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Mixed Effect Modeling: Theory Track 2

ABCD Workshop on Brain Development and Mental Health

Sponsored by NIMH

June 22nd - July 22nd, 2021

Mixed Effect Models Track 2

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- What we will do:
  - Review the hierarchical structure (levels) of the ABCD data
  - Analysis pre-planning:
    - Talk about change over time in a flexible manner
    - Reminder of the value of ICCs
  - Discuss three ways to look at non-linearity associations
    - Polynomials
    - Splines
    - General Additive Mixed Modeling

- What we won't do:
  - Look at statistical equations from a traditional statistical lens
  - Talk about all the actual options in R to obtain each morel

** Disclaimer – I am not a biostatistician and write these experts into every grant to double check my work!

Clustering in ABCD

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Two common examples of clustered data include:

- Individuals were sampled within sites (communities with 3T scanners, from schools, etc.). The site is the cluster.
- Repeated measures or longitudinal data where multiple observations are collected from the same individual. The individual is the cluster in which multiple observations are grouped.

ABCD has both!

Hierarchical Structure of ABCD (4 levels)

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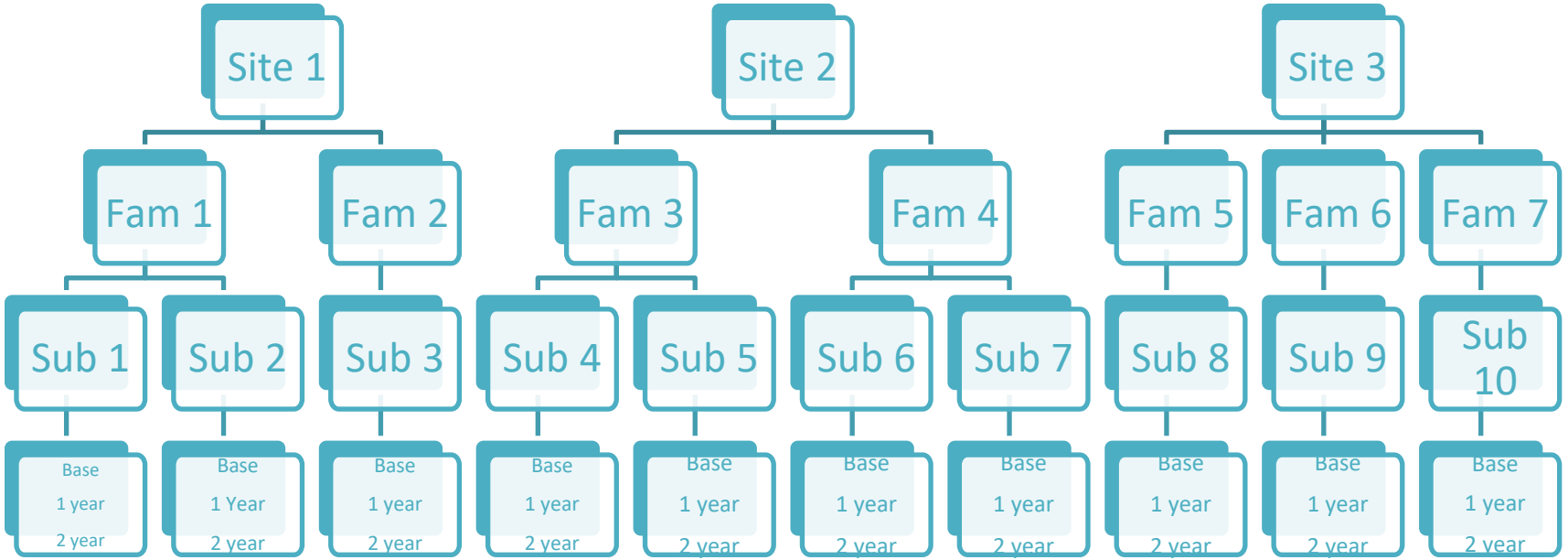

Repeated within-subject assessment, nested by person, nested in families, within site

Hierarchical Structure of ABCD, if chose single sub from each family (3 levels)

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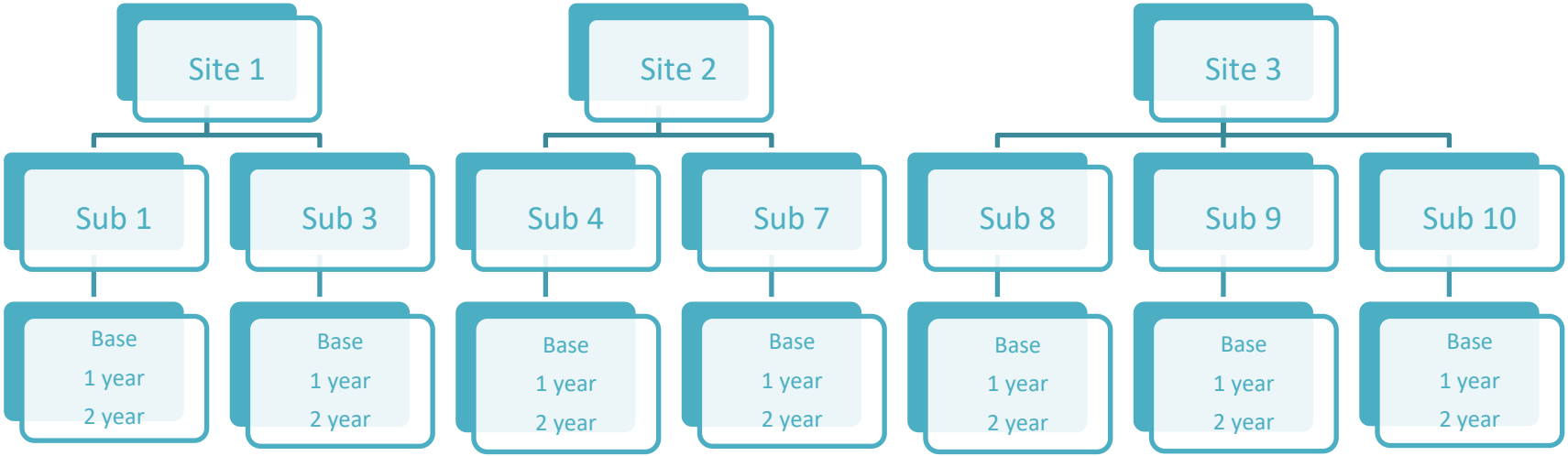

