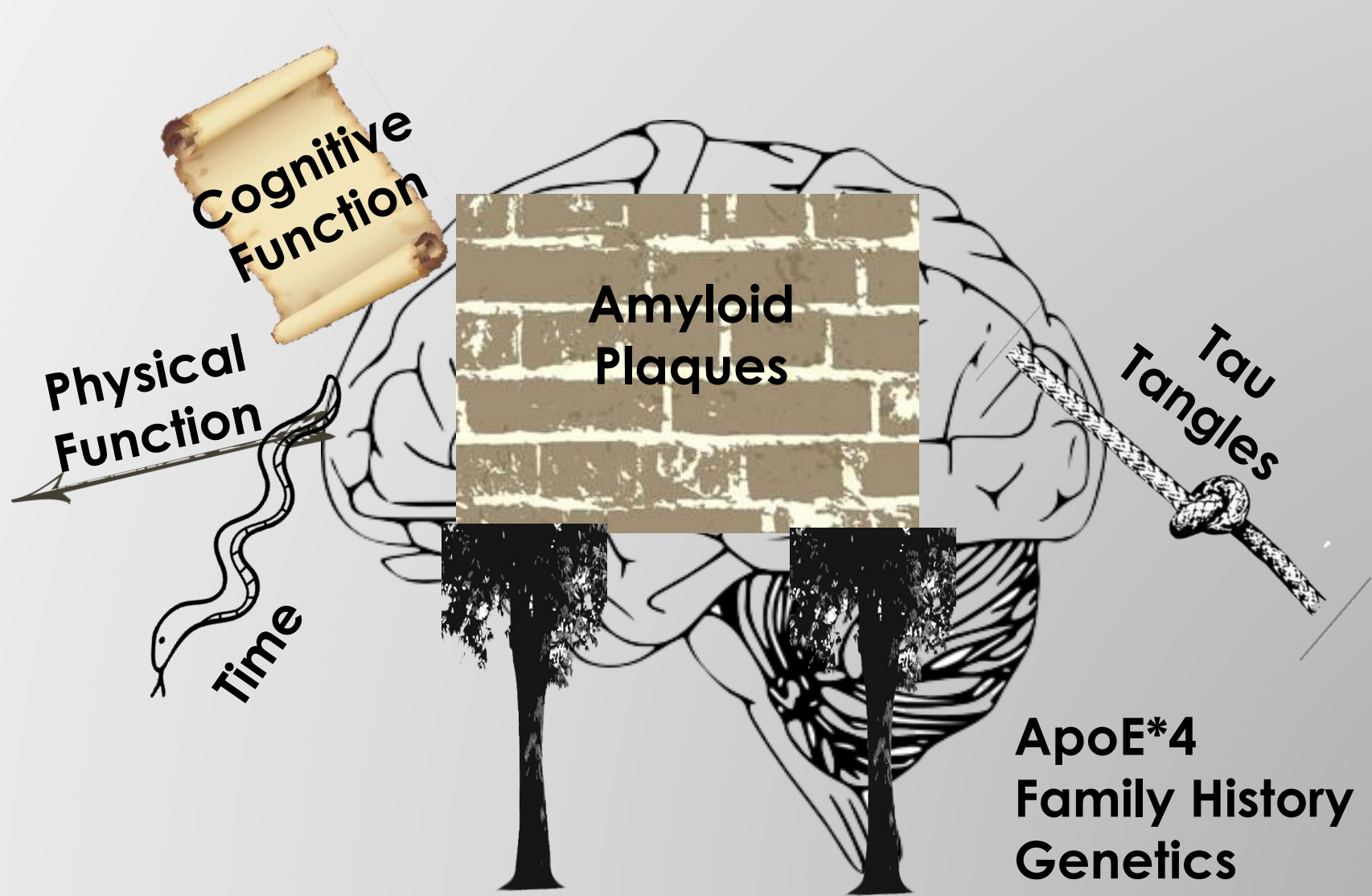
Starring:

The not ready for prevention trial  
pharmaceuticals.

