Biostatistics Core Report to Steering Committee: ADNI-2 Accomplishments and ADNI-3 Challenges

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Outline

Highlights of Biostatistics Core accomplishments in ADNI-2

How have we done on our goals?

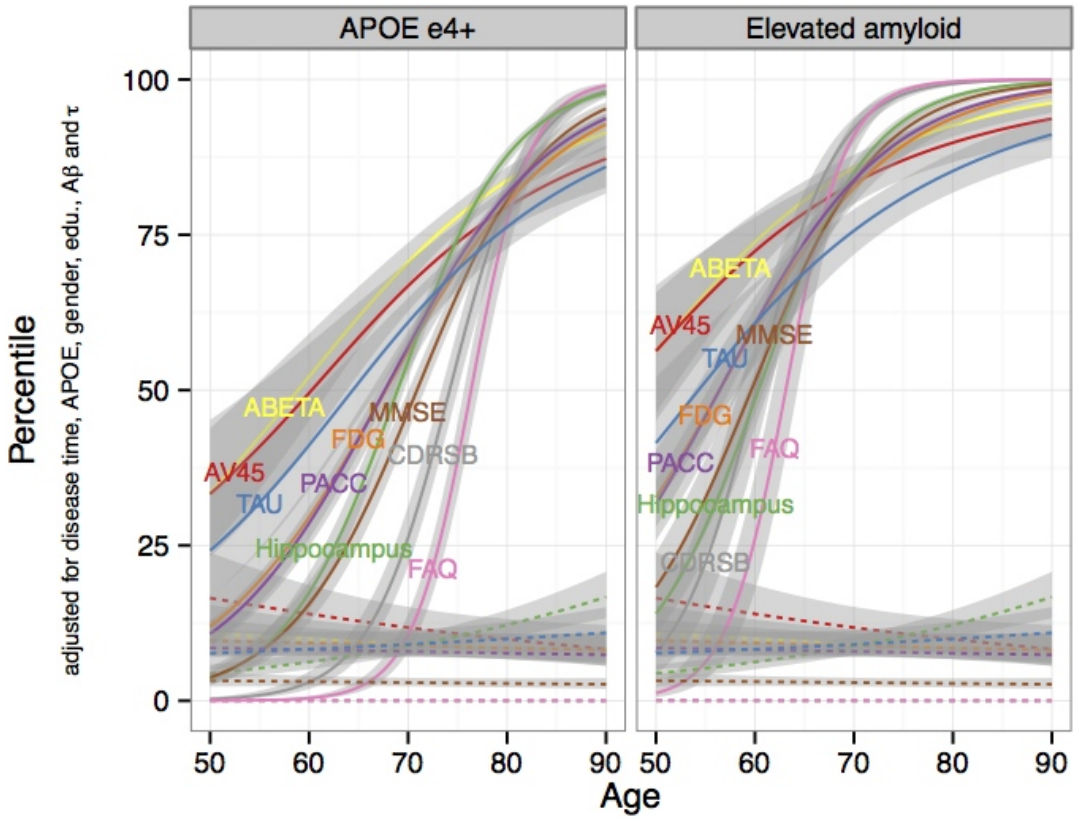
- Participated in ADNI administration, helped other users.
- Design and analysis of ADNI data, including novel statistical approaches:
  - Richer longitudinal data allows modeling trajectories and sequences.
  - New groups (eMCI, SMC) increase breadth of data across disease process.
  - New measures increase depth of data on participants.

Extended longitudinal follow-up: rich but challenging

- Some participants (from ADNI-1) followed almost 10 years now.
- Not everyone has every measurement, and some change, so we've had to work out ways to reconcile.
- For example, is "amyloid positive" the same if based on CSF, PiB, or AV45?
- We cover a wide range from NC to MCI to AD, but rarely in same person!
- Sophisticated statistical methods help us to align people against age or study time.

