

**A joint modelling approach to relate
within-individual variability in a repeatedly measured exposure
to a future outcome, allowing for measurement error in the
repeated measures**

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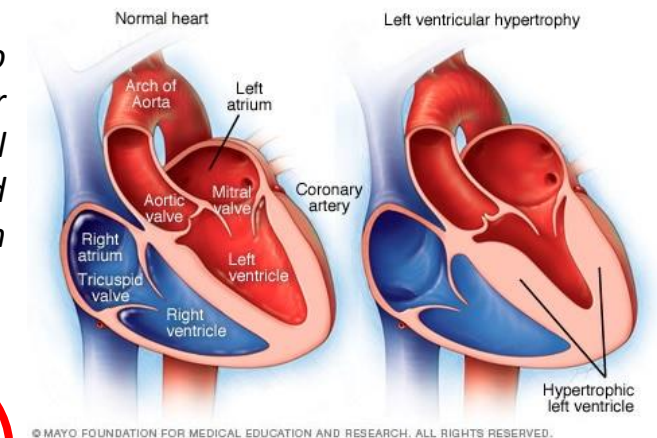
Example: does blood pressure (BP) history predict later biomarkers of cardiovascular disease (CVD)?

- Systolic blood pressure (*mmHg*): repeatedly-measured outcome
- Left ventricular mass ($g/m^{2.7}$): later outcome



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“Left ventricular hypertrophy is both a major maladaptive response to chronic pressure overload and an important risk factor in patients with hypertension.”

Katholi & Couri, 2011

Example: does blood pressure (BP) history predict later biomarkers of cardiovascular disease (CVD)?

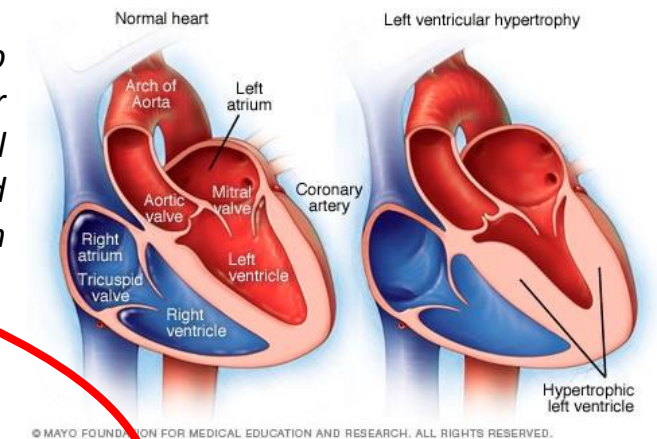
- Systolic blood pressure (*mmHg*): repeatedly-measured outcome
- Left ventricular mass ($g/m^{2.7}$): later outcome

There's been a long-standing interest in investigating whether **mean, or mean trajectory,** of repeatedly-measured BP predicts later signs of CVD...



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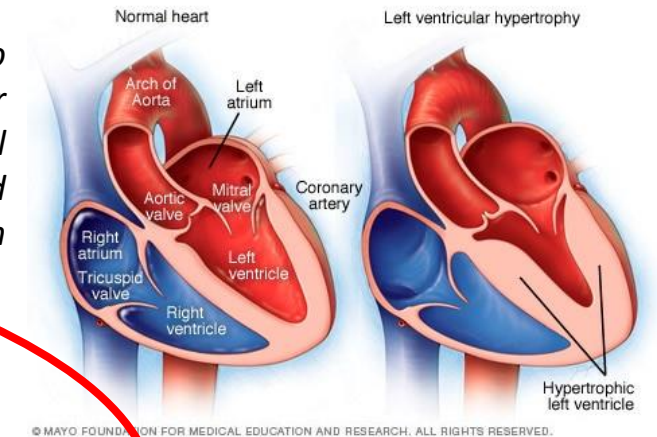
Example: does blood pressure (BP) history predict later biomarkers of cardiovascular disease (CVD)?

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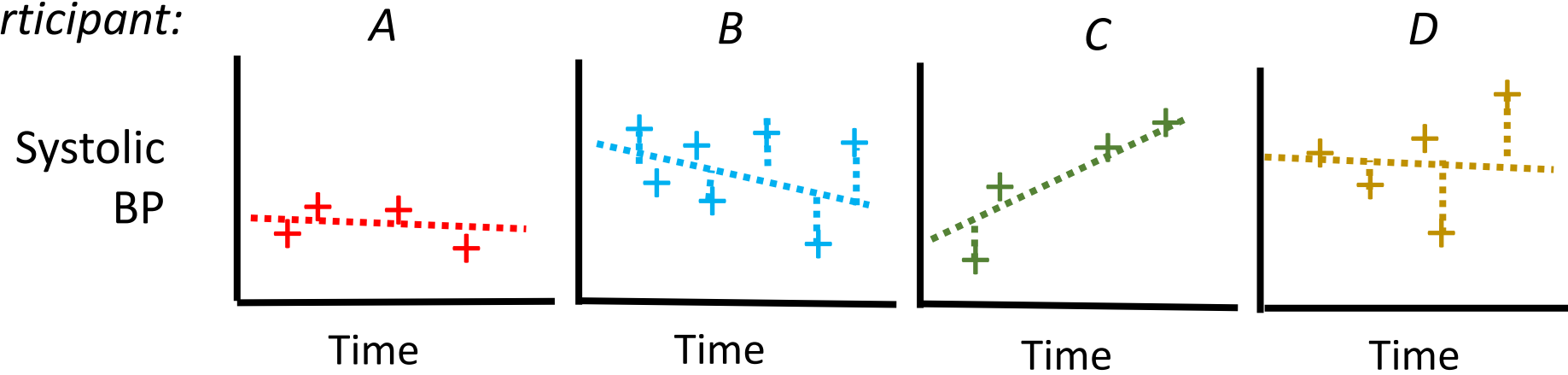
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...but what about **within-individual variability**?