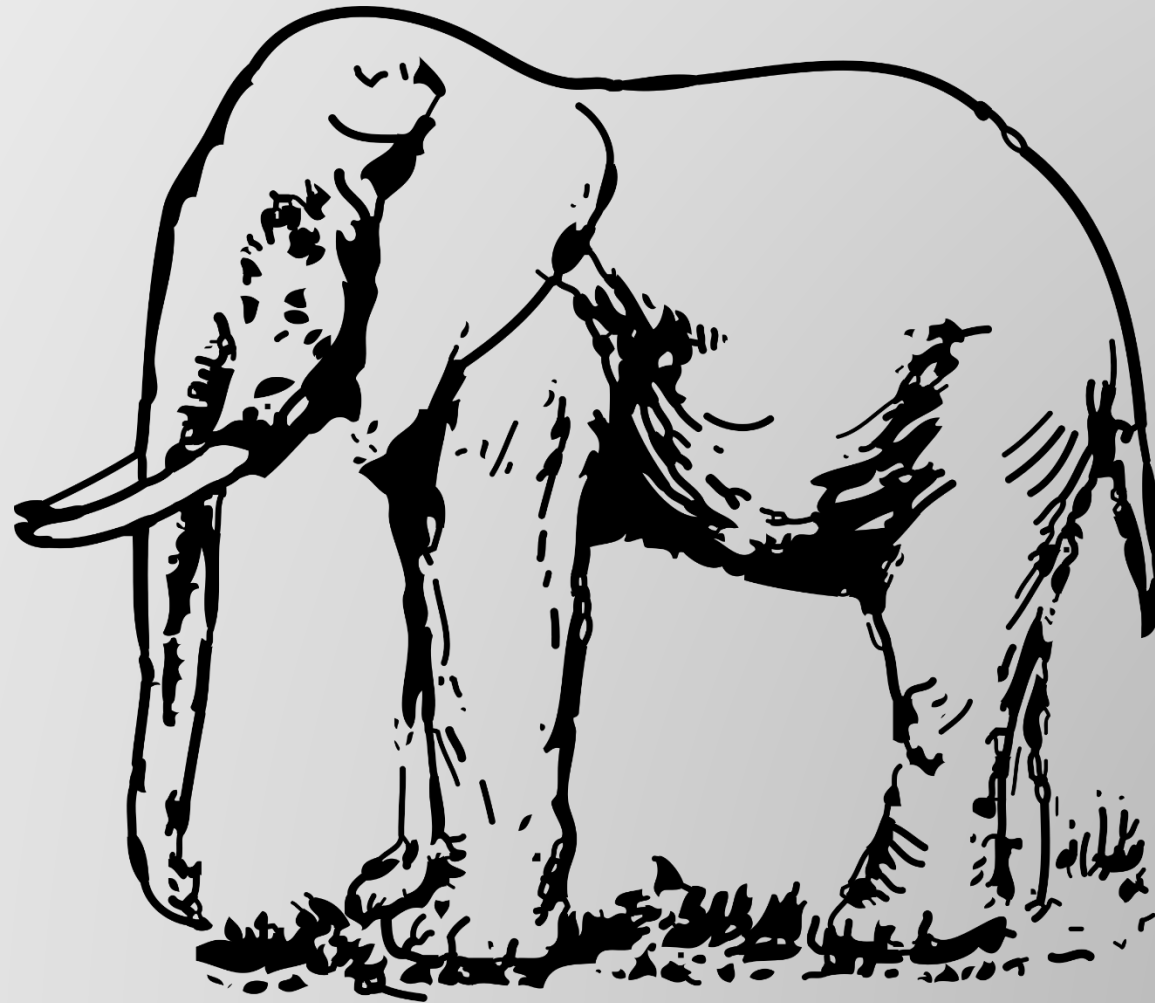
# Disclosures



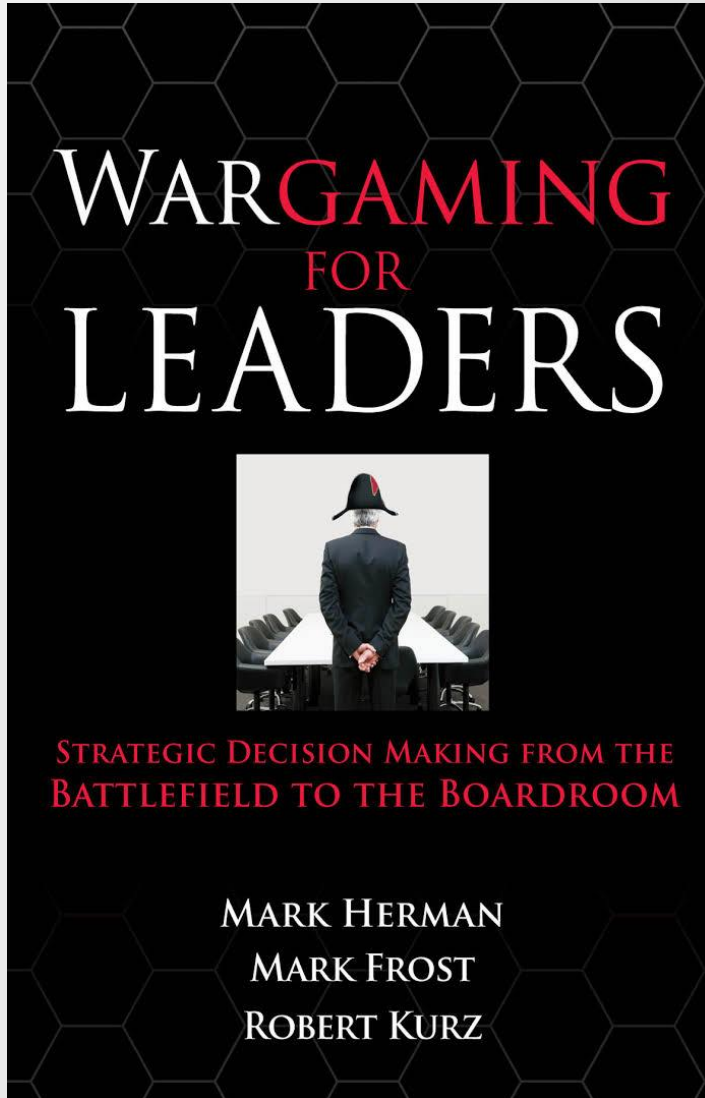
# Pieces of the Puzzle



How do they fit together?



# Data Need



Pharmaceutical Team Participant remarked on the need for

“... an epidemiological study yielding important information on the common characteristics that contribute to Alzheimer’s disease in the same way, for example, that cholesterol contributes to heart disease.”

~September, 2007

*Published 2009*



# Continuing...

“Indeed, the best model, participants felt, was the Framingham Heart Study... (which) has contributed to our understanding of cardiovascular disease, including the impact of cholesterol.”

## FRAMINGHAM Heart Study

A Project of the  
National Heart, Lung, and Blood Institute  
and Boston University

[www.framingheartstudy.org](http://www.framingheartstudy.org)

A vertical strip on the left side of the slide shows the Golden Gate Bridge at sunset. The bridge's towers are illuminated with warm orange and red lights, and the sky is a gradient of orange and red. The bridge's cables are visible against the sky.

# Welcome to Jeopardy

- Alex, I'll take the category, "Years" for "Billions of Dollars"
- The answer is
- 2017
- Why has a decade passed and that industry has spent Billions\$ on AD clinical trials, all of which have failed, but not a penny to address the concern just raised?

Who?



