Bending the Incidence Curve: Toward Prevention of Alzheimer's Disease

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No shortage of discouraging news

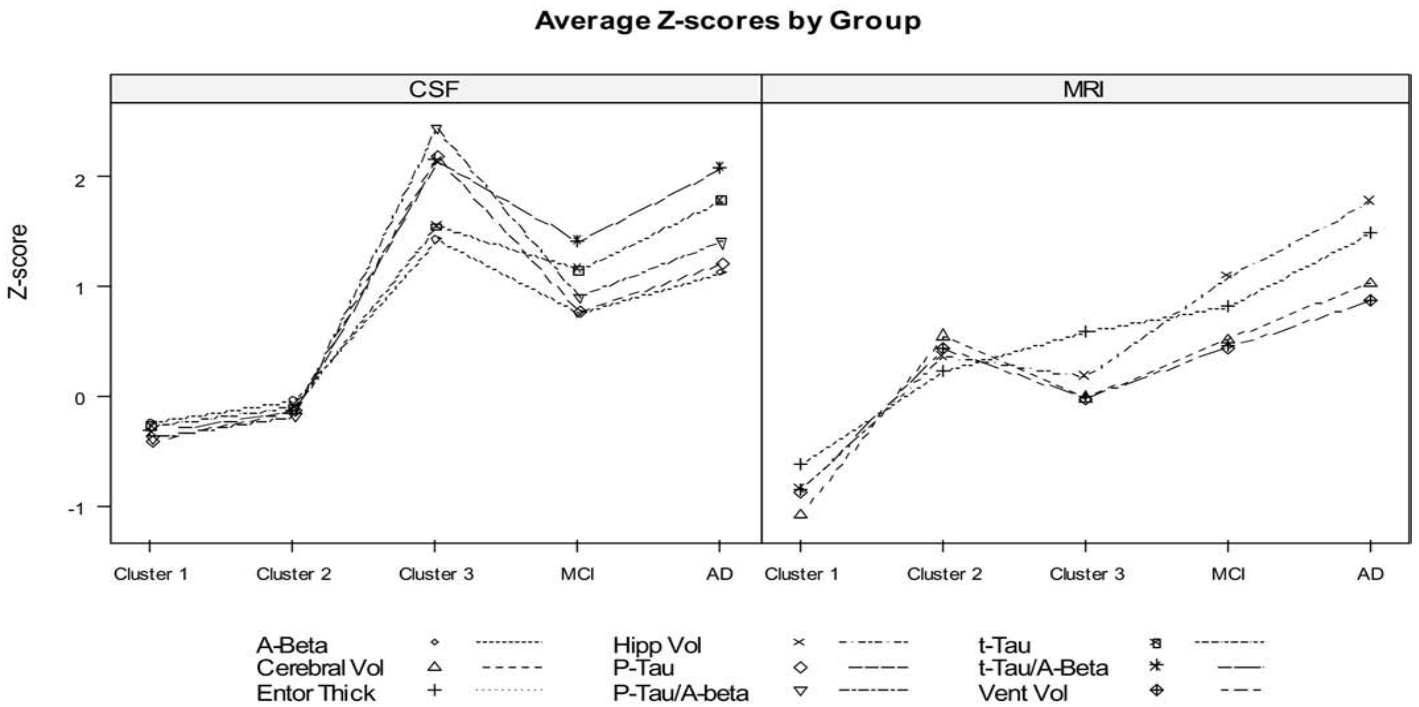
- No new AD drugs approved since 2003 (memantine)
- Merck: EPOCH study of verubecestat terminated early
  - Entry not restricted to amyloid+
  - Prodromal study continues.
- A long list of other unsuccessful trials.
- Other trials ongoing; results not known yet.

Summary: 14 more years, still no effective treatment to cure or even significantly delay onset/progression, despite advances in science.

Possible problems with AD trials

- Wrong drugs?
  - Wrong targets?
  - Need better biomarkers for screening trials?
- Wrong patients?
  - Heterogeneous pathology
  - Need different screening tools?
  - Or just too advanced: need to move earlier in disease process?
  - Moving to prevention will be challenging!