Within-individual variability in BP over the longer-term is an independent CVD risk factor over & above mean blood pressure (e.g. Rothwell, 2010)

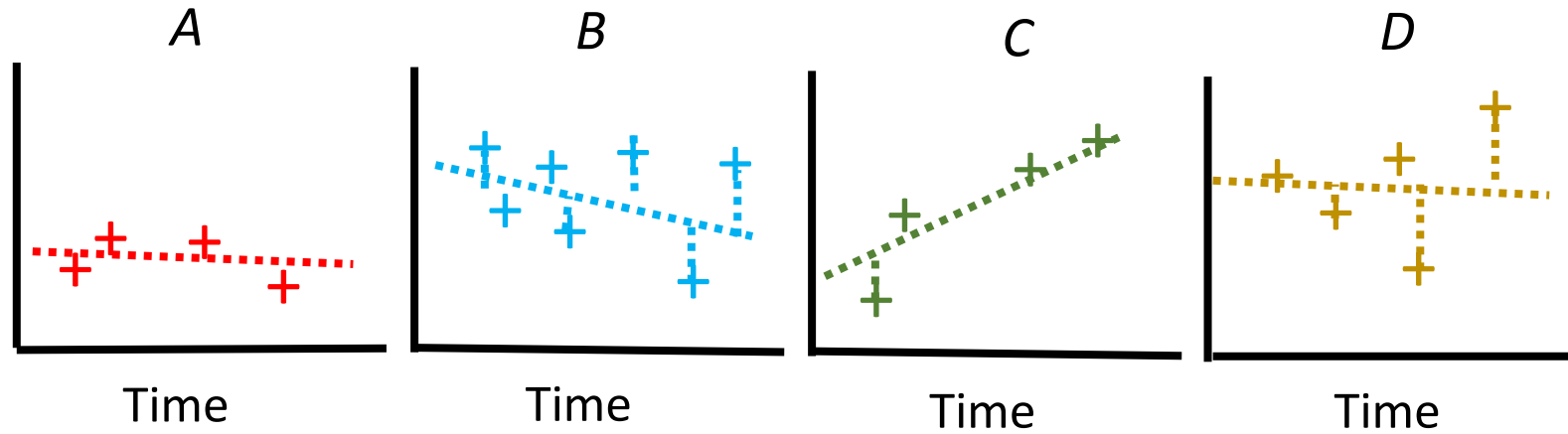
Typical procedures to investigate association of within-individual variability with later outcome include...

Participant:



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Participant:



Stage 1

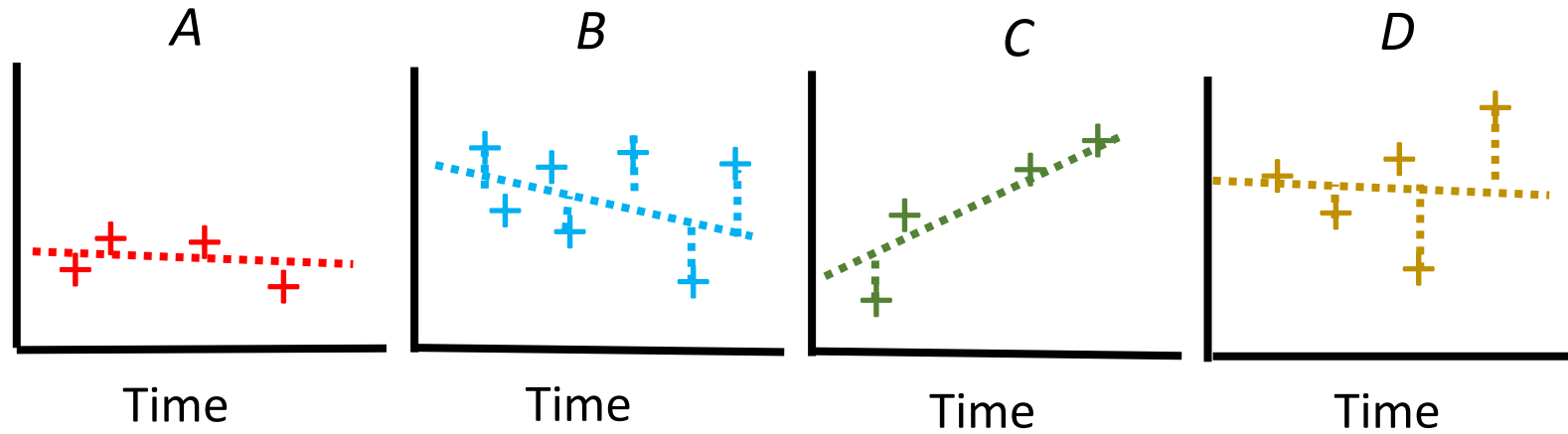
...e.g. residual SD, CV, RMSE, etc., from each person



\mathcal{X}_{1j}

Typical procedures to investigate association of within-individual variability with later outcome include...

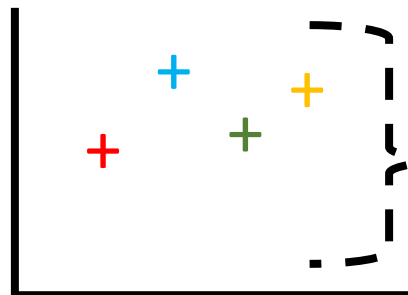
Participant:



