

Longitudinal Follow-up of Cognitively Normal Cases

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Strong interest in in large cohorts of asymptomatic people at risk of dementia

- **Maintain normal controls for comparison with patient groups**
 - **Traditional use of normal controls**
- **Study determinants of cognitive decline**
 - **Impacts of many factors (age, CV risk factors, genetics...)**
 - **Explanation/prevention**
- **Study designs**
 - **Full spectrum of cognitive states (dementia through normal)**
 - **Only “normal” cohort**

Important features of studying normals

- Longitudinal follow-up
 - verify that they continue to be normal
 - Establish longitudinal changes for comparison with disease
- Follow-up concurrent with study is helpful

The problem

- Limited resources for following these participants very closely
- Limited utility of year-by-year visits
 - Have already been on ancillary studies (participant fatigue)
 - Practice effects
- So, what are the important factors for reliable longitudinal data?

Factors that influence ability to detect longitudinal change

- Amount of change – easier to detect large change
- Length of follow-up
 - Amount of change a function of rate of change **and length of follow-up**
 - Change = Rate X Time
- Sample size – Can detect smaller change with larger sample

More factors that influence ability to detect change

- Reliability of outcome measures
 - Cognitive outcomes are notoriously “noisy” – considerable time-to-time variability in individual trajectories
 - More follow-up helps to filter out noise
- Frequency of follow-up – repeated observations help to separate true longitudinal trajectories from random error
- Three or more time points - Necessary to establish reliability of slope
 - Diminishing returns after 3 timepoints

Statistical issues: what's less important

- **Irregular durations of follow-up - Longitudinal analysis methods can handle variable time intervals**
 - Time intervals can differ across individuals
 - Equally spaced time intervals are not necessary (although are simpler to analyze)
- **Missing data - Longitudinal analysis methods can handle missing data – especially if missing by design**

Conclusions

- **Length of follow-up is most critical concern for most applications**
 - **Longer means better chance of detecting (or ruling out) change**
- **Nothing magical about annual evaluations**
 - **Multiple evaluations help to filter out error**
 - **Diminishing returns after 3**
 - **Interval between evaluations less critical**

Recommendations

- **In cross-sectional studies, follow-up concurrent with study procedures is important**
- **In longitudinal studies, longer is always better**
- **Maintaining contact and obtaining follow-up more important than frequency of follow-up**
- **Not a major statistical problem if follow-up interval changes over time or differs across groups**
 - **Especially if by design**