Repeated within-subject assessment, nested by person, within site

Mixed effect models -- two first steps

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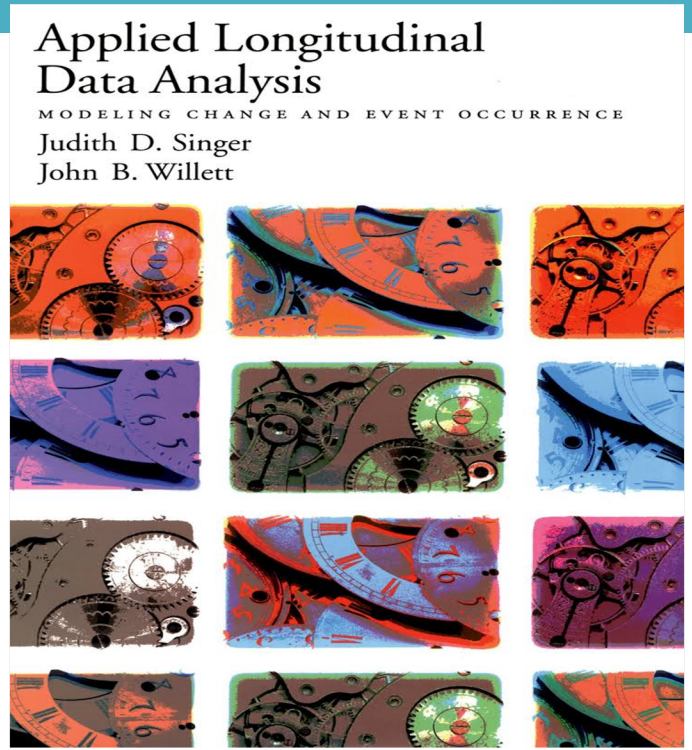
- What's your time variable?
- Calculate your ICCs

Discussion 1:

What does the metric ‘*development*’ mean to you in the Adolescent Brain Cognitive Development?

DEVELOPMENT – Treating time more flexible

- Three important features of a study of *change*
  - 3 or more waves of data
    - process of change
  - An outcome whose values change systematically over time
  - A sensible metric for clocking time



Mixed effect models for development

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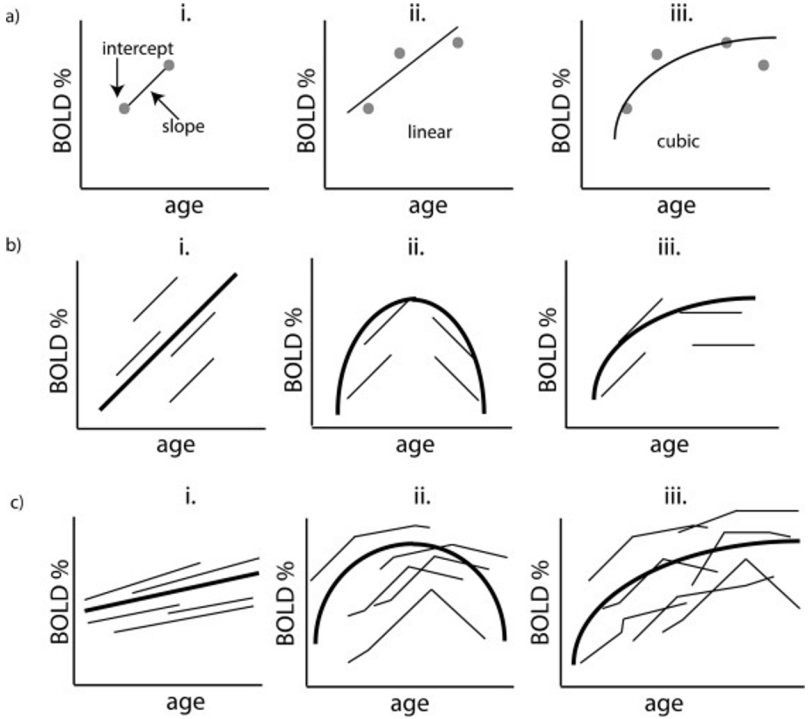

Single subject/participant level:

- 2 timepoints = difference score
- 3 timepoints = individual slope
- 4 timepoints = non-linear

Group level:

- Can explore non-linearity of group with any number of timepoints per subject

Herting et al., 2018 Developmental Cognitive Neuroscience

Mixed effect models for development

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What do these patterns mean for your question?

Biology Age range Measurement

DEVELOPMENT – Treating time more flexible

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- Age (years, months)
- Time point of visits/sessions
- Grades
- Developmental milestones (i.e. pubertal stages, etc.)
- Time since X happened (COVID-19?)