...e.g. residual SD, CV, RMSE, etc., from each person

Stage 2

Left ventricular mass

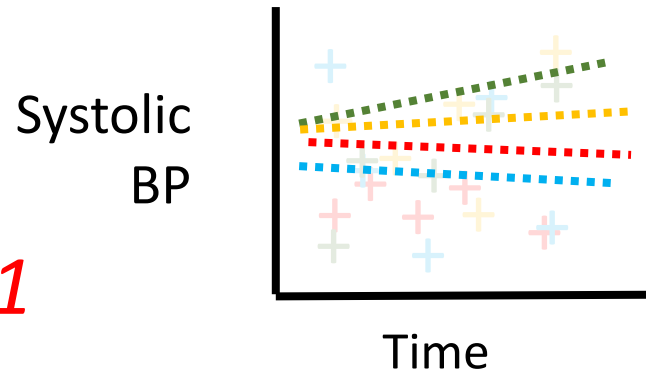


A B C D
Participant

$$y_j = \beta_0 + \beta_1 x_{1j} + e_j$$

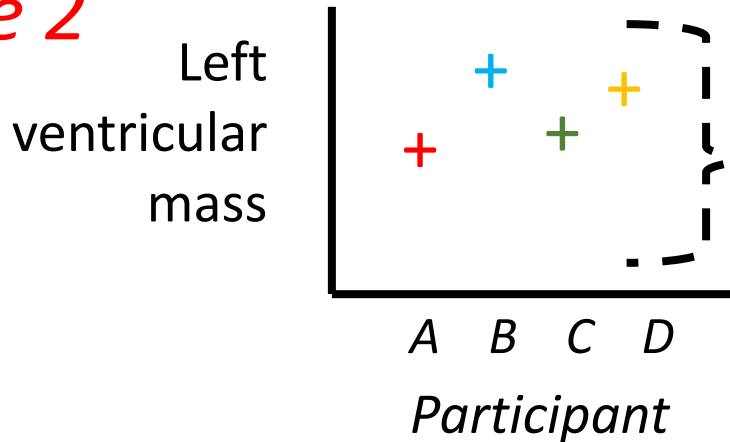
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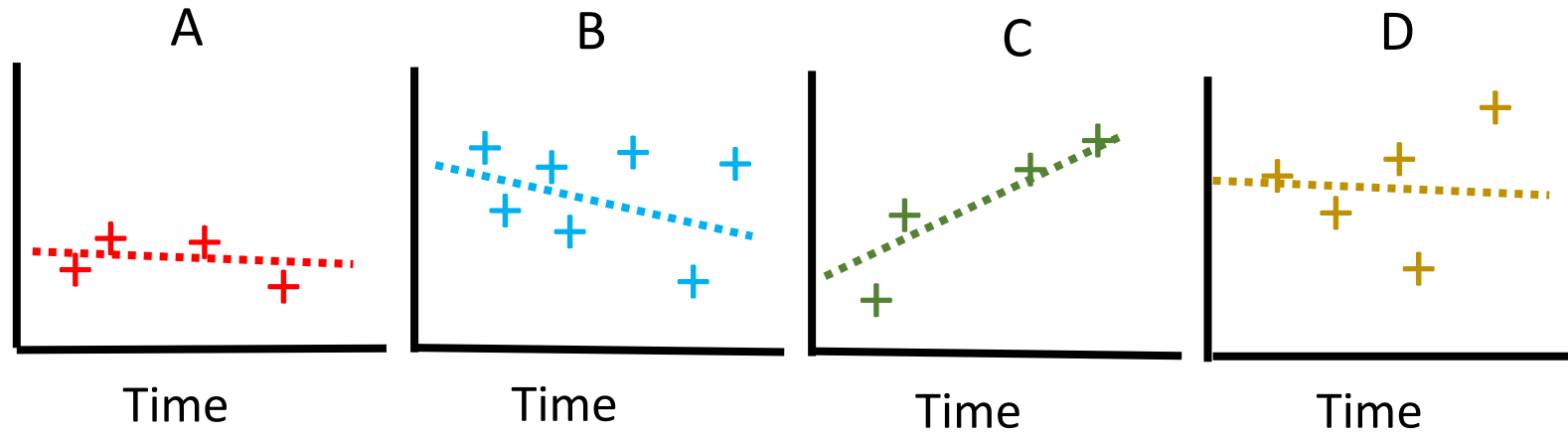
...or e.g. function of residuals from random effects model

Stage 2



$$y_j = \beta_0 + \beta_1 x_{1j} + e_j$$

These 2-stage approaches have important limitations...



Typically a large element of **sampling error** in the estimate of within-individual variability as derived in Stage 1...

...but **information regarding precision of this estimate is lost** between the two stages...

...resulting in regression dilution or attenuation **bias** (towards the null) when fitting model in Stage 2 (akin to measurement error in predictor).

...to address this issue, we use a **joint model, with shared random effects**, to simultaneously estimate within-individual variability in the repeatedly-measured exposure and its association with the later outcome.

Will demonstrate by:

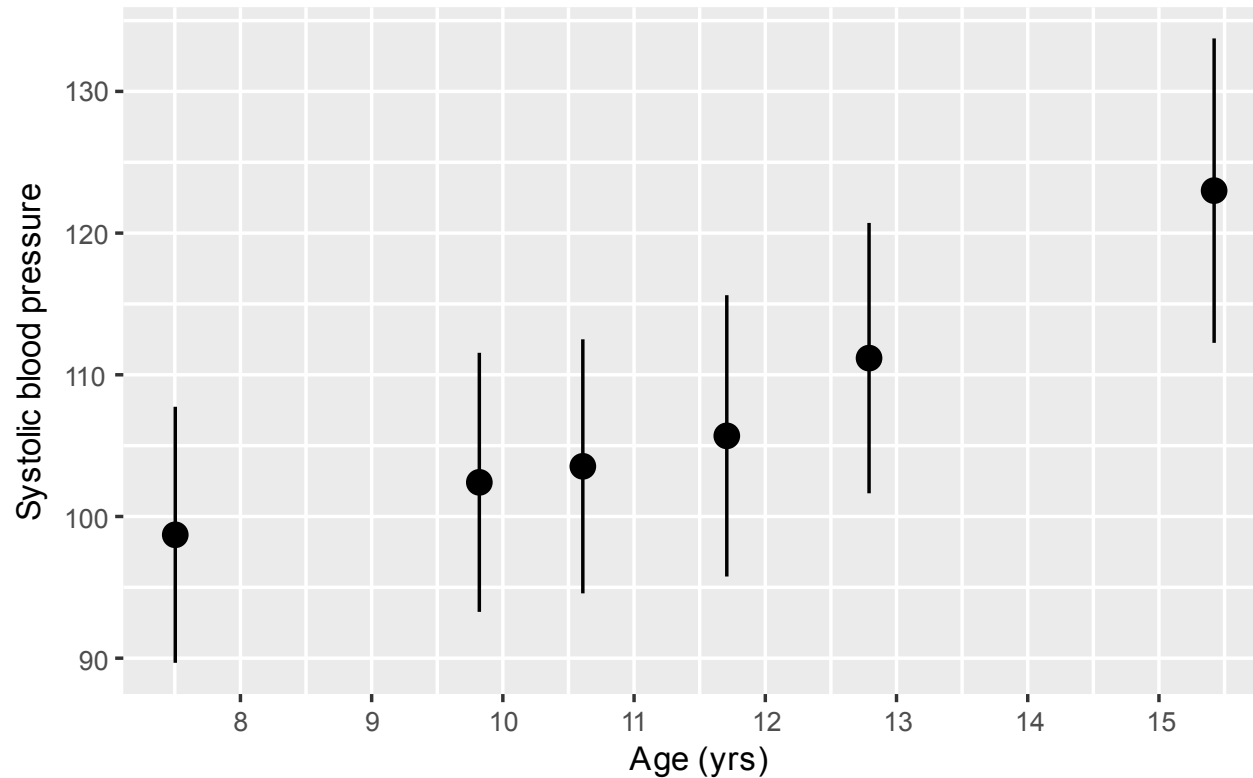
1. Introducing dataset, then stepping through simplified example (with just one covariate)...
2. ...concluding by illustrating with results (from more complex models).

ALSPAC Dataset

n = 1,986

...of the ALSPAC cohort had their systolic blood pressure (SBP) recorded on at least one occasion prior to...