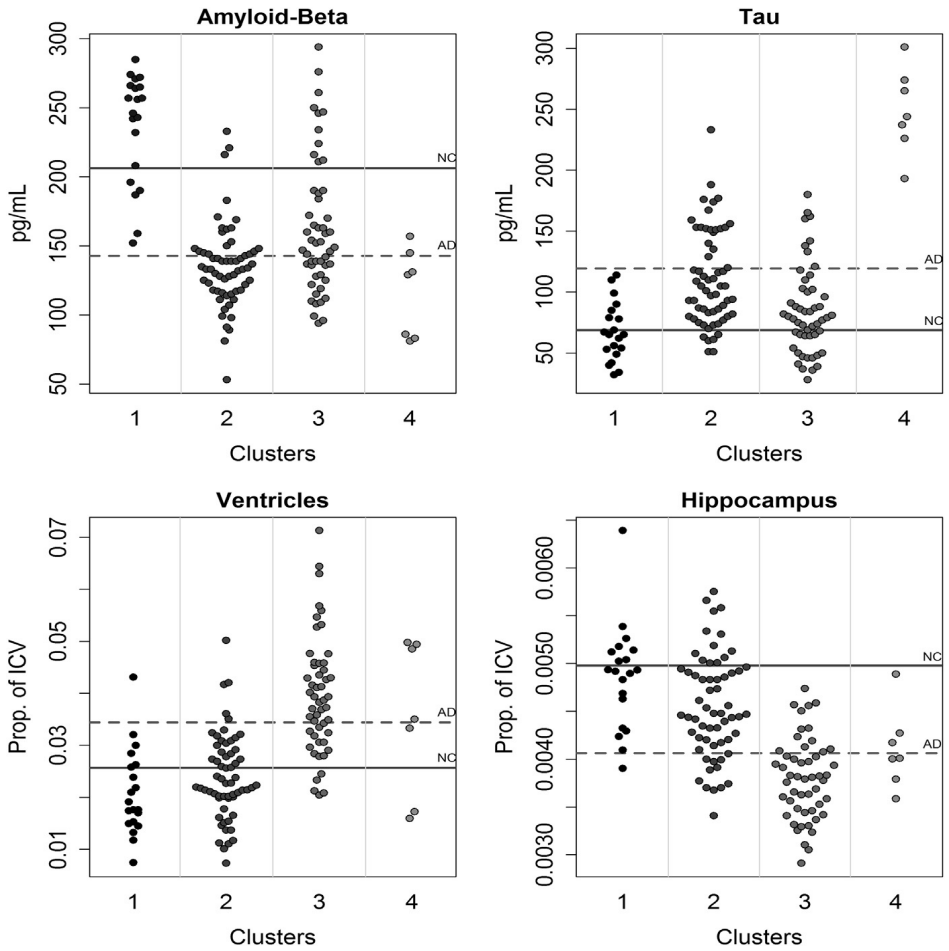
Prevention trials: Who should be in study (1)?



Cognitively normal people are heterogeneous. Select just amyloid positive group?

(Nettiksimmons et al. *Neurobiol Aging* 2010)

Prevention trials: Who should be in study (2)?



(Nettiksimmons *Alz Dement* 2014)

MCI are heterogeneous, too.
Group 1 very normal
Group 4 almost AD
Group 2 almost like NC-3
Group 3 like NCI-2

What is the right outcome measure (1)?

Clinically, we want evidence that we prevent progression or cognitive/ functional decline.

- Progression from normal to MCI or MCI to AD takes very large sample sizes.
- Current cognitive and functional measures also take large sample sizes.
  - Small signal, lots of noise.
  - Both between-person and within-person noise.
  - Can frequent measures help?
  - Can computerized testing (processing speed, e.g.) reduce noise?
  - Need evidence that testing results are relevant to function.

What is the right outcome measure (2)?

Need better biomarkers for screening drugs.

- Extremely costly to keep doing failed Phase III trials.
- Animal studies so far have had limited success in screening.
- Entry criterion markers may not be the best for measuring outcome.
- Different markers in different stages.
- Different markers for different pathology syndromes.
- ADNI and other studies offer rich observational data.