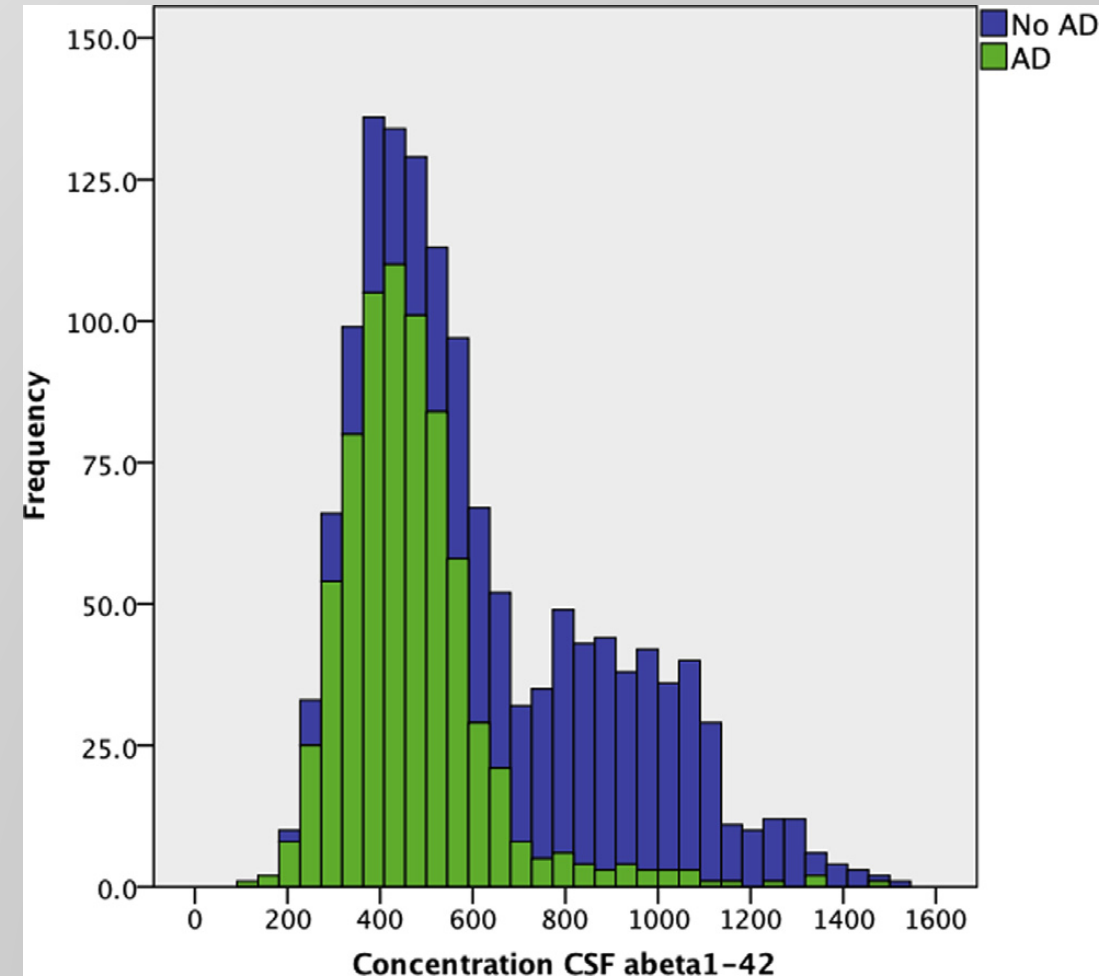


Why do we still need this research?

**Two examples,  
of many,  
outstanding  
questions**

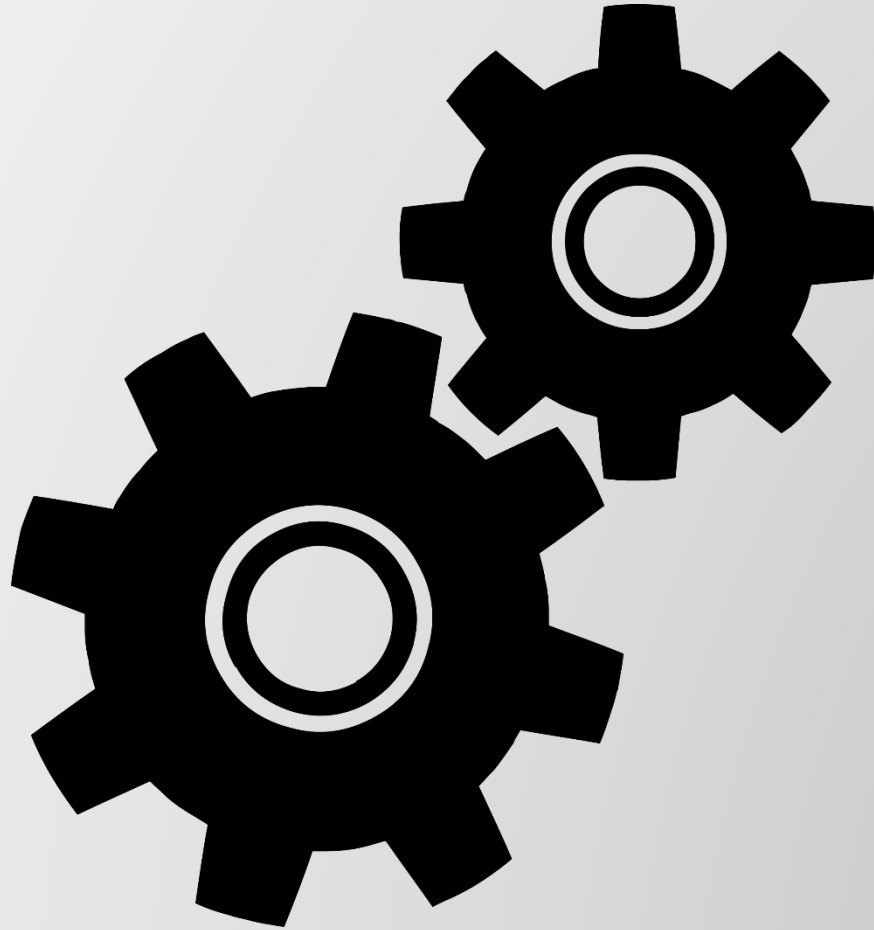
# Amyloid Plaques have a Bimodal Distribution