Mean systolic blood pressure (+/-1SD)
vs. mean age at each clinic

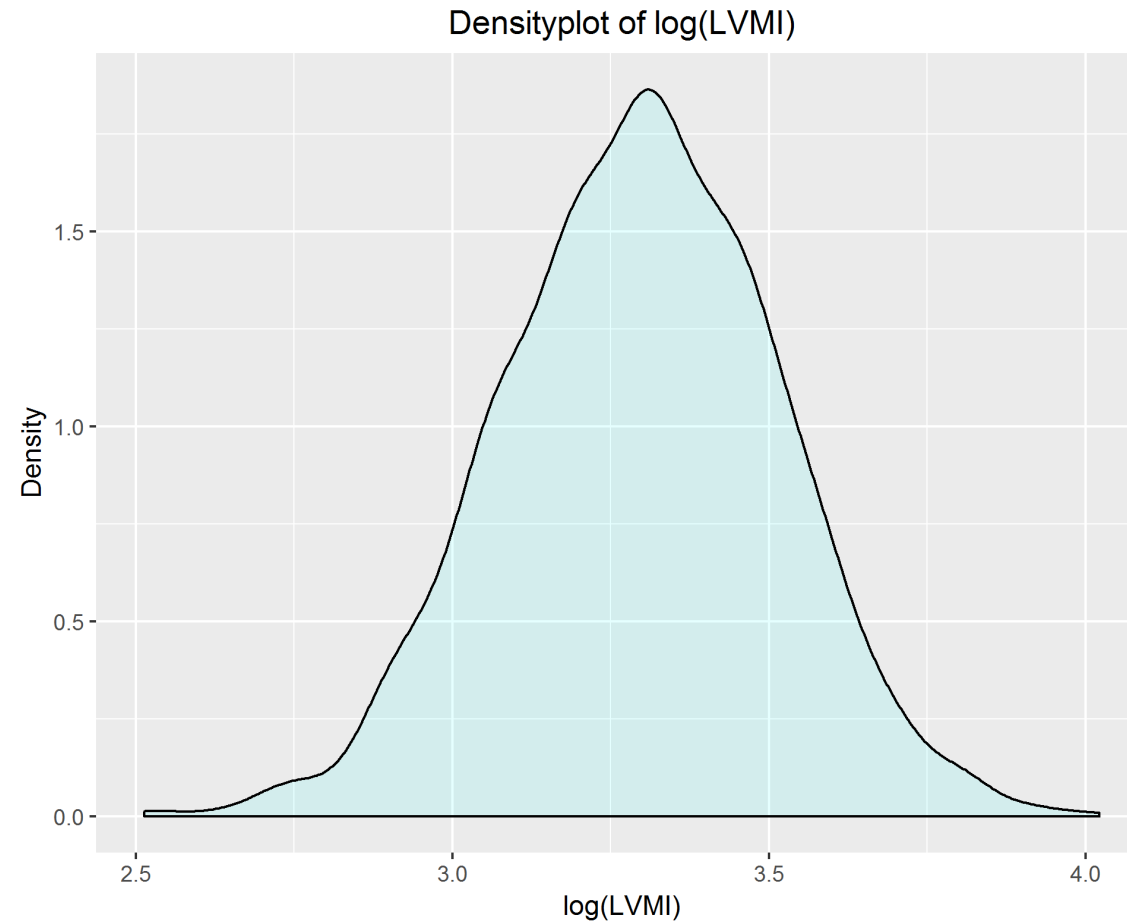


*Repeatedly-
measured
outcome*

ALSPAC Dataset

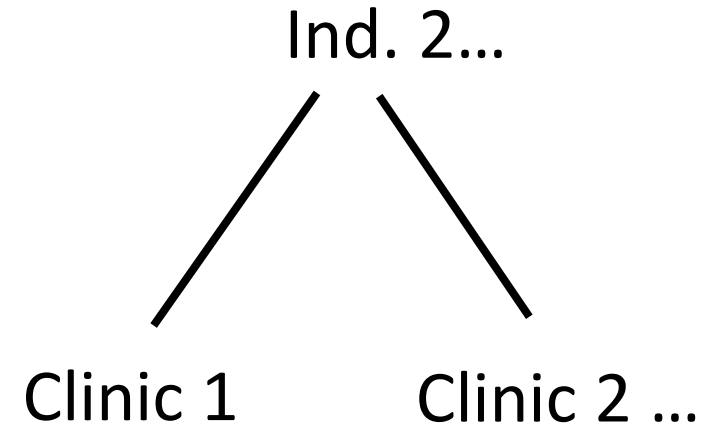
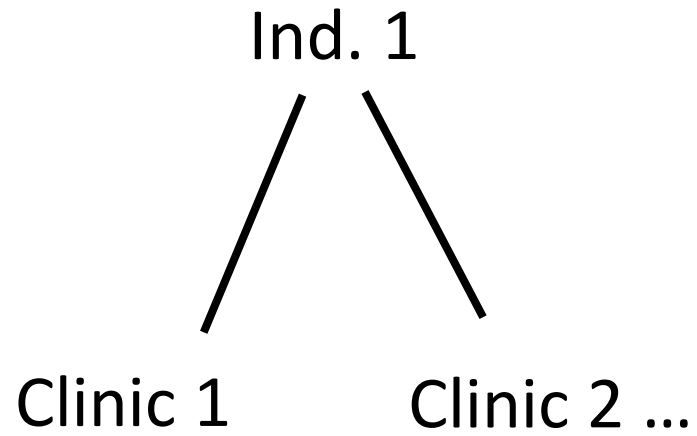
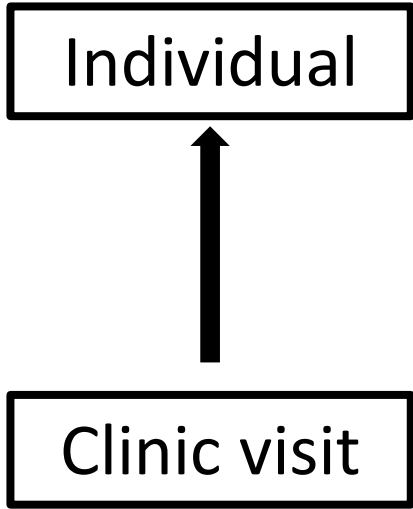
n = 1,986

...having echocardiography at c.18 years of age.



*Later
(individual-
level)
outcome*

Example starts with a 2-level model...