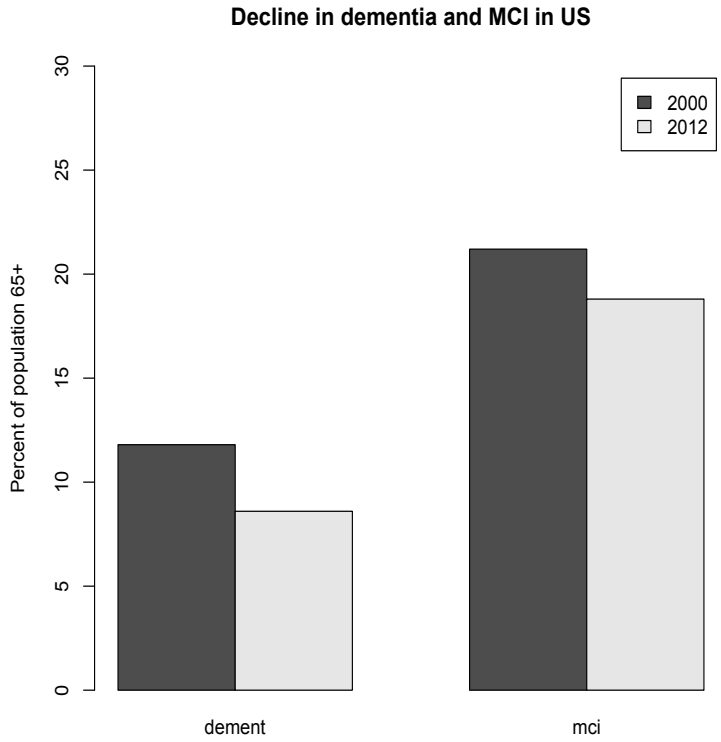
Criteria for surrogate marker

1. High signal-to-noise ratio for change: between- and within-person noise.
2. Change in marker correlates with relevant clinical change. (Hard to show if clinical change noisy?)
3. Change in marker differs for treated and untreated participants.
4. Hardest to show: Change in marker following treatment tracks with clinical impact.

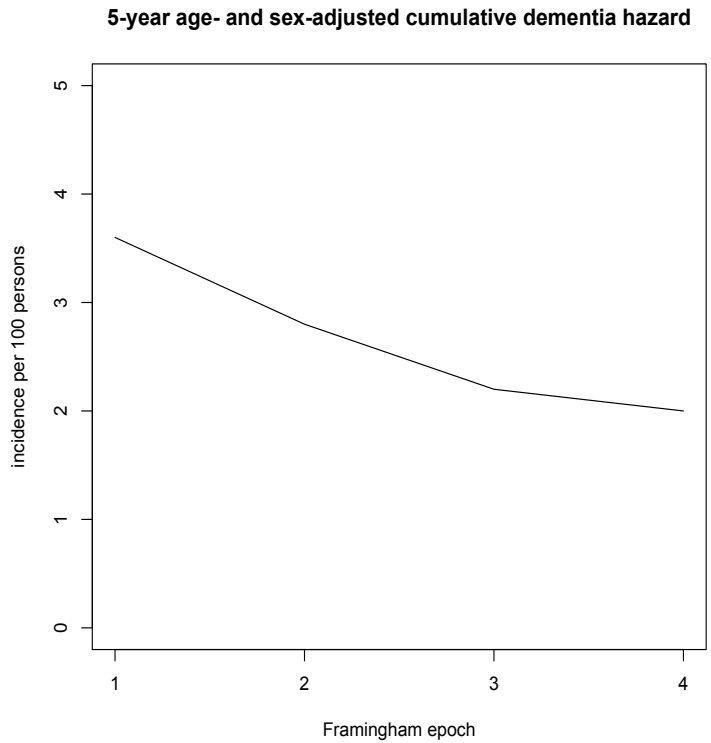
ADNI data available related to (1) and (2) but not (3) and (4).

But we are already bending the curve on AD incidence

Even though we do not have approved treatments for prevention, dementia rates are declining in the US.