- Really?
- Everyone fits into one of two groups
  - Low
  - High, that is, identical to persons with Alzheimer's disease dementia
- Memory Clinic
  - AD Dementia n=631
  - Non-AD Dementia n=270
  - MCI n=236
  - Subjective Complaints n=251



*Alzheimer & Dementia 2013;9:P145 Visser*

# Methodology



Participants not representative  
either proportionally  
or of the population

Retrospective Approach

Clinically Distinct Groups

Exclude many conditions,  
particularly those that are  
“confusing,” eg, mixed clinical  
presentations and other  
conditions.

# What if the Bimodal Distribution is Correct?

**What are the implications?**

# Transition Speed

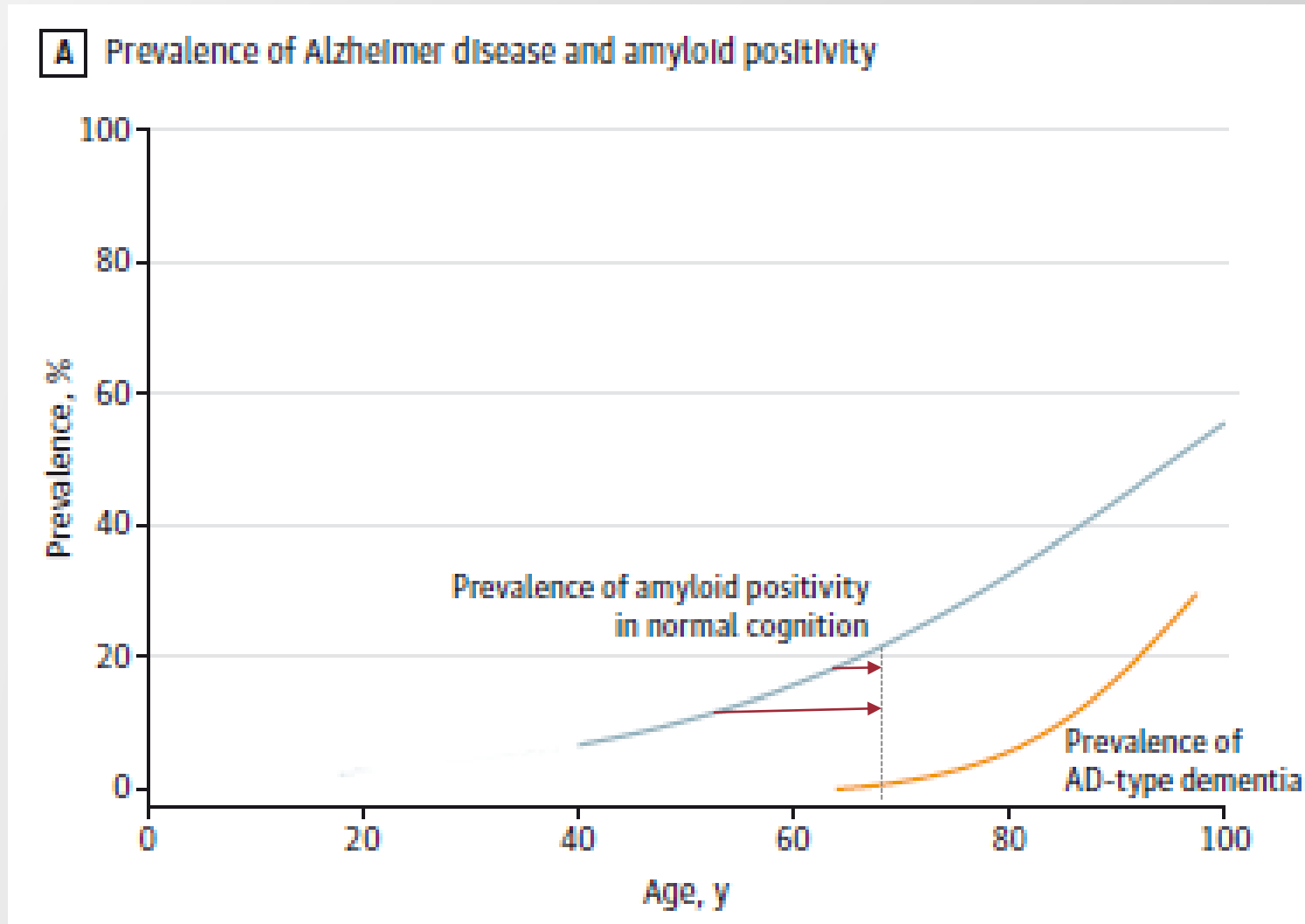


What are the triggers, if any?