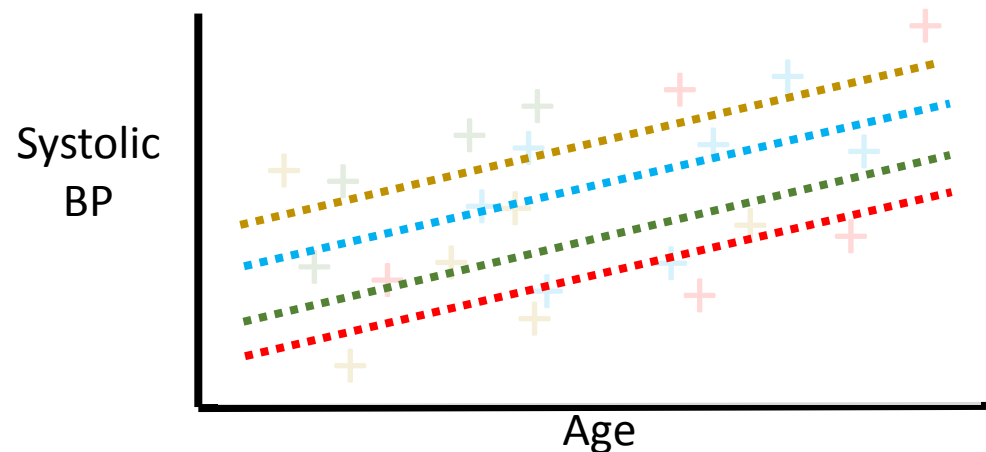


Random (intercept &) slope with complex level 1 variation

$$\text{Clinic BP}_{ij} = \beta_0 + \beta_1 \text{age}_{ij} + u_{0j} + u_{1j} \text{age}_{ij} + e_{ij}$$

$$\begin{pmatrix} u_{0j} \\ u_{1j} \end{pmatrix} \sim \text{N} \left[\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_{u0}^2 & \\ \sigma_{u01} & \sigma_{u1}^2 \end{pmatrix} \right]$$

$$e_{ij} \sim \text{N}(0, \sigma_{eij}^2), \quad \ln(\sigma_{eij}^2) = \alpha_0 + \alpha_1 \text{age}_{ij}$$

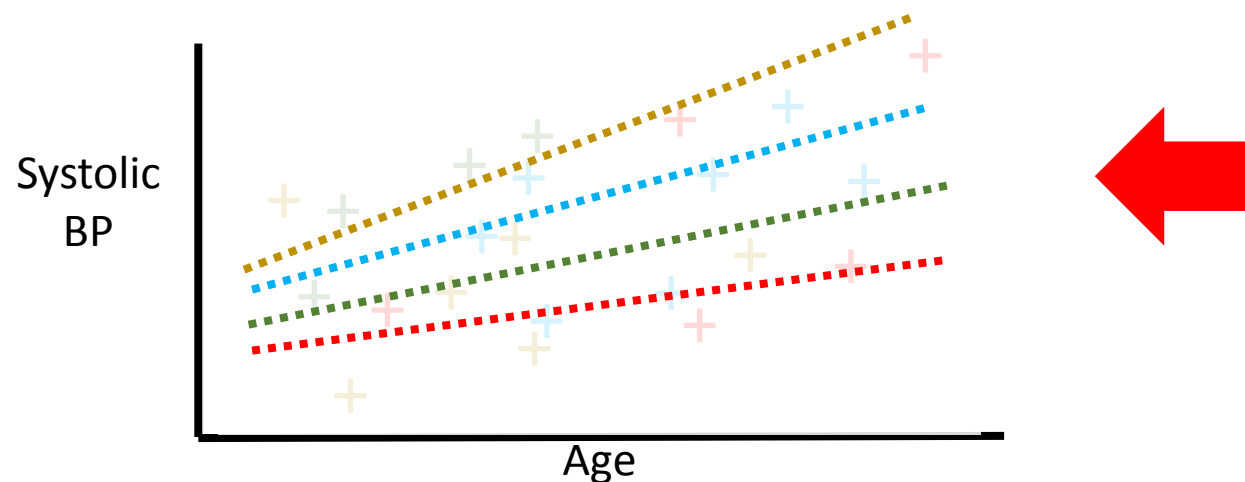


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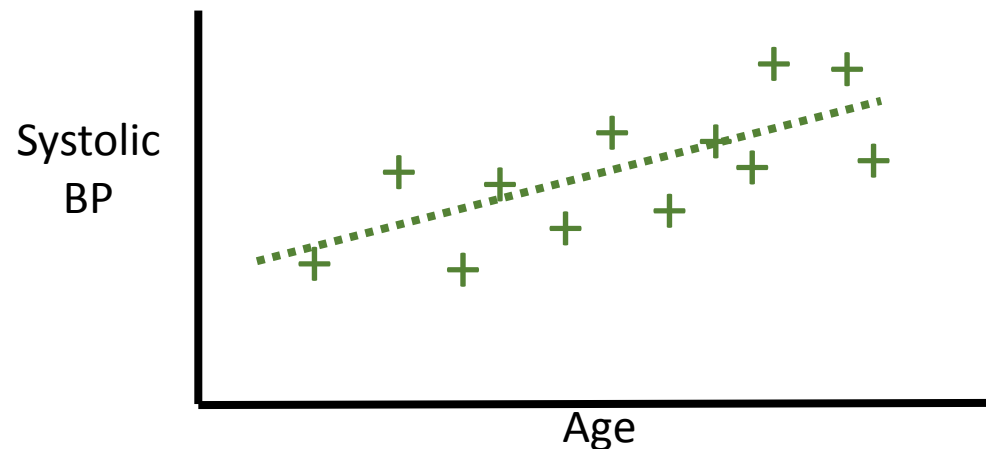
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Participant: C



← ...constant within-individual variation would assume (e.g.) this

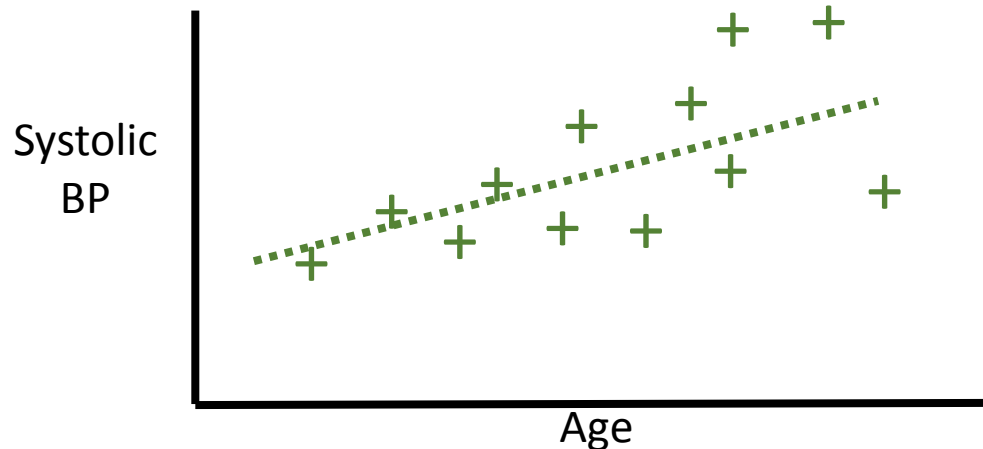
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...but allowing it to be a function of covariates allows for (e.g.) this