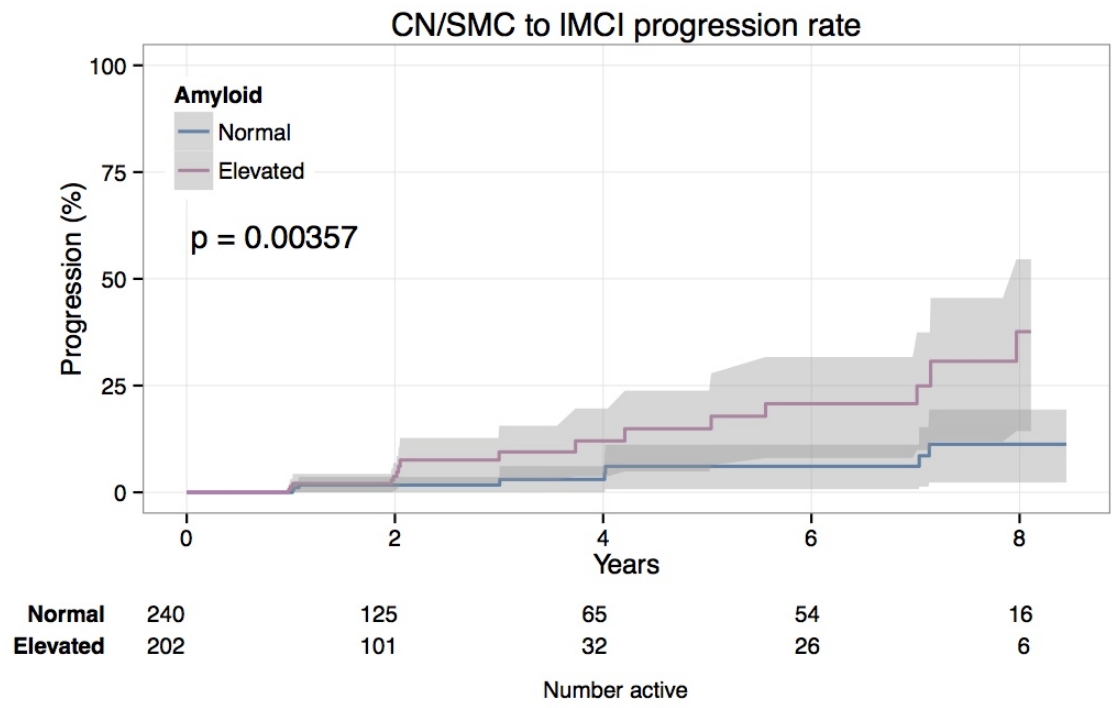
Rich longitudinal panel data allow sophisticated modeling

Figure : Genetics, amyloid play roles. (Donohue *et al*, *JAMA Neur* 2014)



