Relating change in two variables using bivariate multilevel spline models

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Overview

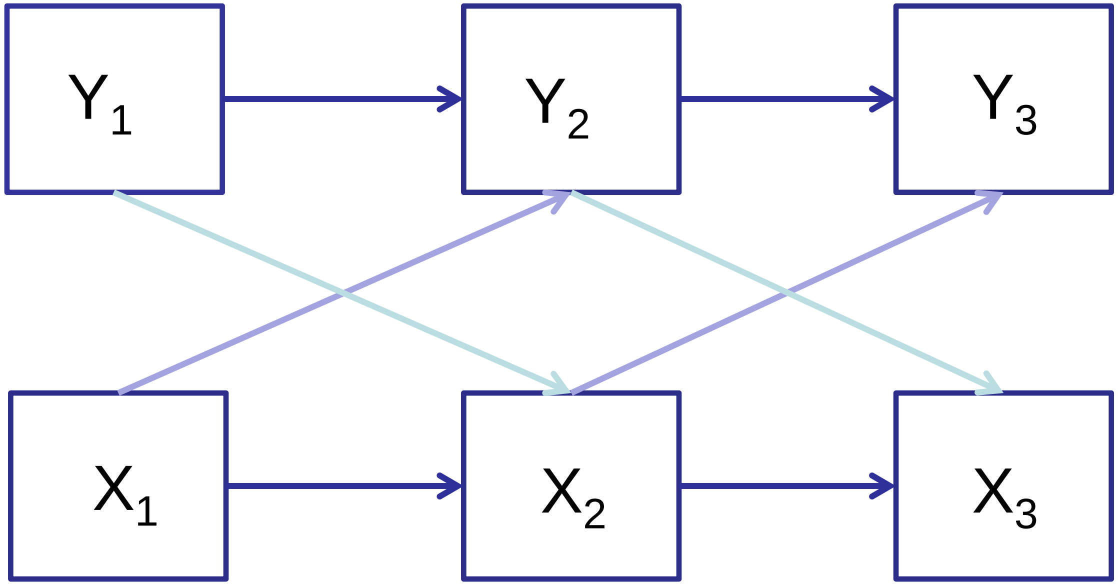
- Rationale
- Motivating example: gestational weight gain and blood pressure change in pregnancy
- Bivariate multilevel linear spline models
- Testing hypotheses about temporal relationships between the variables
- Deriving regression coefficients from the random effects variance-covariance matrix
- Comparison with structural equation model
- Discussion

Rationale

- Multilevel growth models are commonly used to assess determinants of growth/change or the relationships of growth/change with an outcome
- Less often used to examine relationships between changes in two or more variables
- May hypothesise that change in one variable may cause a change in another
- Difficult to derive and interpret associations between non-linear patterns of change and assess whether change in one variable precedes change in the other

Cross-lagged structural equation model

- Useful for investigating temporal associations – does the value of variable X at time t_1 influence the value of variable Y at time t_2?



Cross-lagged SEM

- Granger causality (Granger, 1969) – conditional on earlier observations of Y, do earlier observations of X (and the current observation of X) predict the current observation of Y?

Cross-lagged SEM works well when:

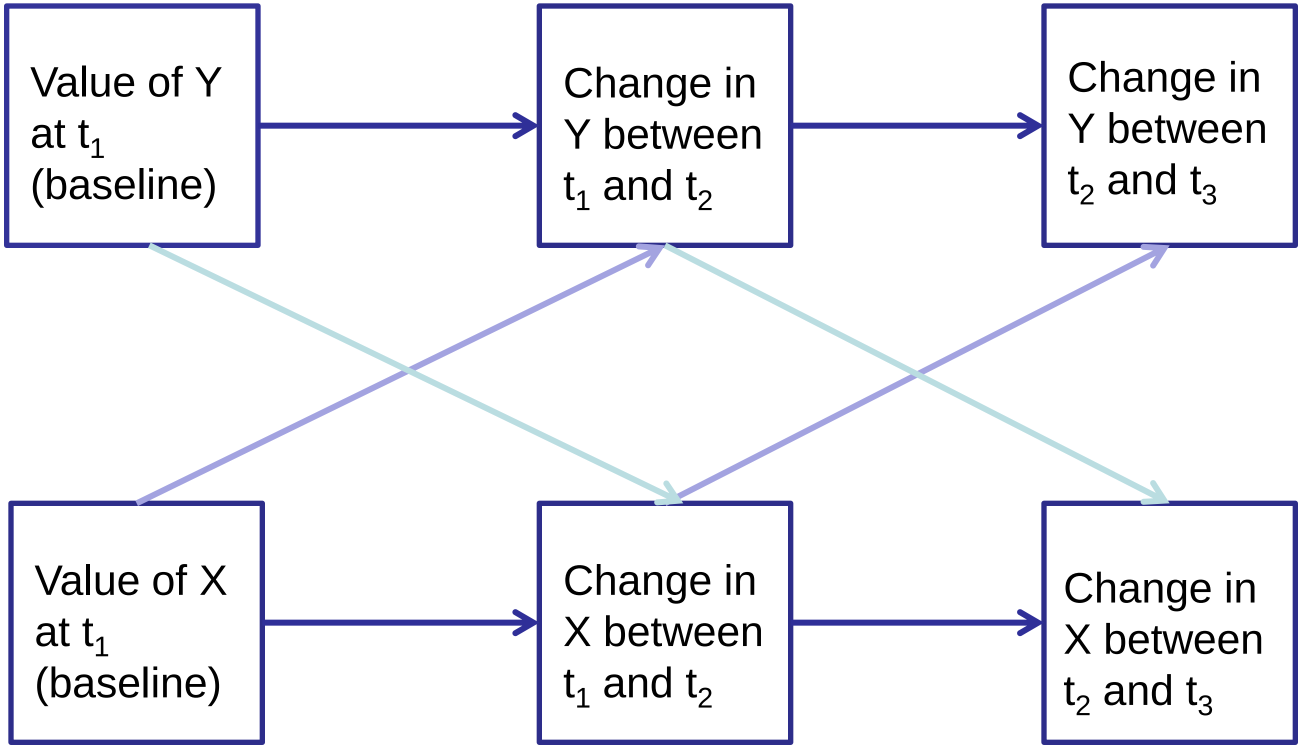
- Repeated measurements are made at the same time points for each individual
- There is a small number of measurement occasions – otherwise many paths to estimate
- Interested in associations between absolute values of the variables at different time points