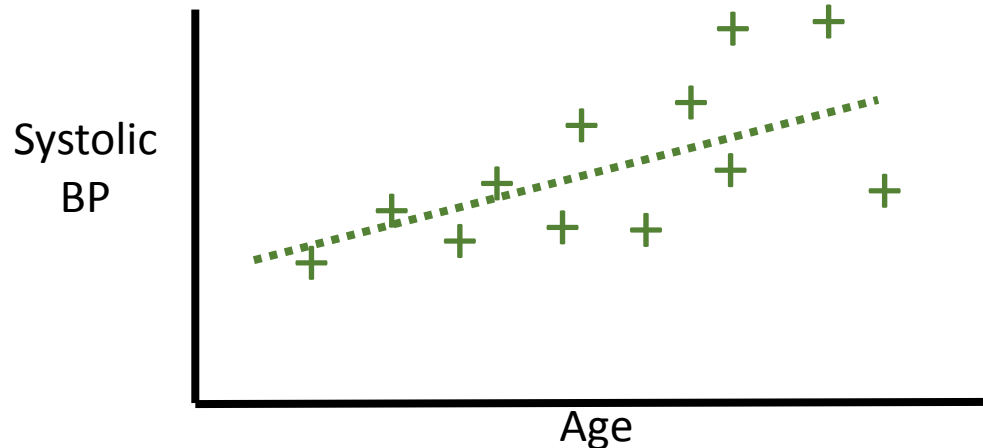
Random (intercept &) slope with complex level 1 variation

$$\text{Clinic BP}_{ij} = \beta_0 + \beta_1 \text{age}_{ij} + u_{0j} + u_{1j} \text{age}_{ij} + e_{ij} \quad (\text{log link ensures within-individual variance remains positive})$$

$$\begin{pmatrix} u_{0j} \\ u_{1j} \end{pmatrix} \sim \text{N} \left[\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_{u0}^2 & \\ \sigma_{u01} & \sigma_{u1}^2 \end{pmatrix} \right]$$

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...adding a random effect for within-individual variance

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“Are some people more variable than others?”

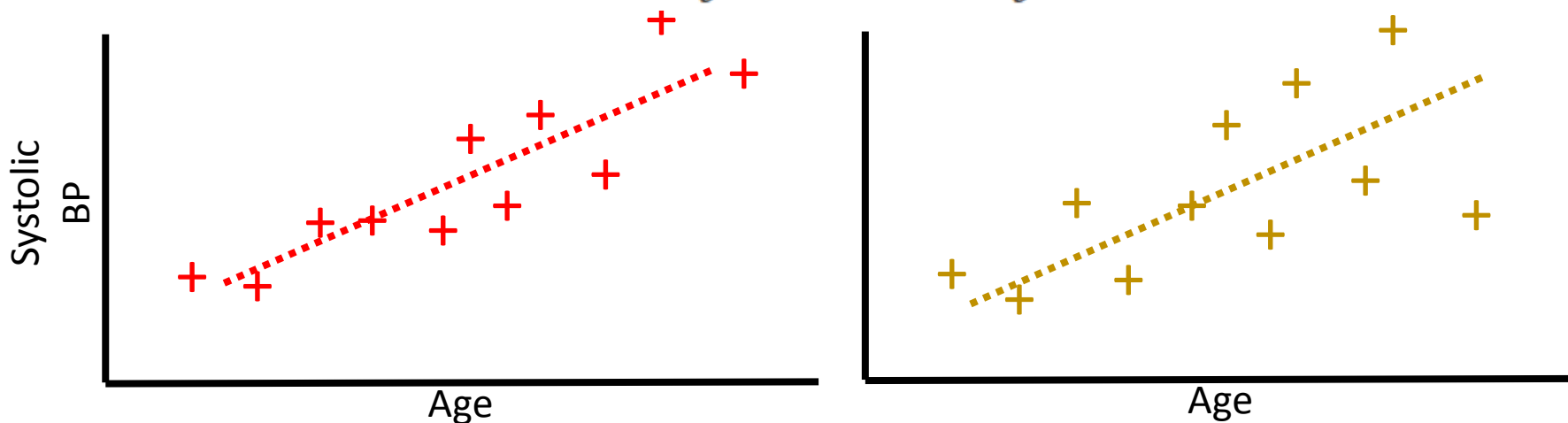
(...having adjusted for other covariates and random effects in the model).

...adding a random effect for within-individual variance

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Hedeker et al. (2008): mixed-effects location scale model

- random scale effects
- random location effects

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Don Hedeker presented this work at the MLM conference in 2009!

...adding the later (individual-level) outcome: joint model

$$\text{Clinic BP}_{ij} = \beta_0 + \beta_1 \text{age}_{ij} + u_{0j} + u_{1j} \text{age}_{ij} + e_{ij}$$

$$\log(\text{LVMI})_j = \gamma_0 + \gamma_1 u_{0j} + \gamma_2 u_{1j} + \gamma_3 u_{2j} + u_{3j}$$

$$\begin{pmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \\ u_{3j} \end{pmatrix} \sim \text{N} \left[\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_{u0}^2 & & & \\ \sigma_{u01} & \sigma_{u1}^2 & & \\ \sigma_{u02} & \sigma_{u12} & \sigma_{u2}^2 & \\ 0 & 0 & 0 & \sigma_{u3}^2 \end{pmatrix} \right]$$


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Later
(individual-
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outcome



$$\begin{pmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \\ u_{3j} \end{pmatrix} \sim \text{N} \left[\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_{u0}^2 & & & \\ \sigma_{u01} & \sigma_{u1}^2 & & \\ \sigma_{u02} & \sigma_{u12} & \sigma_{u2}^2 & \\ 0 & 0 & 0 & \sigma_{u3}^2 \end{pmatrix} \right]$$

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Do estimates of the mean, slope and/or within-individual variability predict later outcome?