- Choice of a time metric affects several interrelated decisions about data collection:
  - Number of waves
  - Spacing of data
  - Precision of the estimate

Examples of Time

- ABCD study design waves:
  - Balanced
    - Everyone is assessed on the identical number of occasions (baseline, 1 year, 2 year etc.)
  - Time structured
    - Each set of occasions is identical across individuals

Examples of Time

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- ABCD study by age:
  - Unbalanced
    - Some time between 9-10 years, 11-12 years, etc.
      - Albeit, some people lied to get in so may have a few outliers!
  - Time structured(ish)
    - Each set of occasions is identical across individuals (~12 months)
      - Mid-year phone calls are 6 week +/- period
      - Annual visits are +/- of 3 months

Examples of Time

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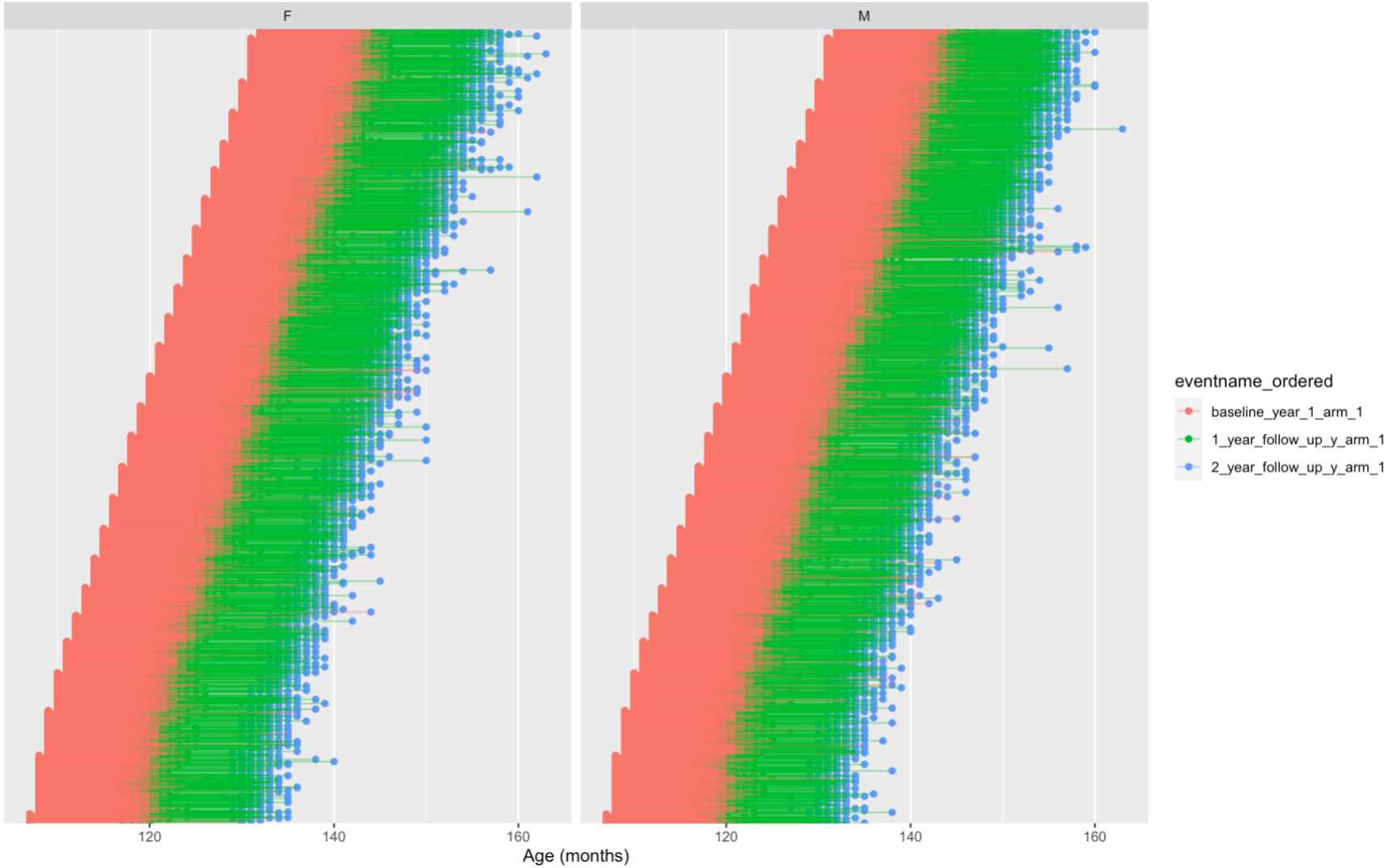
- ABCD study by age during COVID
  - Time structured(ish)
    - Each set of occasions is identical across individuals (~12 months)
  - Except COVID:
    - » 2nd year visit had a wider window due to
    - » Mid-year and annual visit orders may flipflop during COVID
    - » A problem for future us! And a good reason to use age!

*despite valiant attempts to collect time-structured data, actual measurement occasions will differ


F
M
120
140
160
120
140
160
Age (months)
eventname_ordered
baseline_year_1_arm_1
1_year_follow_up_y_arm_1
2_year_follow_up_y_arm_1