What if…

- Different numbers and timings of repeated measurements for different individuals? eg. routine data
- Large number of possible measurement times and it is not clear how to select important time points to include in the model?
- Repeated measurements are highly correlated and there are collinearity problems when examining associations between these?
- We are most interested in associations between rates of change in two variables, rather than their absolute values?

  eg. how is a unit increase in X between times t_1 and t_2 associated with change in Y between times t_2 and t_3

Relating change in two variables



Use a multilevel model to derive these parameters and a data-driven approach to selecting the time points t_1, t_2, etc.

Example: weight gain and mean arterial pressure change in pregnancy

- Greater gestational weight gain (GWG) is associated with a higher risk of developing a hypertensive disorder of pregnancy: gestational hypertension and pre-eclampsia

- Reverse causality?

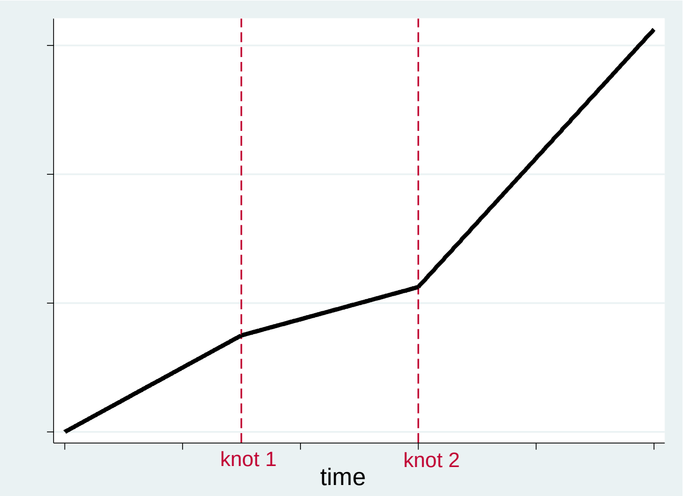
  Pre-eclampsia is associated with increased oedema
  → greater weight gain

- Do changes in weight precede changes in blood pressure or vice versa?

ALSPAC

- 14,541 women living in Avon, UK with expected delivery dates between April 1991 and December 1992 recruited
- Routine antenatal BP (median 14 per woman) and weight (median 12 per woman) measurements abstracted from obstetric records
- MAP calculated as (SBP + 2 x DBP)/3
- Included 11,650 women who had a live term birth and did not develop pre-eclampsia or have previous hypertension

Linear splines



- Linear pattern of change between knot points

- For a model with *m* linear splines, with earliest observation at time t_0, latest observation at time t_m, and *m-1* knots at times, $t_1 < t_2 < \ldots < t_{m-1}$, the linear splines, s_l, are defined as:

$$
\begin{aligned}
s_{ljk} &= 0 && \text{if} \quad t_{jk} \le t_{l-1}, \\
s_{ljk} &= (t_{jk} - t_{l-1}) && \text{if} \quad t_{l-1} < t_{jk} \le t_l, \qquad \text{for } l = 1,.., m; \\
s_{ljk} &= (t_l - t_{l-1}) && \text{if} \quad t_{jk} > t_l,
\end{aligned}
$$

for the j^{th} observation on the k^{th} individual

Multilevel linear spline model

A two-level univariate linear spline model for an outcome *y*, with measurements, *j*=1,…,*J*, within individuals, *k*=1,…,*K*,