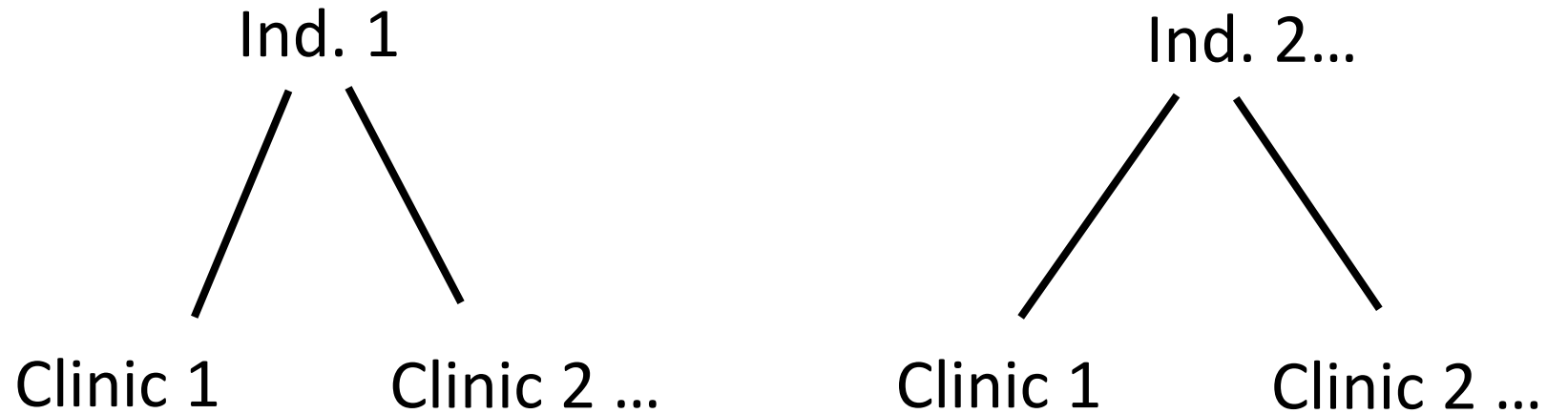
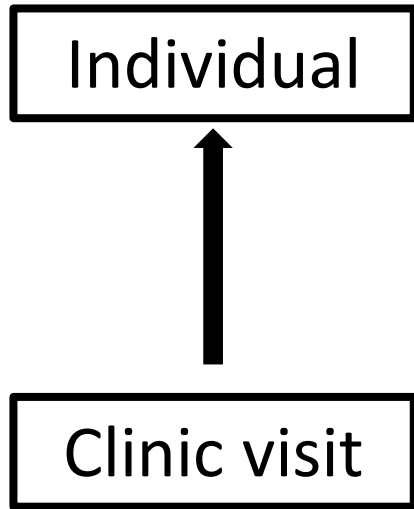
Later (individual-level) outcome

$$\begin{pmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \\ u_{3j} \end{pmatrix} \sim N \left[\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_{u0}^2 & & & \\ \sigma_{u01} & \sigma_{u1}^2 & & \\ \sigma_{u02} & \sigma_{u12} & \sigma_{u2}^2 & \\ 0 & 0 & 0 & \sigma_{u3}^2 \end{pmatrix} \right]$$

...uncertainty in estimates of random effects incorporated into estimates of their effect on later outcome.

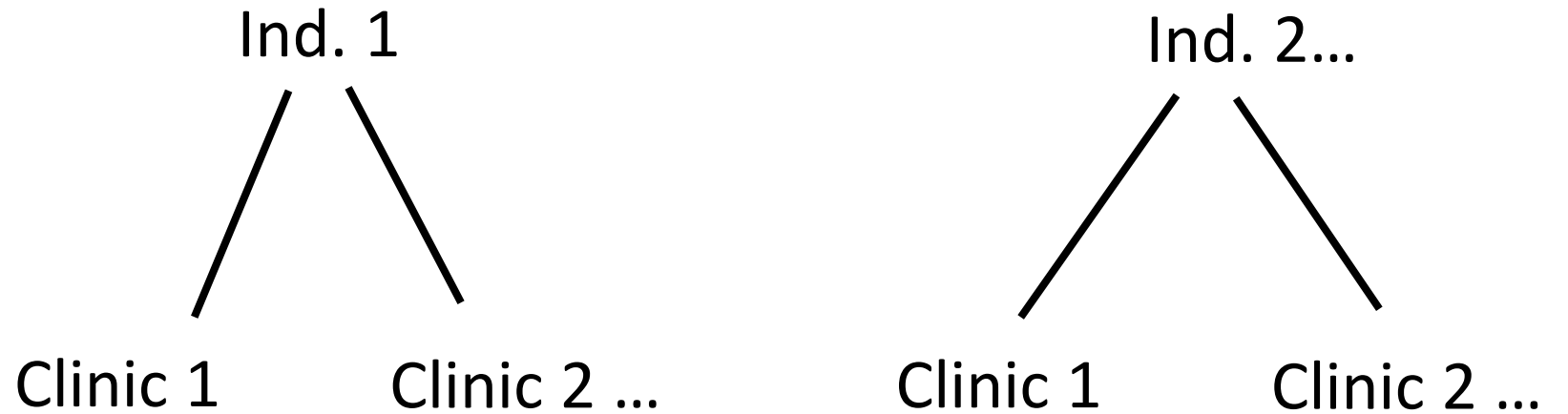
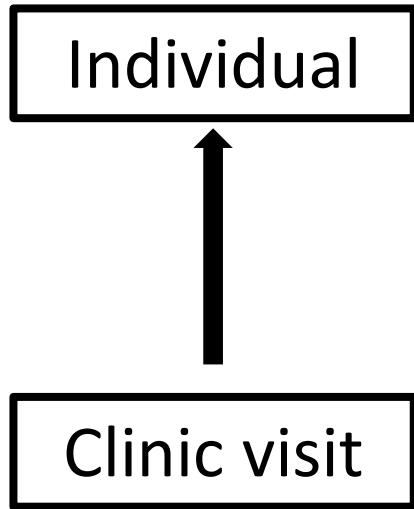
$$e_{ij} \sim N(0, \sigma_{eij}^2), \quad \ln(\sigma_{eij}^2) = \alpha_0 + \alpha_1 \text{age}_{ij} + u_{2j}$$

Example starts with a 2-level model...