Extended follow-up picks up conversion of NC

Figure : Amyloid+ (CSF or PET) predicts longer-term risk of MCI

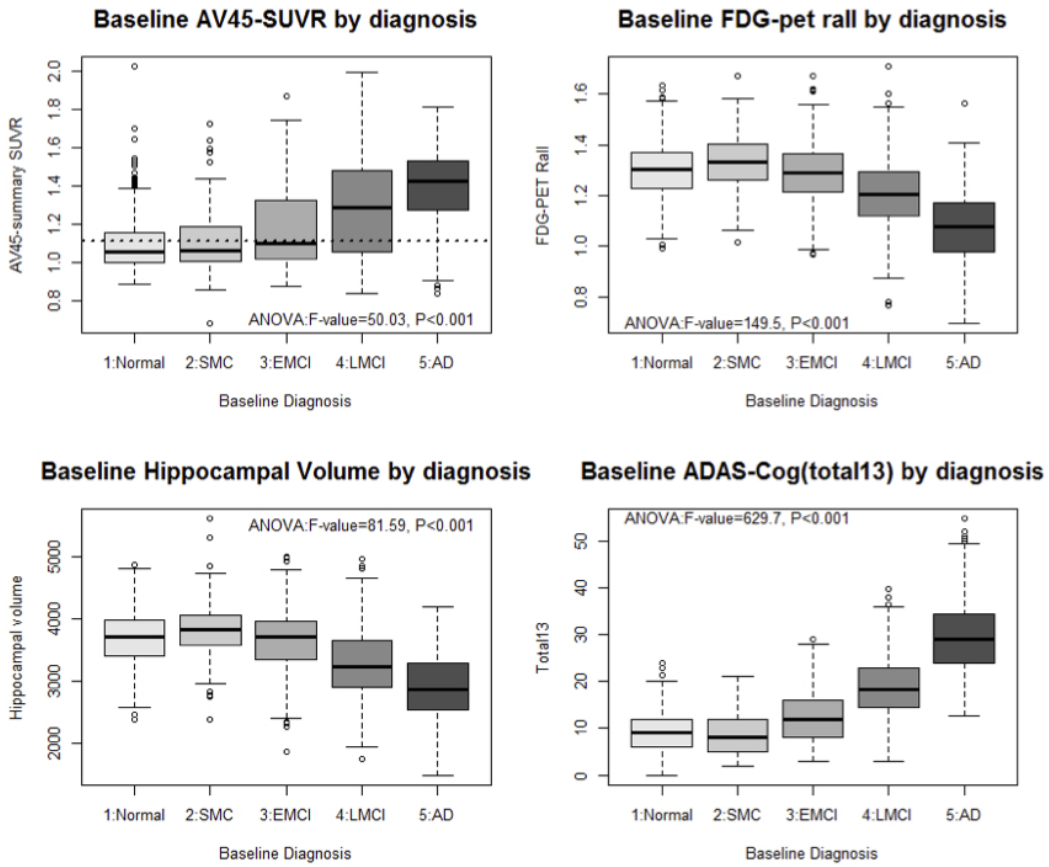


Two new groups added since ADNI-1: eMCI and SMC

- Goal was to fill in gap between NC and later MCI.
- Are some biomarkers already bad in eMCI and SMC?
- Do some problems not show up until later in MCI?
- We tried to get later MCI and AD groups to be "pure" but it's harder in earlier stages.
- What have we learned about heterogeneity of subtle, early clinical problems?

New groups fill in the gaps between NC and MCI

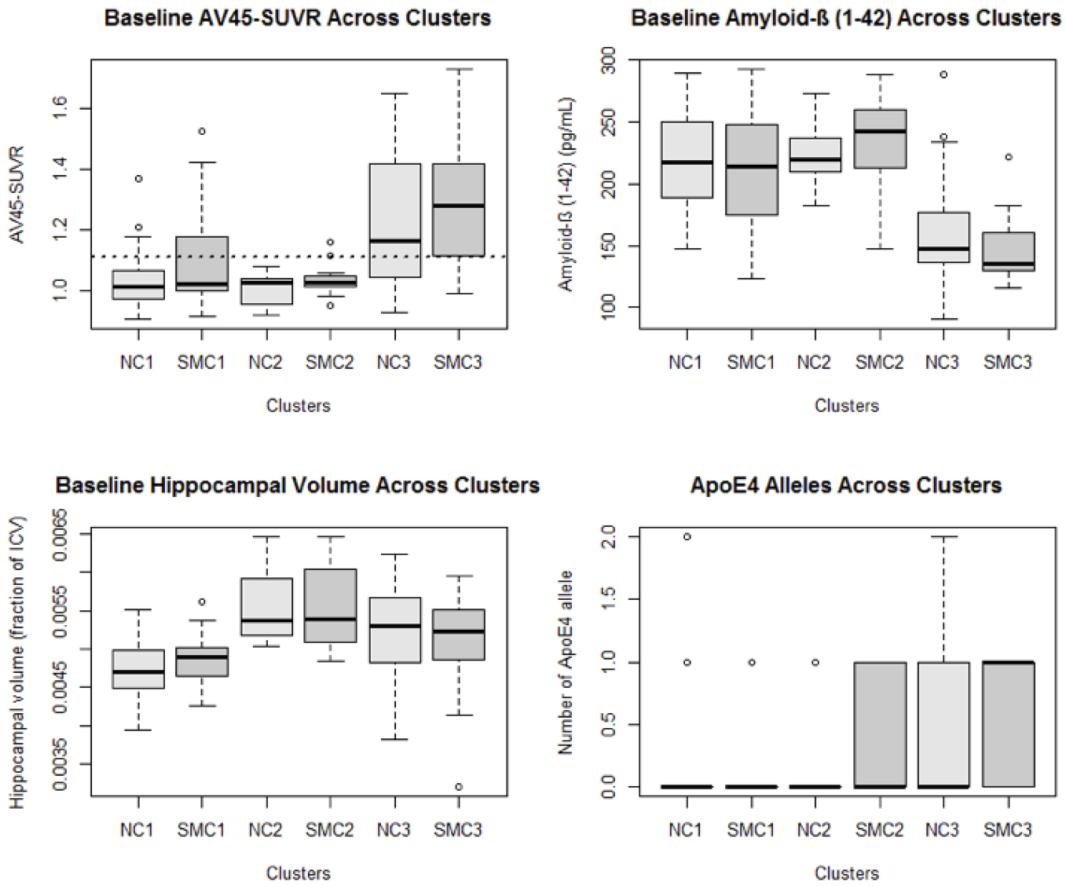
Figure : SMC and eMCI fit in between NC and MCI, as expected