which has *m* linear splines, s_l for *l*=1,…,*m*, is defined as:

$$y_{jk} = \beta_0 + \sum_{l=1}^{m} (\beta_l + u_{lk}) s_{ljk} + u_{0k} + \varepsilon_{0jk}$$

with assumptions:

$$\begin{bmatrix} u_{0k} \\ u_{1k} \\ \vdots \\ u_{mk} \end{bmatrix} \sim N(\mathbf{0}, \Omega_u), \quad \Omega_u = \begin{bmatrix} \sigma^2_{u0} & & & \\ \sigma_{u01} & \sigma^2_{u1} & & \\ \vdots & & \ddots & \\ \sigma_{u0m} & \sigma_{u1m} & \cdots & \sigma^2_{um} \end{bmatrix}$$

$$\varepsilon_{0jk} \sim N(0, \sigma^2_{\varepsilon})$$

Bivariate multilevel linear spline model

Now have a three-level model, with measurements, *(i)*=1,2, within measurement occasions, *j*=1,…,*J*, within individuals, *k*=1,…,*K*.

$$y_{jk}^{(i)} = \beta_0^{(i)} + \sum_{l=1}^{m^{(i)}} (\beta_l^{(i)} + u_{lk}^{(i)}) s_{ljk}^{(i)} + u_{0k}^{(i)} + \varepsilon_{0jk}^{(i)} \qquad \text{for } i=1,2$$

$$\begin{bmatrix} u_{0k}^{(1)} \\ u_{1k}^{(1)} \\ \vdots \\ u_{m^{(1)}k}^{(1)} \\ u_{0k}^{(2)} \\ u_{1k}^{(2)} \\ \vdots \\ u_{m^{(2)}k}^{(2)} \end{bmatrix} \sim N(\mathbf{0}, \Omega_u), \qquad \Omega_u = \begin{bmatrix} \sigma_{u0}^{2(1)} & & & & & & & \\ \sigma_{u01}^{(1)} & \sigma_{u1}^{2(1)} & & & & & & \\ \vdots & & \ddots & & & & & \\ \sigma_{u0m^{(1)}}^{(1)} & \sigma_{u1m^{(1)}}^{(1)} & \cdots & \sigma_{um^{(1)}}^{2(1)} & & & & \\ \sigma_{u00}^{(1)(2)} & \sigma_{u10}^{(1)(2)} & \cdots & \sigma_{um^{(1)}0}^{(1)(2)} & \sigma_{u0}^{2(2)} & & & \\ \sigma_{u01}^{(1)(2)} & \sigma_{u11}^{(1)(2)} & \cdots & \sigma_{um^{(1)}1}^{(1)(2)} & \sigma_{u01}^{(2)} & \sigma_{u1}^{2(2)} & & \\ \vdots & & & \vdots & \vdots & & \ddots & \\ \sigma_{u0m^{(2)}}^{(1)(2)} & \sigma_{u1m^{(2)}}^{(1)(2)} & \cdots & \sigma_{um^{(1)}m^{(2)}}^{(1)(2)} & \sigma_{u0m^{(2)}}^{(2)} & \sigma_{u1m^{(2)}}^{(2)} & \cdots & \sigma_{um^{(2)}}^{2(2)} \end{bmatrix}$$

$$\begin{bmatrix} \varepsilon_{0jk}^{(1)} \\ \varepsilon_{0jk}^{(2)} \end{bmatrix} \sim N(\mathbf{0}, \Omega_\varepsilon), \qquad \Omega_\varepsilon = \begin{bmatrix} \sigma_{\varepsilon 0}^{2(1)} & \\ \sigma_{\varepsilon 00}^{(1)(2)} & \sigma_{\varepsilon 0}^{2(2)} \end{bmatrix}$$