# Duration (and Risk)

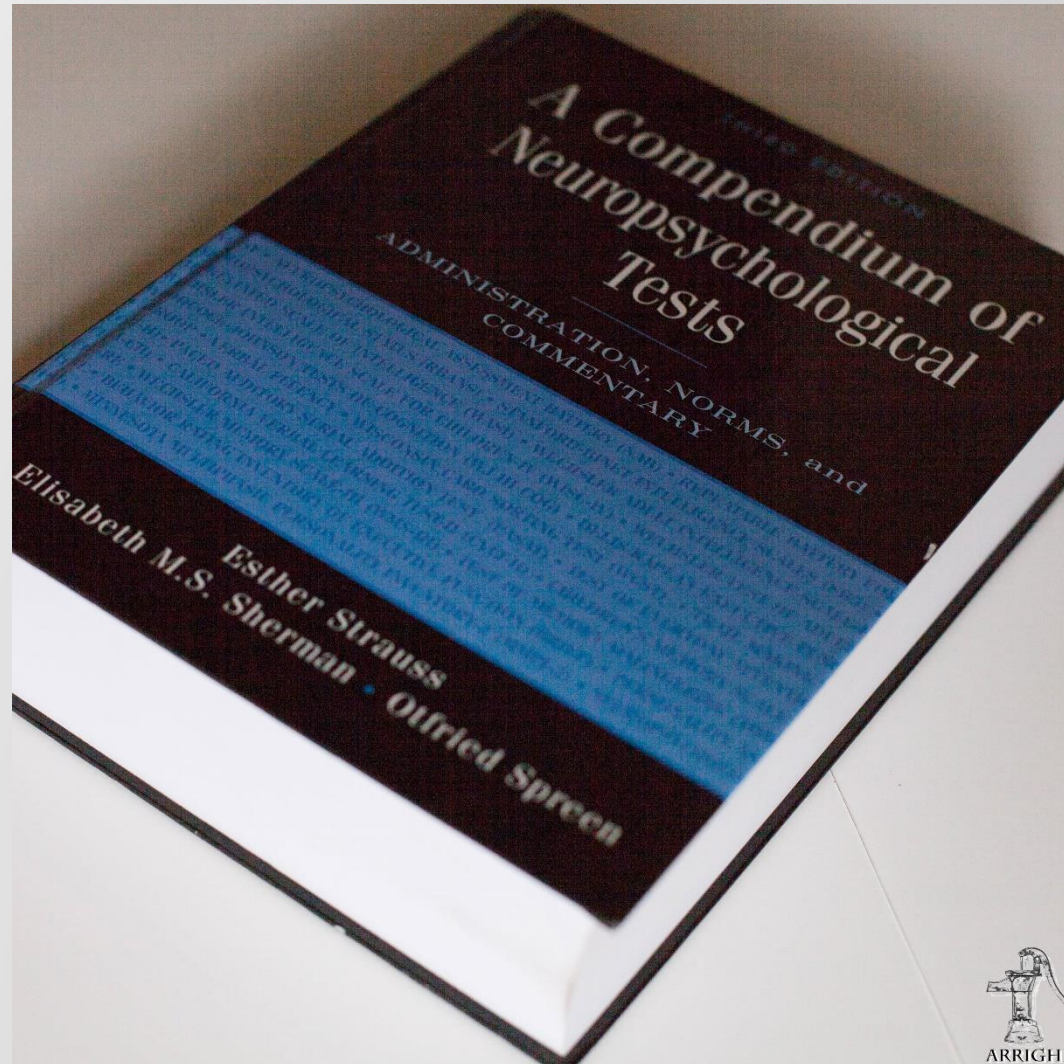


# Prevalence (?) of Amyloid Burden





# How to measure...





# A New Composite Measure

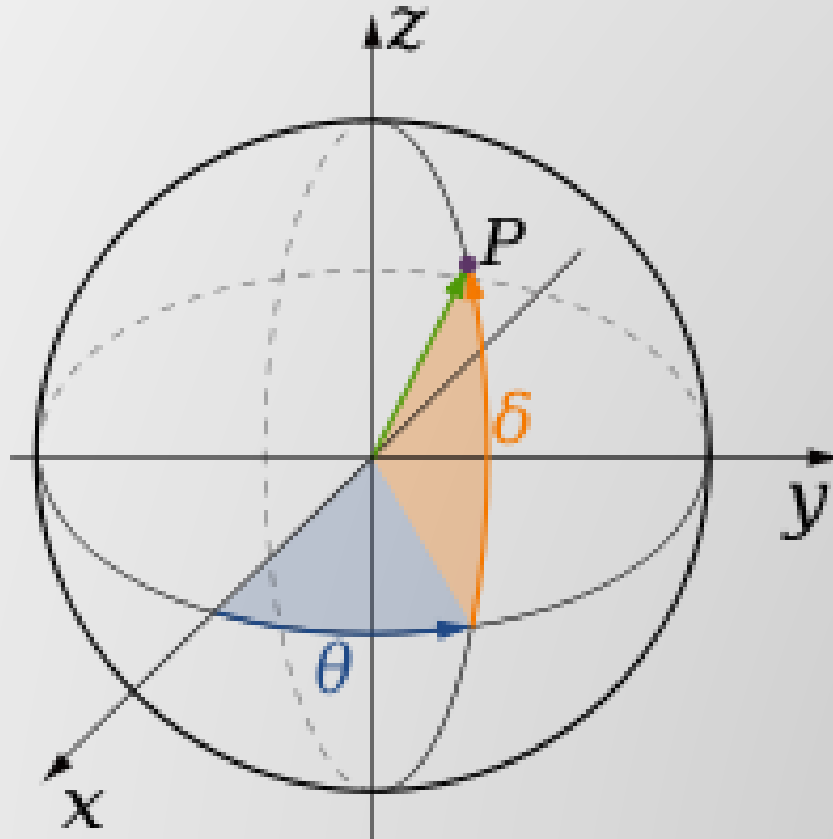
- For 2<sup>0</sup> prevention trials (aka prodromal AD),
  - with pathology and no evidence of cognitive decline
- Expert opinion determined and first published the concept in 2014
- “Three Key Domains”
  - Episodic Memory
  - Executive Function
  - Orientation
- In clinical trials since February, 2014.



# The New Composite

- Four Measures
  - Total Recall Score from the Free and Cued Selective Reminding Test
  - Delayed Recall on the Logical Memory Story IIa sub-test of the Wechsler Memory Scale
  - Digit Symbol Substitution Test Score from Wechsler Adult Intelligence Scale-Revised
  - Mini-Mental State Examination (total score)
- Scored
  - Internal Z-Score for each measure
  - The four scores are summed