SMC similar to NC but both are heterogeneous

- We used unsupervised clustering to look for subgroups in ADNI-2 NC and SMC.
- Similar method to Nettiksimmons 2010 in ADNI-1 NC, 2014 in ADNI-1 MCI.
- Clusters based on volumetrics, CSF measures.
- Similar results to Nettiksimmons for both NC and SMC.
- Three subgroups in each diagnostic group, quite similar.

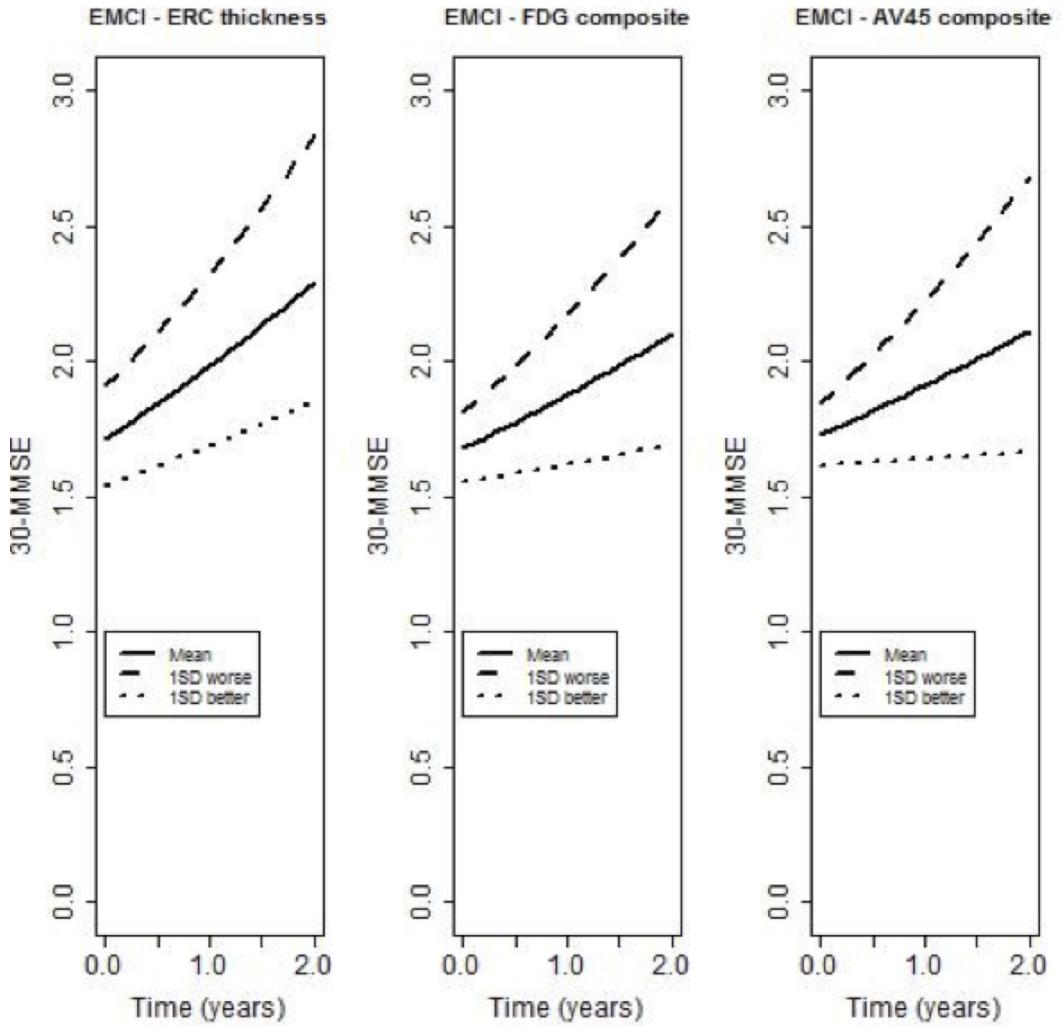
Clusters look healthy, pre-AD-like, and maybe vascular