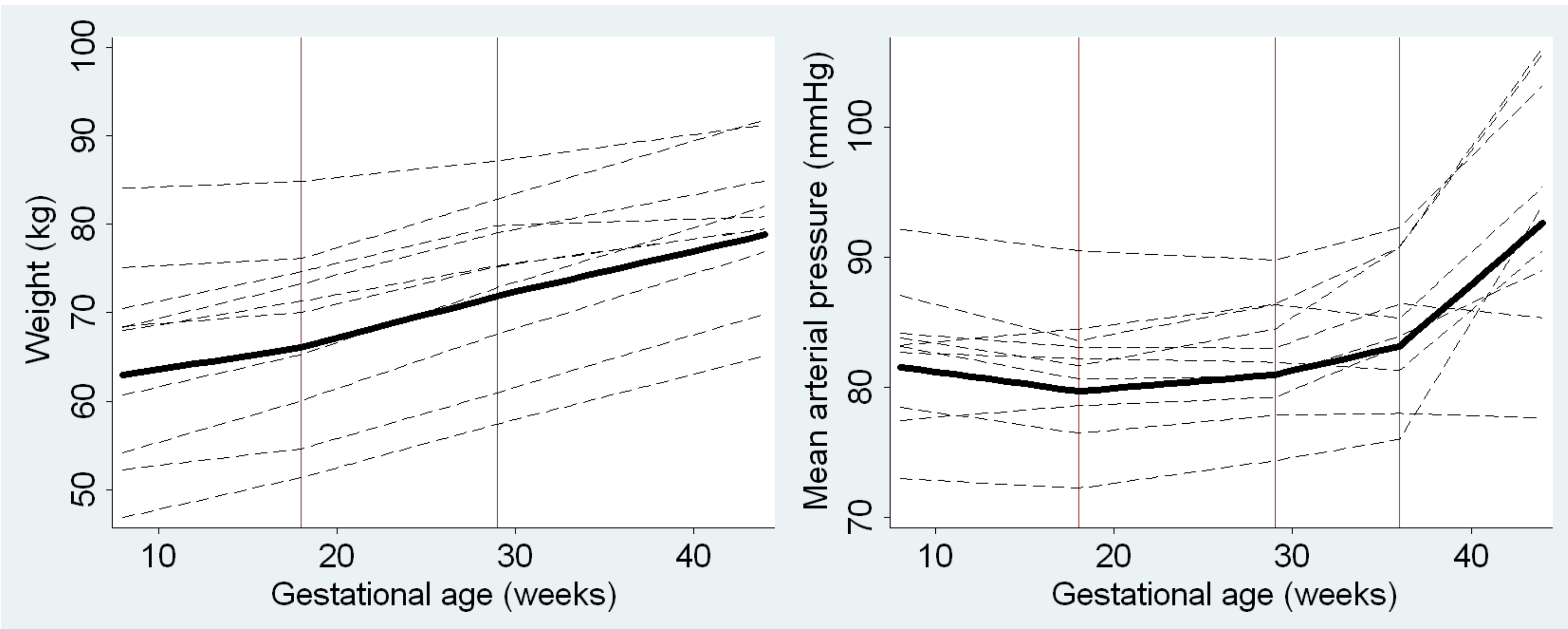
Knot point selection for weight and MAP

- Fitted fractional polynomial curves – “eyeballed” approximate change points
- Compared log-likelihood of different 2 and 3 knot models with knot points varied around these values
- For models with high log-likelihoods, calculated mean difference between observed and predicted values for each 4-week period of gestation and averaged this
- Knot points of best-fitting models were at:
  - 18 and 28 weeks gestation for weight
  - 18, 30 and 36 weeks gestation for MAP
- For simplicity used knot points of 18 and 29 weeks for weight and 18, 29 and 36 weeks for MAP in the bivariate model

Multilevel linear spline models for weight and MAP

Weight

MAP



Hypothesis testing

- Fit series of nested models with different sets of covariances between the individual-level random effects constrained to be 0
- Compare the fit using likelihood ratio tests (null hypothesis that the constrained model fits the data as well as the unconstrained model)
- Sets of constraints chosen so that a particular hypothesis about the relationships between changes in each of the variables can be tested

Hypothesis 1: Changes in the two variables are only correlated in the same and adjacent time periods

- Constrain covariances between random effects relating to changes in the two variables in non-adjacent time periods to be 0
- Compare the fit of the model to that of the full model with these covariances freely estimated
- Simplifies the model if the null hypothesis is not rejected

Hypothesis 1: Constrained model

		Weight				MAP				
		At 8 wks	Change 8-18 wks	Change 18-29 wks	Change 29+ wks	At 8 wks	Change 8-18 wks	Change 18-29 wks	Change 29-36 wks	Change 36+ wks
Weight	At 8 wks	X								
	Change 8-18 wks	X	X							
	Change 18-29 wks	X	X	X						
	Change 29+ wks	X	0	X	X					
MAP	At 8 wks	X	X	X	X	X				
	Change 8-18 wks	X	X	X	0	X	X			
	Change 18-29 wks	X	X	X	X	X	X	X		
	Change 29-36 wks	X	0	X	X	X	0	X	X	
	Change 36+ wks	X	0	0	X	X	0	0	X	X

X indicates a freely estimated parameter; 0 indicates a parameter constrained to 0

Hypothesis 2: Change in variable 1 precedes change in variable 2 (and not vice versa)

- For each period of change in variable 2, constrain random effect covariances with changes in variable 1 in all subsequent time periods to be 0
- Compare the fit of the model to that of the full model with these covariances freely estimated
- May obtain some indication of the direction (if any) of causality