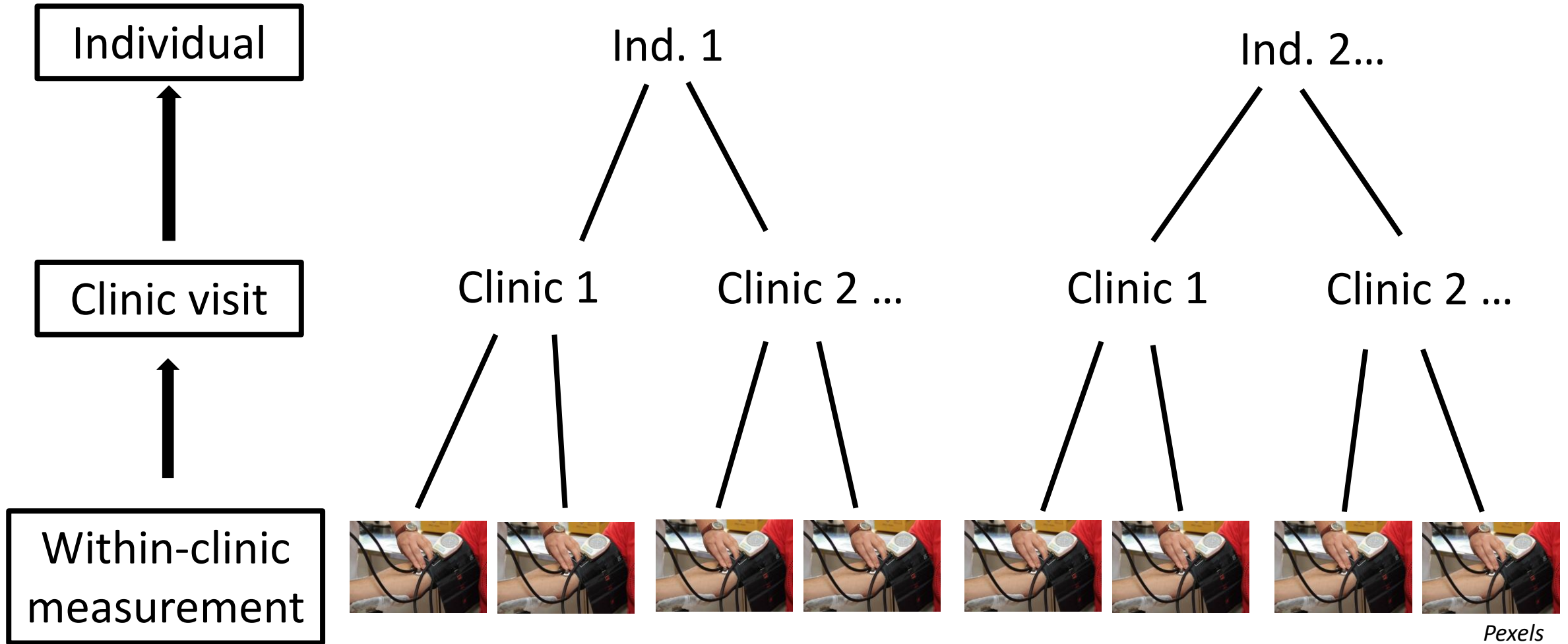
NB: Clinic BP outcome in these initial models is the mean of two measurements taken in that clinic

Example starts with a 2-level model...



A large red arrow points downwards from the 2-level model diagram to a red oval. Inside the oval, the text reads: *...but we have access to those two individual measurements, so...*

...can expand to 3 levels, distinguishing within-clinic (short term) from between-clinic (longer term) within-individual variability



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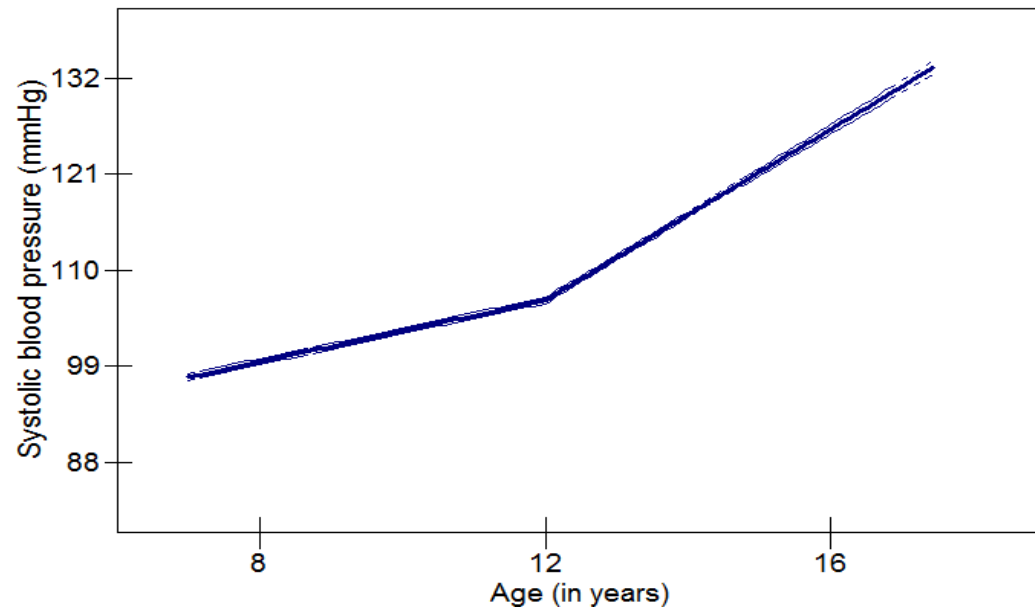
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$$e_{ijk} \sim \text{N}(0, \sigma_e^2)$$

Fitting the models...

- Bayesian estimation in Stan (via rstan)
- Model age via linear spline with a knot point at 12 years of age in fixed part of model (*after: Staley et al, 2015; O’Keeffe et al., 2018*)
- Covariates:
 - Age
 - Sex
 - Weight
 - Height



Fitting the models...

- **Evidence of differences between individuals in their extent of within-individual variability; SD on the log scale = 0.40 (0.27, 0.50).**
- Positive correlation between random intercept and random within-individual variability term: i.e. **people with higher BP tend to have more fluctuation in their BP; $Cor(v_0, v_2) = 0.48 (0.31, 0.69)$.**
- On average, **greater within-individual variability in BP ($\ln(\sigma_{u_{jk}}^2)$):**
 - **at older ages; 0.12 (0.06, 0.17)**
 - **in females; 0.17 (0.05, 0.29)**
 - **for heavier log(bodyweights); 0.56 (0.19, 0.93)**

NB: estimates given as: mean (95% credible interval)

Fitting the models...

What about the later outcome, log(LVMI)?

*NB these estimates are * 10⁻²*

- **Higher within-individual variability predicted greater log(LVMI);**
 $\beta = 0.47 (-0.03, 1.07)$
- ...**but not** when the random intercept and random slope terms were also included as exposures in the linear model for log(LVMI):
 - Random intercept: $\beta = 0.07 (0.02, 0.14)$
 - Random slope: $\beta = 0.40 (0.08, 0.78)$
 - Random within-individual variability: $\beta = -0.85 (-2.77, 0.22)$

NB: estimates given as: mean (95% credible interval)

Further work

Applying this joint modelling approach to other topics:
e.g. within-individual variability in cognitive functioning
at older ages, and relation to dementia...

...with such psychometric measurements, relationship
between random intercept and random scale effects
may be non-linear, due to bounded scale: need to
model this appropriately.

Any questions?

**Want to run a sub study?
Questions for 2019 questionnaire?
Get in touch: alspac-exec@bristol.ac.uk**



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