We also added new measures: are they prognostic?

- Amyloid imaging now done on everyone.
- What is prognostic value?
- Does it truly show up really early? How early?
- It's early to see much in NC or SMC.
- But eMCI have been followed longer.

New measures have prognostic value even in eMCI



Biostatistics goals for ADNI-3 not greatly changed

The Biostatistics Core will:

- Provide analytic support for planning and efficient designs.
- Carry out interim and final analyses to address key research questions.
- Participate in ongoing operations and administration.
- Provide intellectual leadership for academic and industry biostatisticians interested in ADNI.
- Develop new biostatistical methodology needed for ADNI-3.

ADNI-3 Challenges

Immediate challenge: ADNI-3 design, and implications for sample size, power.

- How many measurements, and how frequently, will determine precision and power.
- What is the impact of drop-out assumptions?
- Many possible designs proposed, to balance burden, cost, and knowledge gained.
- Example question: Should we consider dropping one of the 5 proposed Tau PET observations for MCI?
  - Could save on cost, add more people, or replace with longitudinal FDG.
  - But what impact on precision, power?

We developed systematic approach to address design questions

- Direct calculation if no drop-out, simulation if drop-out assumed.
- Estimate precision of estimated annualized change, power for comparisons.
- Need to know or guess ratio of between-to-within-person noise.
- Example: Drop 3rd or 4th Tau PET observation for MCI
  - If no drop-out: no loss in precision for dropping 3rd, 2% loss for dropping 4th.
  - If 10% drop-out/yr, 3% loss for dropping 3rd, 8.8% for dropping 4th.
  - Program allows varying scenario, assumptions; results quite robust.
  - Will be used for final ADNI-3 sample size and power calculations.

Another statistical challenge: complicated longitudinal data

- Participants: mix of carry-over from ADNI-1, ADNI-GO, ADNI-2, and new recruits.
- Measurements: new ones keep getting added, old ones changed.
  - Amyloid imaging added in ADNI-GO.
  - PiB replaced by AV45.
  - Now Tau imaging to be added, FDG dropped.
  - Only half had FDG in ADNI-1, only half had CSF.
  - Some people drop out of some measures (e.g. CSF rate now low.)
- Resulting data very challenging for statistical modeling; new tools needed!

Partnerships help to address challenges

- New NACC/IALSA project: AD biostat folks to develop methods and try out using different datasets.
  - Natural history with some kinds of observations showing up late.
  - Clinical trials: novel ways to get better outcome measures.
  - One-day conference in Chicago, Sept 24 (funded).
  - Idea: people working with datasets they know, then compare findings for robustness.
- ADNI-DIAN partnership: Compare images and biomarkers and clinical findings in early-onset disease with ADNI.

Any questions about the next adventure?