Hypothesis 2: Weight change precedes MAP change constrained model

		Weight				MAP				
		At 8 wks	Change 8-18 wks	Change 18-29 wks	Change 29+ wks	At 8 wks	Change 8-18 wks	Change 18-29 wks	Change 29-36 wks	Change 36+ wks
Weight	**At 8 wks**	X								
	Change 8-18 wks	X	X							
	Change 18-29 wks	X	X	X						
	Change 29+ wks	X	X	X	X					
MAP	**At 8 wks**	X	X	X	X	X				
	Change 8-18 wks	X	X	0	0	X	X			
	Change 18-29 wks	X	X	X	0	X	X	X		
	Change 29-36 wks	X	X	X	X	X	X	X	X	
	Change 36+ wks	X	X	X	X	X	X	X	X	X

Hypothesis 2: MAP change precedes weight change constrained model

		Weight				MAP				
		At 8 wks	Change 8-18 wks	Change 18-29 wks	Change 29+ wks	At 8 wks	Change 8-18 wks	Change 18-29 wks	Change 29-36 wks	Change 36+ wks
Weight	At 8 wks	X								
	Change 8-18 wks	X	X							
	Change 18-29 wks	X	X	X						
	Change 29+ wks	X	X	X	X					
MAP	At 8 wks	X	X	X	X	X				
	Change 8-18 wks	X	X	X	X	X	X			
	Change 18-29 wks	X	0	X	X	X	X	X		
	Change 29-36 wks	X	0	0	X	X	X	X	X	
	Change 36+ wks	X	0	0	X	X	X	X	X	X

Hypothesis 3: There is a lag time between change in variable 1 and change in variable 2

- Constrain covariances between random effects relating to change in variable 1 and change in variable 2 in the immediately subsequent time period(s) to be 0
- Allow covariances of change in variable 1 with change in variable 2 in later time periods (after the lag time) to be freely estimated
- Compare the model fit with that of the full model

Hypothesis 3: Possible constrained model

		Weight				MAP				
		At 8 wks	Change 8-18 wks	Change 18-29 wks	Change 29+ wks	At 8 wks	Change 8-18 wks	Change 18-29 wks	Change 29-36 wks	Change 36+ wks
Weight	At 8 wks	X								
	Change 8-18 wks	X	X							
	Change 18-29 wks	X	X	X						
	Change 29+ wks	X	X	X	X					
MAP	At 8 wks	X	X	X	X	X				
	Change 8-18 wks	X	X	X	X	X	X			
	Change 18-29 wks	X	0	X	X	X	X	X		
	Change 29-36 wks	X	X	0	X	X	X	X	X	
	Change 36+ wks	X	X	X	X	X	X	X	X	X

Hypothesis testing in GWG and MAP example

Model	Deviance	Difference in df compared with Model 1	P-value
Model 1: Full model	984212.0		
Model 2: Changes in weight and MAP are only associated in the same and adjacent periods of gestation	984277.6	8	<0.001
Model 3: Weight change precedes MAP change	984241.5	3	<0.001
Model 4: MAP change precedes weight change	984235.5	5	<0.001

Deriving regression coefficients for change in one variable on change in another

- Eg. Is rate of change in variable 1 in time period 1 associated with rate of change in variable 2 in time period 2?

$$\text{Correlation} = \frac{\text{cov(slope of variable1 in period 1, slope of variable 2 in period 2)}}{\sqrt{\text{var(slope of variable 1 in period 1) x var(slope of variable 2 in period 2)}}}$$

$$= \frac{\sigma_{u12}^{(1)(2)}}{\sqrt{\sigma_{u1}^{2(1)}\sigma_{u2}^{2(2)}}}$$

Regression coefficient (rate of change in variable 2 in period 2 regressed on rate of change in variable 1 in period 1)

$$= \frac{\text{cov(slope of variable1 in period 1, slope of variable 2 in period 2)}}{\text{var(slope of variable 1 in period 1)}}$$

$$= \frac{\sigma_{u12}^{(1)(2)}}{\sigma_{u1}^{2(1)}}$$

Adjusting for baseline values

- The regression coefficient formula in the previous slide may be extended to produce adjusted regression coefficients eg. adjusted for baseline values or change in earlier periods of time
- Again uses estimates of the variances and covariances of the random effects from the multilevel model
- Likely that baseline values will be associated with later change in each of the variables and can adjust for confounding by baseline values in the estimate of the association between change in one variable and change in the other

Adjusting for baseline values

The regression coefficient for the rate of change in variable 2 in time period 2 regressed on the rate of change in variable 1 in time period 1, adjusted for the baseline value of variable 1 is:

var(variable 1 at baseline) x

cov(slope of variable 1 in period 1, slope of variable 2 in period 2)

- cov(variable 1 at baseline, slope of variable 1 in period 1) x

cov(variable 1 at baseline, slope of variable 2 in period 2)

---

var(variable 1 at baseline) var(slope of variable 1 in period 1)

- cov(variable 1 at baseline, slope of variable 1 in period 1)^2

$$= \frac{\sigma_{u0}^{2(1)}\sigma_{u12}^{(1)(2)} - \sigma_{u01}^{(1)}\sigma_{u02}^{(1)(2)}}{\sigma_{u0}^{2(1)}\sigma_{u1}^{2(1)} - (\sigma_{u01}^{(1)})^2}$$