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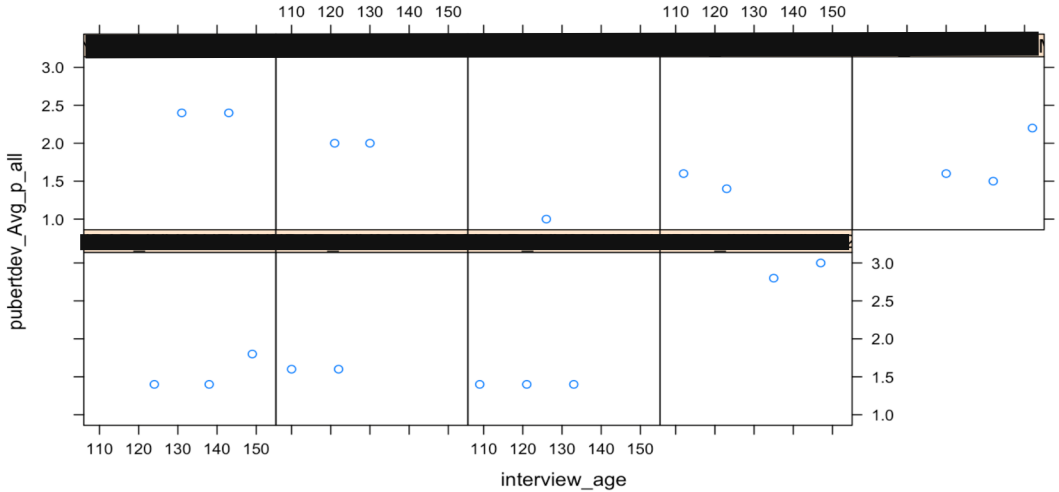
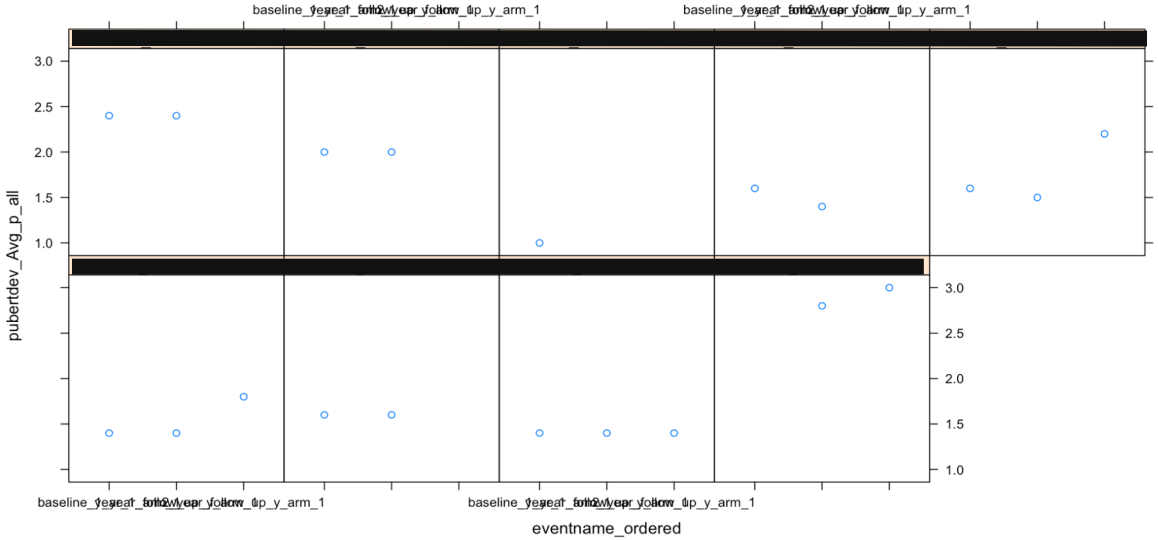


Puberty by age

Puberty by wave



DEVELOPMENT – Treating time more flexible

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- Choose a metric for time that reflects the cadence you expect to be most useful for your outcome
- Equally spaced waves may offer balance and symmetry, but if you expect rapid nonlinear change during some time periods you should collect more during this time
- Individual modeling can handle if everyone is measured using same schedule (time structured) or different schedules (time unstructured)
- Not every person need not have the same number of waves

*Take home: must think about question of interest

Mixed effect models -- two first steps

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- What's your time variable?
- Calculate your ICCs

Intraclass correlation coefficient (ICC)

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- A descriptive statistic used when quantitative measurements are organized into groups
- It describes how strongly units in the same group resemble each other
- Can be important for test-retest reliability, but also used in mixed effect modeling to see if people are changing over time

Mixed Effect Models & ICC

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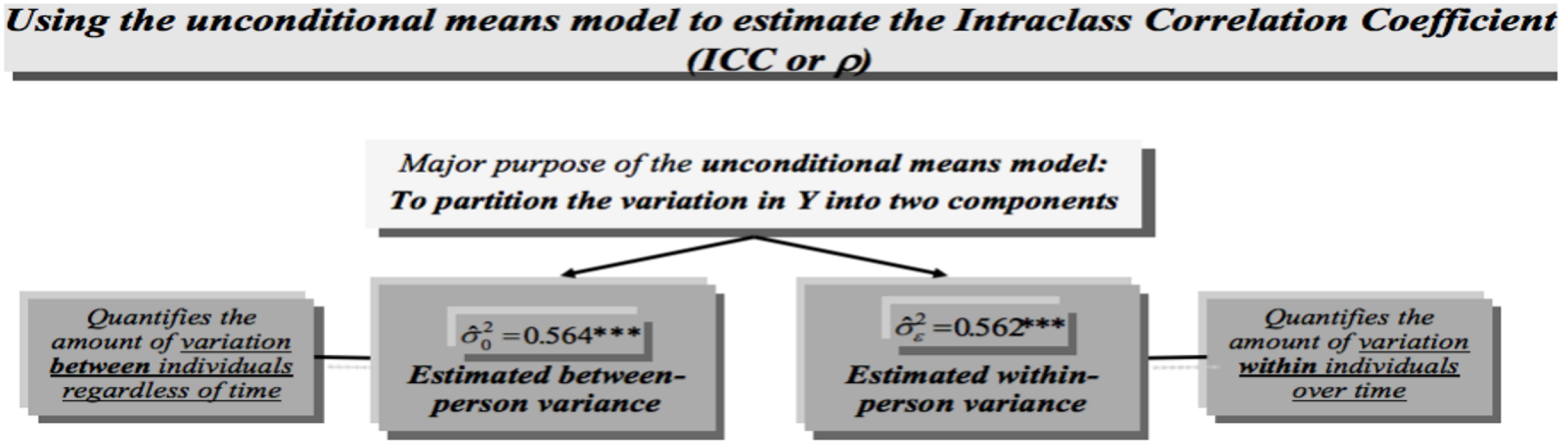
- Observations from the same cluster are *usually* more similar to each other than observations from different clusters.