# MMSE: Orientation



## Orientation – Time

Year

Season

Date

Day

Month

## Orientation – Place

Building name

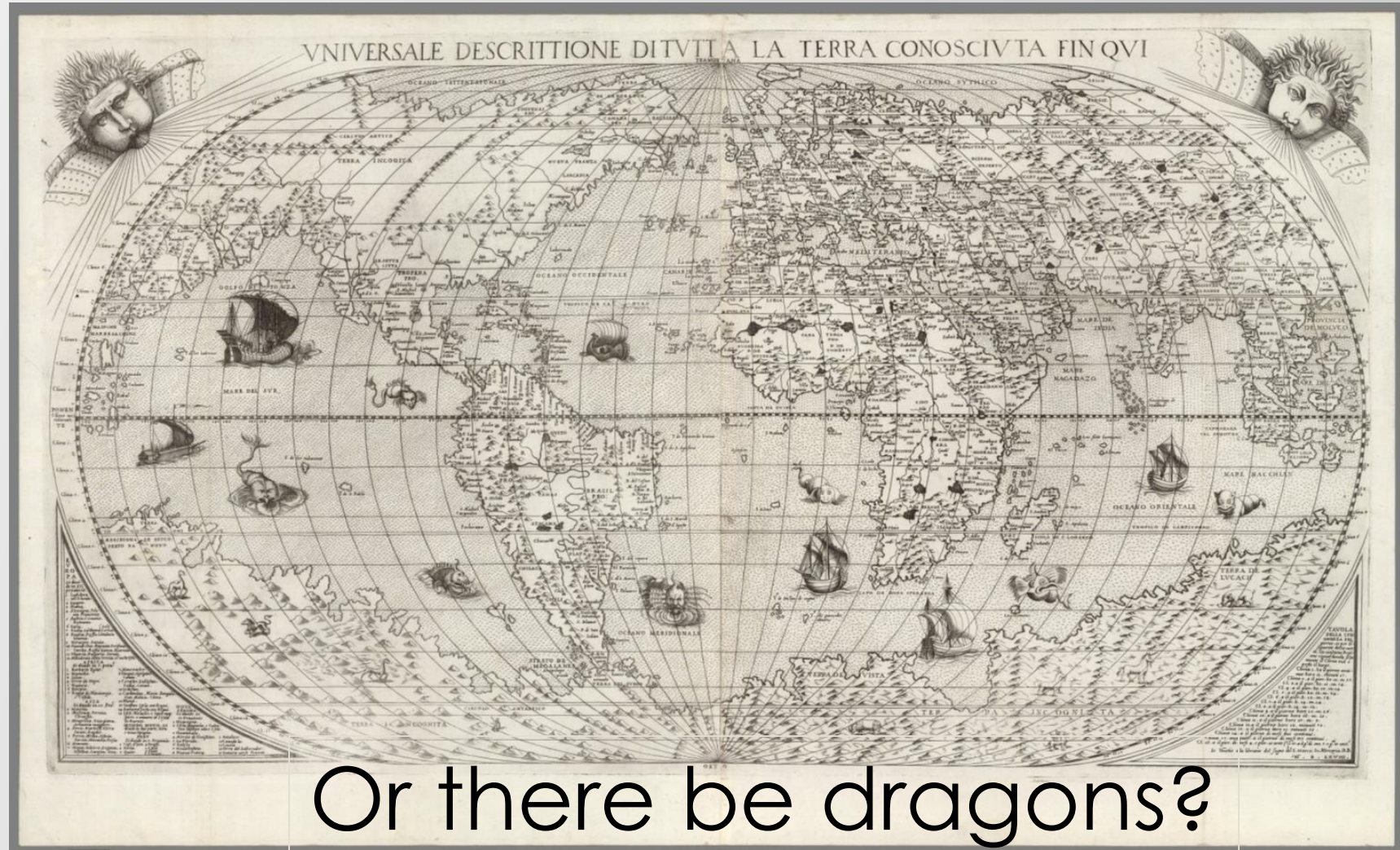
Floor

City

County

State

Is the current map correct?





# What we don't know

- Incidence & Prevalence of high amyloid and tau
  - Particularly in cognitively intact individuals
  - Risk factors (even ApoE\*4 has yet to be demonstrated)
  - Which comes first, amyloid or tau
- Relationship of high amyloid, high tau and cognition across the spectrum
- Relative and Absolute performance of the cognitive measures in the early stages of AD with pathology.



# 1<sup>0</sup> and 2<sup>0</sup> Trials for Alzheimer's Disease

- Golden except for a few minor issues:
- Who to enroll, the appropriate population?
  - Those likely to progress, what are the 'risk factors'
  - Is using increased amyloid burden sufficient?
    - What about Tau?
    - What about duration?
- Which cognitive measure(s)?
  - Is one more sensitive to another?
- What is the optimal Sample Size?
- How long should the trial run to observed change?



# What is (still) needed after all these years

- Longitudinal Study
- ~Annual Assessment
- Representative Population
  - Not selected by disease status or from memory clinics
- Aged 40 years and more
  - Younger would be better
- Measures of Cognition to address the domains
  - Do not use global screening tests as domain measures
  - Include some head to head comparisons
- Measures of Amyloid and Tau
  - Use a quantitative assay with or without semi-quantitative imaging

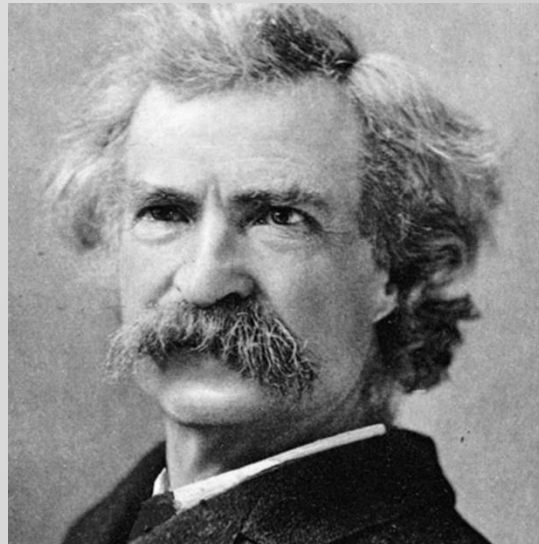
Who?





It ain't what you don't know that gets you into trouble.

It's what you know for sure that just ain't so.



*~ Mark Twain*