Adjusted regression coefficients from variance-covariance matrix of random effects

In general, to regress one random effect, $u_0^{(i_0)}$, on p other random effects, $u_1^{(i_1)}, u_2^{(i_2)}, \ldots, u_p^{(i_p)}$.

$$\boldsymbol{\beta} = \Sigma^{-1}\boldsymbol{\sigma_0}$$

where $\boldsymbol{\beta} = (\beta_1, \beta_2, \ldots, \beta_p)'$, the vector of regression coefficients relating to $u_1^{(i_1)}, u_2^{(i_2)}, \ldots, u_p^{(i_p)}$ respectively,

$\boldsymbol{\sigma_0} = (\sigma_{u_0u_1}^{(i_0)(i_1)}, \sigma_{u_0u_2}^{(i_0)(i_2)}, \ldots, \sigma_{u_0u_p}^{(i_0)(i_p)})'$ and

$$\Sigma = \begin{bmatrix} \sigma_{u_1}^{2(i_1)} & \sigma_{u_1u_2}^{(i_1)(i_2)} & \cdots & \sigma_{u_1u_p}^{(i_1)(i_p)} \\ & \ddots & & \vdots \\ & & \ddots & \vdots \\ & & & \sigma_{u_p}^{2(i_p)} \end{bmatrix}$$

Deriving standard errors for regression coefficients

- Regressing random effects relating to change in one period on random effects relating to change in another, but random effects have not been directly observed
- Variances and covariances of the random effects have been estimated by the model – uncertainty associated with these estimates
- We compared three different methods for deriving standard errors for the regression coefficients on the GWG and MAP change data

Deriving standard errors of regression coefficients

- Method 1: SE for regression coefficients obtained from a random sample

Let $\boldsymbol{SE_\beta} = (SE(\beta_1), SE(\beta_2), \ldots, SE(\beta_p))'$. Then,

$$\boldsymbol{SE_\beta} = \sqrt{\frac{(\sigma_{u_0}^{2(v_0)} - \boldsymbol{\beta}' \boldsymbol{\sigma_0})\boldsymbol{d}}{n - p - 1}}$$

with $\boldsymbol{\beta}$ and $\boldsymbol{\sigma_0}$ as before and $\boldsymbol{d} = (\Sigma^{-1}[1,1], \Sigma^{-1}[2,2], \ldots, \Sigma^{-1}[p, p])'$.

Deriving standard errors of regression coefficients

- Method 2: Use the delta method to calculate the standard errors

- Method of deriving standard errors for non-linear combinations of parameter estimates
- Eg. for an unadjusted regression coefficient:

$$\hat{var}\left(\frac{\sigma_{u12}^{(1)(2)}}{\sigma_{u1}^{2(1)}}\right)=\frac{var(\hat{\sigma}_{u12}^{(1)(2)})}{(\hat{\sigma}_{u2}^{2(2)})^2}+\frac{(\hat{\sigma}_{u12}^{(1)(2)})^2 var(\hat{\sigma}_{u1}^{2(1)})}{(\hat{\sigma}_{u1}^{2(1)})^4}-\frac{2\hat{\sigma}_{u12}^{(1)(2)}cov(\hat{\sigma}_{u12}^{(1)(2)},\hat{\sigma}_{u1}^{2(1)})}{(\hat{\sigma}_{u1}^{2(1)})^3}$$

- Requires that the formula for the regression coefficient is defined explicitly – only appropriate for up to 4 independent variables

Deriving standard errors of regression coefficients

- Method 3: Simulating from the distribution of the random effects variance-covariance matrix
- Generate a large number, N, of realisations of the variance-covariance matrix of random effects using a multivariate normal distribution based on the estimates from the multilevel model
- Derive the regression coefficient within each of these N simulated matrices and use the 2.5th and 97.5th percentiles of the distribution of the regression coefficients over all of the realisations as the lower and upper 95% confidence interval limits

Comparison of SE methods

Associations of weight change up to 18 weeks with MAP changes (per 400g/week weight gain)

Exposure: Weight change 8-18 weeks	Outcome: MAP change 8-18 weeks		Outcome: MAP change 18-29 weeks	
	Mean diff	95% confidence interval	Mean diff	95% confidence interval
Method 1	0.011	(-0.004, 0.026)	0.095	(0.083, 0.106)
Method 2	0.011	(-0.046, 0.068)	0.095	(0.055, 0.134)
Method 3	0.011	(-0.046, 0.068)	0.094	(0.054, 0.134)
Method 1	0.031	(0.017, 0.045)	0.079	(0.067, 0.091)
Method 2	0.031	(-0.015, 0.077)	0.079	(0.038, 0.120)
Method 3	0.031	(-0.015, 0.076)	0.079	(0.038, 0.120)

shaded cells are regression coefficients adjusted for baseline values of weight and MAP