- Mixed models not only account for the correlations among observations in the same cluster, they give you an estimate of that correlation.

- The ratio of the between-cluster variance to the total variance is called the **Intraclass Correlation**. It tells you the proportion of the total variance in Y that is accounted for by the clustering.

https://www.theanalysisfactor.com/the-intraclass-correlation-coefficient-in-mixed-

Intraclass correlation coefficient (ICC)



Intraclass Correlation (ICC):

$$\text{ICC} = \frac{\text{BP}}{\text{BP} + \text{WP}} = \frac{\text{Intercept Variance}}{\text{Intercept Variance} + \text{Residual Variance}}$$

Unconditional Means Model Examples

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Sample R code for fitting the unconditional means model (where "id" = person-level grouping indicator):

```
library(nlme)
lme(response ~ 1, data=dataset, random= ~ 1 | id)
```

Or this:

```
library(lme4)
lmer(response ~ 1 + (1 | id), dataset)
```

ICC is a standardized way of expressing how much we need to worry about dependency due to person mean differences

Intraclass correlation coefficient (ICC)

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1. It can help you determine whether or not a linear mixed model is even necessary
   - Correlation = zero, means the observations within clusters are no more similar than observations from different clusters → Use a simpler analysis technique

2. It can be theoretically meaningful to understand how much of the overall variation in the response is explained simply by clustering
   - Example: repeated measures might tell you to what extent mood is a trait (varies among people, but not within a person on different occasions) or state (varies little on average among people, but varies a lot across occasions)

3. It can also be meaningful to see how the ICC (as well as the between and within cluster variances) changes as variable are added to the model

Reliability of a metric can also impact measuring TRUE change

- If an outcome has poor reliability, this will affect the measurement error term during statistical testing

- So in a longitudinal study, poor test-retest reliability may impact our ability to detect the true rate of change – McArdle and Woodcock 1997

Change vs. Fluctuation?!

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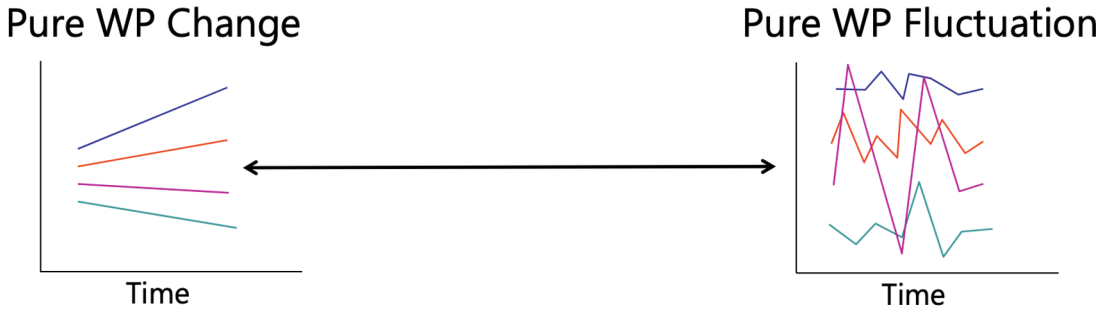
- **Within-Person Change**: Systematic change
  - Magnitude or direction of change can be different across individuals
  - "Growth curve models" → Time is meaningfully sampled
- **Within-Person Fluctuation**: No systematic change
  - Outcome just varies/fluctuates over time (e.g., emotion, stress)
  - Time is just a way to get lots of data per individual



Slide from: Lesa Hoffman

Intraclass correlation coefficient (ICC) of FMRI

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- Values range between 0-1
  - Classified by Cicchetti 2001:
  - Poor (<.04)
  - Fair (0.41-.59)
  - Good (0.6-0.74)
  - Excellent (0.75-1)

- Bennett and Miller, 2010
  - Adult fMRI ICCs from .16-.88, average ~ .5
  - Varies by task/contrast/ROIs

- Herting et al., 2018
  - 12 developmental studies report ICCs
  - Range
    - Occipital – good/excellent
    - Subcortical – fair/poor

Poor reliability or true change?

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- Lower ICC may be poor reliability of the BOLD signal

AND/OR

- Subjects BOLD signal changed over time

(what we hope to see)

Poor reliability or true change?

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Low ICC here = poor reliability

Adult Study ICC

Child Study ICC

Low ICC here = poor reliability OR they changed!!

Days/Weeks

Time

1 or 2 years later!

Test

Exception: Van den Bulk 2013 – 3-6 mo

Discussion 2:

Go find the ICCs from your favorite longitudinal study! Or the most recent study you've read!

ICC: What can I do?

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- Calculate the ICC between timepoints for your metric
- Compare it with the known test-retest reliability estimates for the measurement
- If test-retest reliability estimate is unknown, it will be unclear as to what is real and what is also error in the measurement
- Report all of these details & limitations in your manuscript!