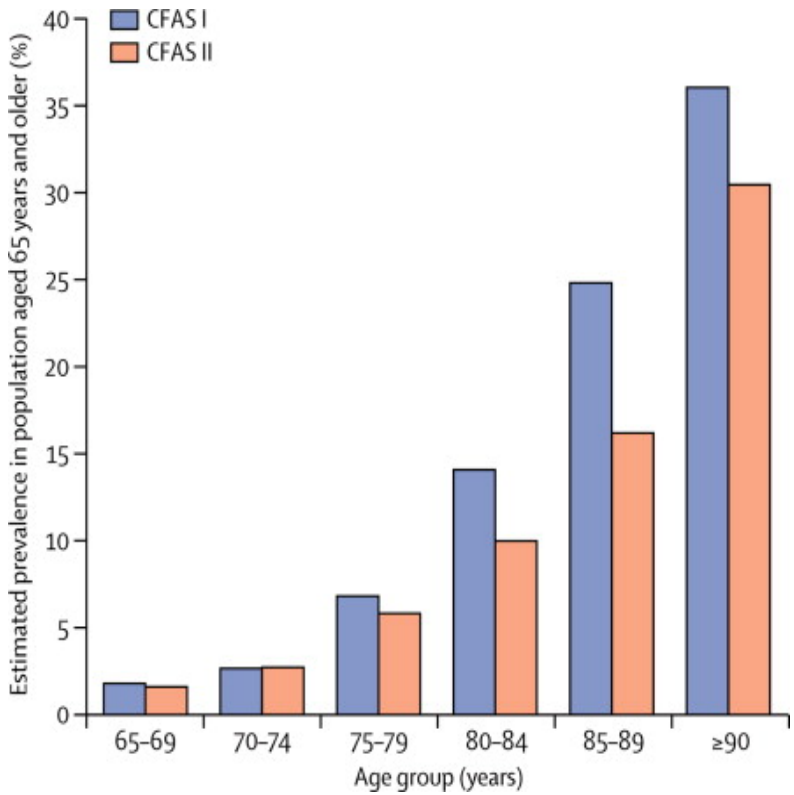
(Langa, *JAMA Int Med* 2017)



(Satizabal *NEJM* 2016)

Similar findings in other countries

Declines found also in Rotterdam, Sweden, and England (shown at right)



(Matthews, *Lancet* 2013

If we aren't doing prevention, what's going on?

- Multiple population-based studies in different countries agree that incidence of dementia, and AD specifically, is declining.
- Some studies suggest rising levels of education account for part of this.
- Neuropathology studies suggest that AD pathology rarely occurs in isolation; often with vascular problems.
- More aggressive treatment of hypertension and hypercholesterolemia may be behind the decline.
- Can we learn anything about possible intervention studies from observation of this phenomenon?

Some questions we could look at

- What brain biomarkers show different changes in people who were successfully “treated"?
  - Higher education?
  - Successful short-term or long-term control of blood pressure, cholesterol?
  - Restrict to higher-risk subgroups?
- Can we learn something from disparities?
- Lots of study data out there now: Can we combine our knowledge?
- Caution: can surrogate markers in later stages really translate to earlier stages?

Summary:

- Many emerging biology insights offer hope for prevention strategies.
- In order for these ideas to be screened and effectiveness confirmed, we need actual surrogate markers:
  - High signal of change, low noise
  - Change correlates to meaningful clinical factors.
  - Demonstrate that slowing, halting, or reversing biomarker change via treatment directly relates to clinical outcomes.
- Big barrier: so far no successful treatment to prove marker as a surrogate!
- Nonetheless, we are already decreasing incidence. Can we make use of that fact?

Thanks from (very wet) California!

This guy is cognitively intact, and just celebrated his 101st birthday!
(The cake with 101 candles was not *his* idea.)
Maybe a good education and successful control of hypertension played a role.

Some references

Graham WV *Annual Rev Med* 2017; **68**:413-430.
Langa et al. *JAMA Intern Med* 2017.
Matthews et al, *Lancet* 2013.
Nettiksimmons et al., *Neurobiol Aging* 2010.
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