Comparison of SE methods

- In general Method 1 underestimated the standard errors – does not take into account the uncertainty in the estimates of the variances and covariances of the random effects
- Delta method (Method 2) takes into account the uncertainty in the parameter estimates and simulation method (Method 3) produced comparable CIs
- Methods 2 and 3 implemented in the REFFADJUST package in Stata (Palmer et al, 2012):

http://ideas.repec.org/c/boc/bocode/s457403.html

- Implements delta method for up to 4 independent variables and simulation method for any number of variables

Associations of GWG with concurrent and subsequent MAP change

Mean differences (95% confidence interval) in MAP change in each period associated with a 400g/week increase in weight change

Weight variable (exposure)	MAP change 8-18 weeks (mmHg/wk)	MAP change 18-29 weeks (mmHg/wk)	MAP change 29-36 weeks (mmHg/wk)	MAP change 36+ weeks (mmHg/wk)
Weight change 8-18 wks (400g/wk)	0.03 (-0.02, 0.08)	0.08 (0.04, 0.12)	-0.09 (-0.16, -0.03)	0.00 (-0.12, 0.13)
Weight change 18-29 wks (400g/wk)		0.11 (0.07, 0.15)	0.05 (-0.03, 0.13)	0.06 (-0.09, 0.21)
Weight change 29+ wks (400g/wk)			0.27 (0.20, 0.33)	0.29 (0.15, 0.43)

Adjusted for maternal height, age, parity, smoking, education and offspring sex and also for weight and MAP at 8 weeks (baseline) and weight and MAP changes prior to the exposure period

Associations of MAP change with subsequent weight change

Mean differences (95% confidence interval) in weight change in each period associated with a mmHg/week increase in MAP change

MAP variable (exposure)	Weight change 18-29 weeks (400g/wk)	Weight change 29+ weeks (400g/wk)
MAP change 8-18 weeks (mmHg/wk)	0.07 (-0.01, 0.15)	0.09 (0.00, 0.18)
MAP change 18-29 weeks (mmHg/wk)		0.03 (-0.06, 0.12)

Adjusted for maternal height, age, parity, smoking, education and offspring sex and also for weight and MAP at 8 weeks, weight and MAP change prior to the exposure period and weight change in the exposure period

GWG and MAP - findings

- Greater weight gain in early pregnancy associated with a greater rise in MAP in mid-pregnancy, but a smaller rise in late pregnancy
- Weight gain in mid and late pregnancy positively associated with the concurrent rise in MAP
- Also some evidence that MAP change in early pregnancy is positively associated with weight gain in mid and late pregnancy