Additional Resources for ICC

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1. ICC overview: https://www.theanalysisfactor.com/the-intraclass-correlation-coefficient-in-mixed-models/
2. How does ICC impact my AIC? Vajargah et al.
3. ICC for lme: https://rdrr.io/cran/psychometric/man/ICC.lme.html

Analysis Pre-plan Review: Time & ICC

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For all outcomes:

1. Empty Model; Calculate ICC
2. Decide on a metric of time
3. Decide on a centering point
4. Estimate means model and plot individual trajectories

If your outcome shows systematic change:

5. Evaluate fixed and random effects of time
6. Still consider possible alternative models for the residuals

If your outcome does NOT show ANY systematic change:

5. Evaluate alternative models for the variances

Slide from: Lesa Hoffman

Mixed effect models -- non-linear

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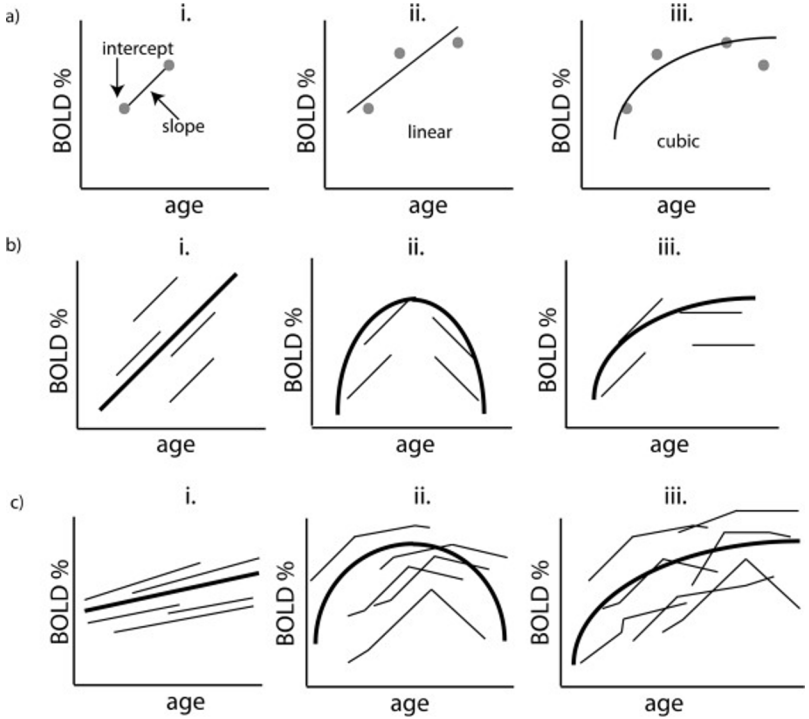

Single subject/participant level:

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Group level:

- Can explore non-linearity of group with any number of timepoints per subject

Herting et al., 2018 Developmental Cognitive Neuroscience

3 Common Methods for Non-Linearity

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- **Polynomial regression**. This is the simple approach to model non-linear relationships. It add polynomial terms or quadratic terms (square, cubes, etc) to a regression.
- **Spline regression**. Fits a smooth curve with a series of polynomial segments. The values delimiting the spline segments are called **Knots**.
- **Generalized additive models** (GAM). Fits spline models with automated selection of knots.

Tutorial to all 3 (polynomial, splines, and GAM): http://www.sthda.com/english/articles/40-regression-analysis/162-nonlinear-regression-essentials-in-r-polynomial-and-spline-regression-models/

Mixed effect models -- Polynomials

- A common application in regression to deal with nonlinear relationships involves polynomial regression.
- For the predictor in question, x, we add terms e.g. quadratic (x2), cubic (x3) etc. and then do multiple linear regression on the transformed variables
- BUT, Polynomials have unpredictable tail behavior – very bad for extrapolation

Mixed effect models -- Regression Splines

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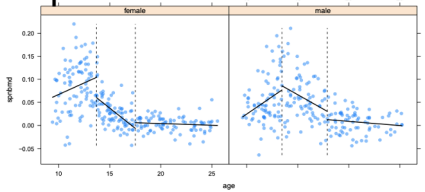
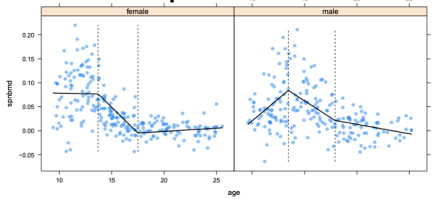
- Splines are used in statistics in order to mathematically reproduce flexible shapes
- Knots are placed at several places within the data range; the points where adjacent functional pieces join each other
- Smooth functional pieces (low-order polynomials) fit the data between two consecutive knots
  - The type of polynomial and the number and placement of knots is what then defines the type of spline

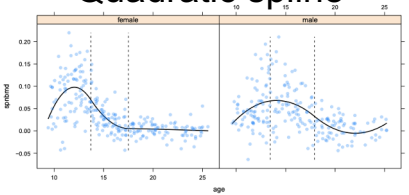
piecewise linear model



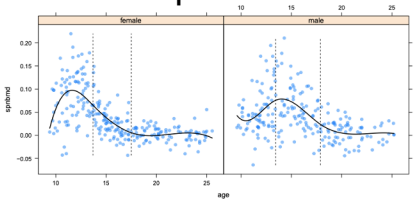
Continuous piecewise linear model



Quadratic spline



Cubic spline



Mixed effect models -- Regression Splines

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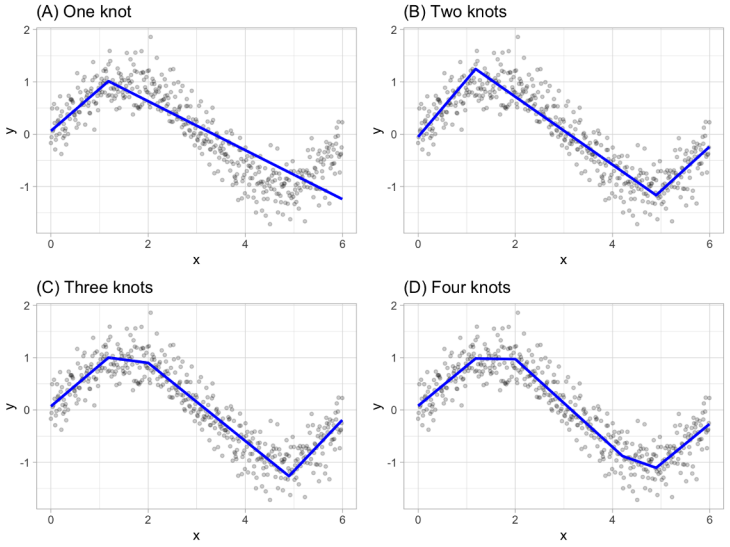
- A spline $f(X)$ will be a smooth function, satisfying certain differentiability properties mentioned below, such that $f(X)$ is a polynomial of degree d

- A spline can be linear or interpolated beyond the last knot and we may impose a further constraint:
  - Natural splines are cubic splines that have the additional constraints that they are linear in the tails of the boundary knots



In order to obtain more flexible curves the number of knots or the degree of the polynomial can be increased.

Mixed effect models -- Regression Splines

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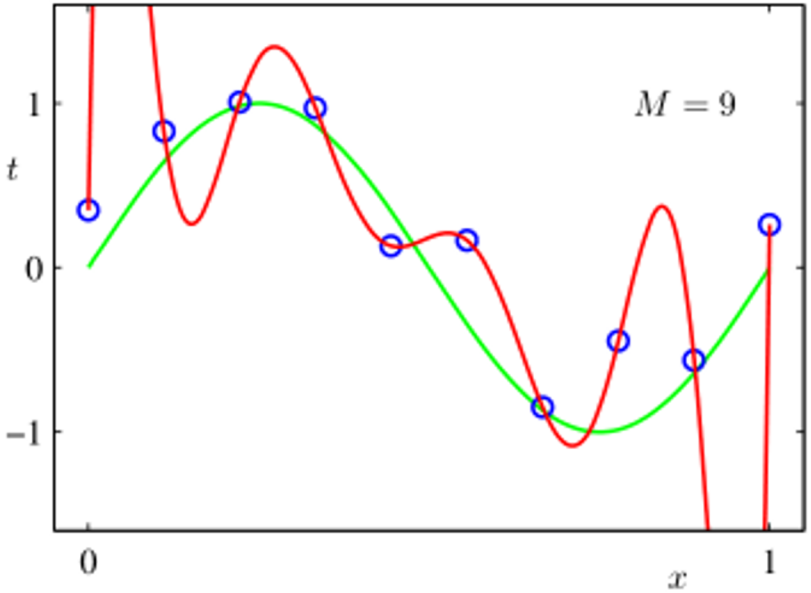
- Spline Trade-off:
  - Increasing the number of knots
    - overfit the data and increase the variance
  - Decreasing the number of knots
    - rigid and restrictive function that has more bias



Additional Resources for Splines

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1. Perperoglou et al. 2019: https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-019-0666-3
2. Explanation for different types of splines: https://www.hds.utc.fr/~tdenoeux/dokuwiki/_media/en/splines.pdf
3. Introduction to splines in R: https://cran.r-project.org/web/packages/splines2/vignettes/splines2-intro.html

Mixed effect models -- GAMM

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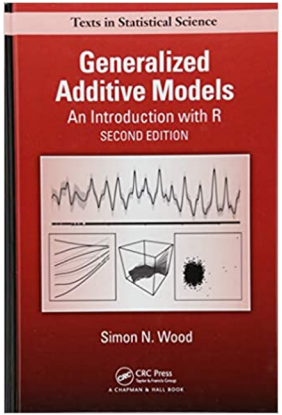
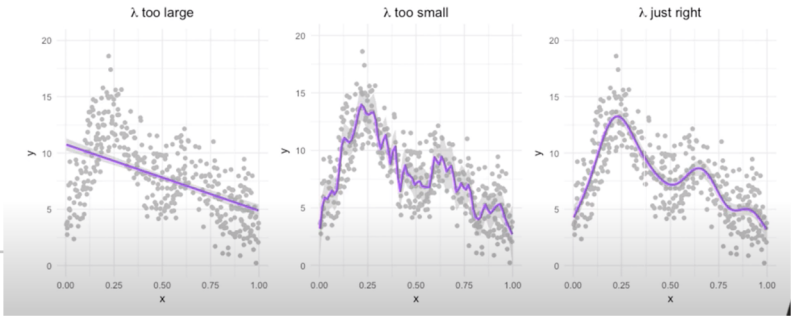
- Using smooth functions of our predictor variables
- The key difference in GAMM vs. say GLMM is that the linear predictor now incorporates smooth functions of at least some covariates, represented as s(x), and this will allow for nonlinear relationships between the covariates and the target variable y
- It involves choosing a basis, which in technical terms means choosing a space of functions for s(x)





GAMM in R

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- Two R packages by Simon Wood:
  - GAMM4 (used in the back-end of DEAP): https://cran.r-project.org/web/packages/gamm4/gamm4.pdf
  - MGCV: https://cran.r-project.org/web/packages/mgcv/mgcv.pdf

- Gamm4 vs MGCV
  - **gamm4** is based on gamm from package **mgcv**, but uses lme4 rather than nlme as the underlying fitting engine via a trick due to Fabian Scheipl. **gamm4** is more robust numerically than gamm, and by avoiding PQL gives better performance for binary and low mean count data.