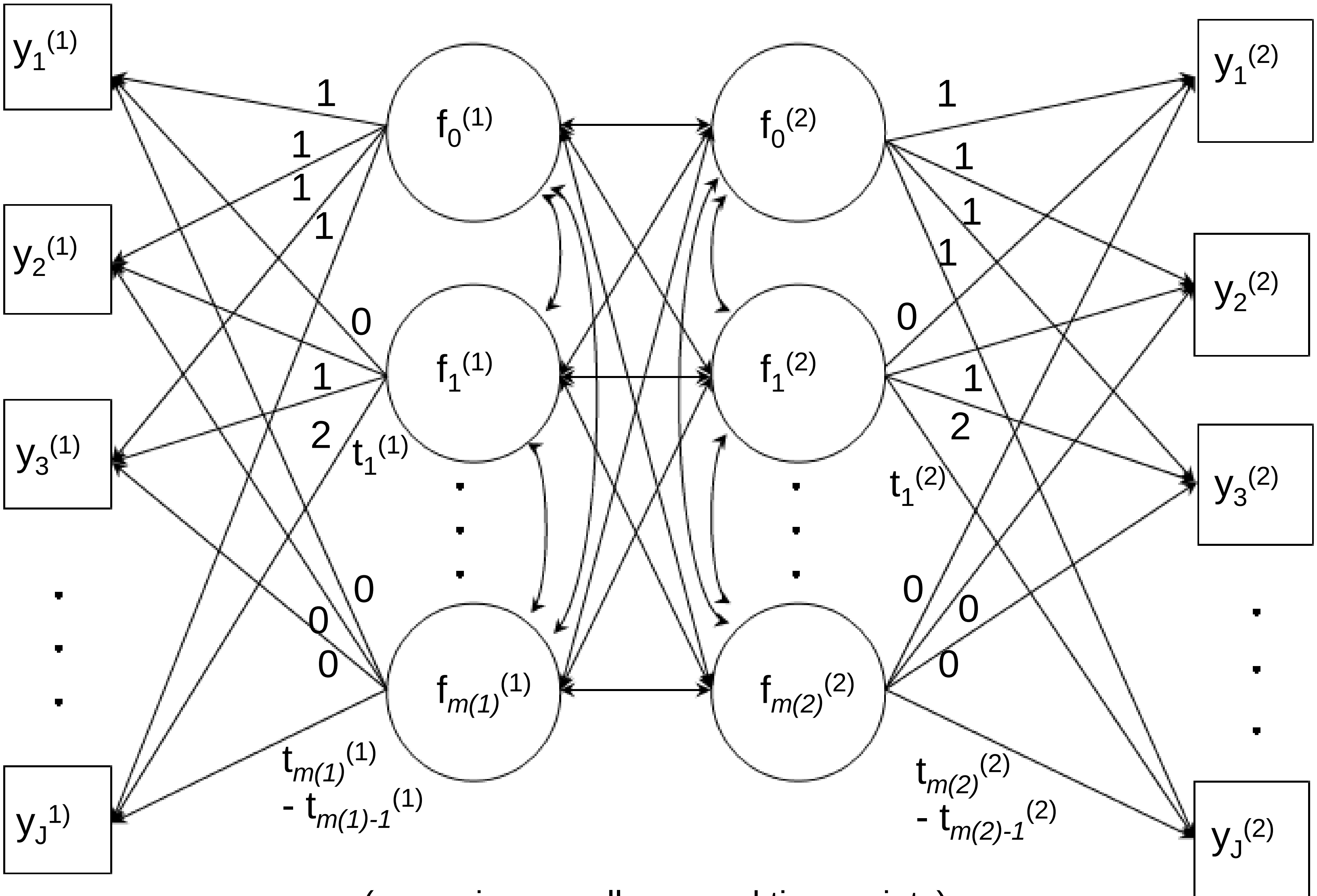
Comparison with SEM

- A number of papers have demonstrated the equivalence of multilevel and structural equation models (Curran (2003), Bauer (2003))
- Straight forward to fit a multilevel model in an SEM framework for balanced data
- Data with different numbers and timings of measurements for each individual may also be fit in an SEM framework by defining timepoints and treating timepoints where observations were not taken as missing data for that individual (Steele, 2008).

Bivariate linear spline model as an SEM

- Define growth factors $f_0^{(1)}$, $f_1^{(1)}$,..., $f_{m(1)}^{(1)}$ for the intercept and rates of change in each period of gestation for variable 1 and growth factors $f_0^{(2)}$, $f_1^{(2)}$,..., $f_{m(2)}^{(2)}$ for variable 2
- The loadings of variable 1 and variable 2 at each time pointon each of the growth factors are fixed (as shown on next slide)
- Variances and covariances estimated for each of the growth factors, as for the random effects in a multilevel model – also growth factor means estimated (similar to fixed effects in a multilevel model)

Bivariate linear spline model as an SEM



(assuming equally spaced time points)

GWG and MAP model as an SEM

- Rounded measurements to the nearest week of gestation – 43 measurement occasions, from 2 to 44 weeks
- Weeks of gestation where a measurement was not observed were treated as having missing data and maximum likelihood estimation used
- Estimates of means, variances and covariances of the growth factors from the SEM were equivalent to the nearest ~3 sf to those of the fixed and random effects from the multilevel model

Comparison of MLM and SEM approaches

- SEM approach more complicated data management task and more computationally intensive than MLM approach when there are varying numbers and timings of observations

- More flexibility in SEM framework to include different pathways between variables, eg. path analysis and to extend the model to include latent variables eg. growth mixture model

- Wider range of model fit statistics generally available in SEM software than MLM software

Discussion

Decision on the number of splines to include and positioning of knot points:

- Data driven – select knot points which have best fit to the data
- Interpretability – relating meaningful periods of change in the regression models to answer the research question
- Sample size – may have convergence problems if try to fit too many splines without sufficient data

Discussion

Extensions:

- Could potentially extend the model to include categorical outcomes – assumptions of normality may be stretched
- Include more than two outcomes – multivariate model
- Regression coefficients for associations between periods of change in the two variables may be adjusted for periods of change between the exposure and outcome period to assess mediation

Discussion

Assumptions:

- Missing at random – both multilevel and structural equation models assume that whether a measurement is observed at a particular time point does not depend on its value at that time. Any reasons for missingness are explained by measurements we have observed or covariates
- Normality – the delta and simulation methods of deriving standard errors for regression coefficients both assume that the variances and covariances of the random effects are normally distributed. This approximation is only justified in large samples

Conclusions

- The method is useful for determining whether changes in one variable are associated with changes in another, particularly when the pattern of change is nonlinear or it is of interest which particular periods of change are associated

- May provide evidence towards a causal influence of change in one variable on change in another by showing an association with change in a subsequent time period

- Could also be used when the changes do not occur in parallel, eg. relating maternal blood pressure changes in pregnancy to offspring blood pressure change in childhood

Reference

Macdonald-Wallis C, Lawlor DA, Palmer T, Tilling K. Multivariate multilevel spline models for parallel growth processes: application to weight and mean arterial pressure in pregnancy. *Statistics in Medicine* 2012; 31(26): 3147-3164

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