Additional Resources for GAMM

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Some great tutorials & slides:

1. https://www.r-bloggers.com/2021/05/generalized-additive-models-allowing-for-some-wiggle-room-in-your-models/
2. https://jacolienvanrij.com/Tutorials/GAMM.html
3. https://eric.univ-lyon2.fr/iec/material/1-GAM.pdf
4. http://www.sfs.uni-tuebingen.de/~hbaayen/publications/BaayenLinke2020.pdf
5. https://wiki.qcbs.ca/r_workshop8

Mixed effect models -- Nonlinear

Discussion 3:

How would you determine which nonlinear approach to use or if it is even needed?

Mixed effect models

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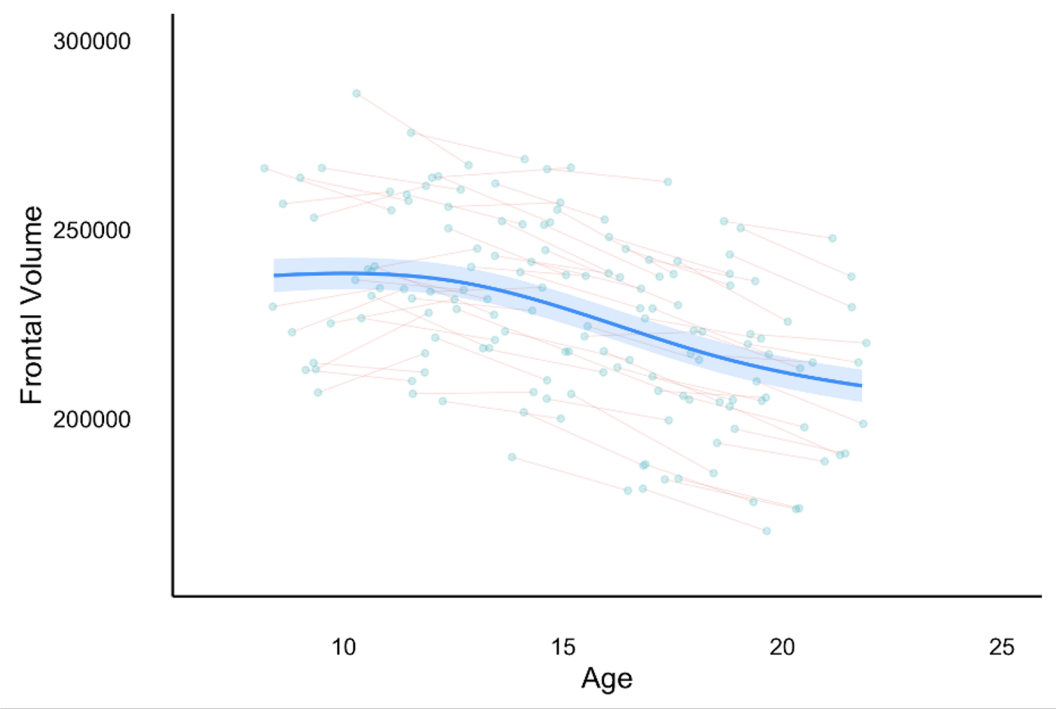

Examine nonlinear Mixed Effect: What can I do?

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Options:

- Fit linear models and look at the model fits to see if non-linearity is present
- Test known polynomials in neurodevelopment (i.e. quad, cubic)
  - Compare unconditional model vs.linear, quadratic, cubic using AIC/BIC
- Look at the data for the shape and natural breakpoints
  - Use regression splines and consider natural spline to control wiggle at edges
- Let the data speak for themselves
  - GAMM (vs. linear)
- Explain your rationale in your paper! :)

Thanks for joining us today!

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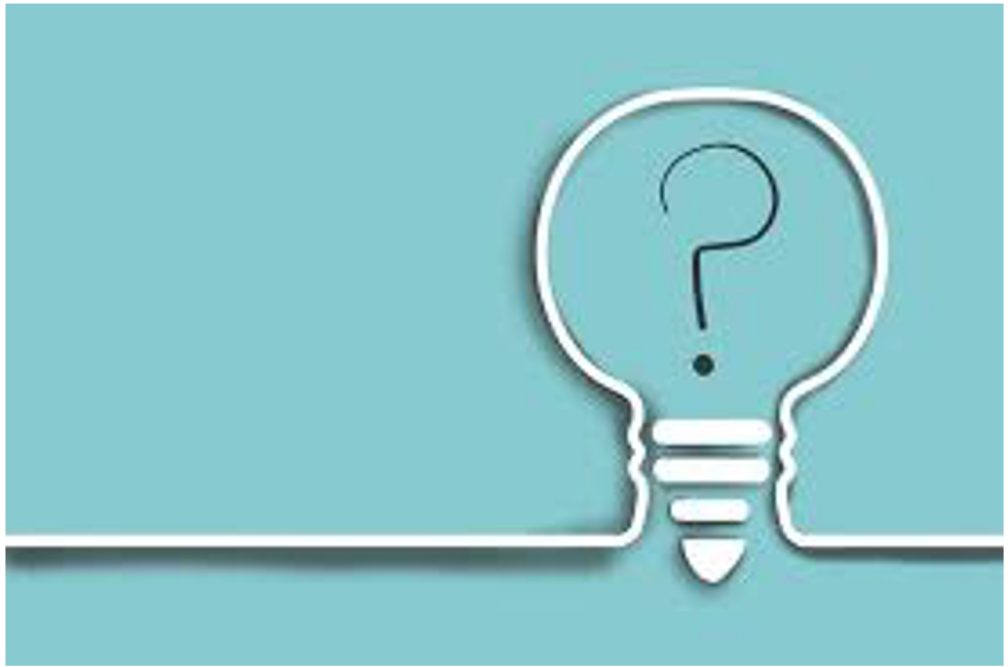

Questions?

Comments?

Ideas?

Will mixed models address your research question?