

Investigating Mood Regulation and Smoking: An Introduction to Mixed Effects Location Scale Models for Intensive Longitudinal Data

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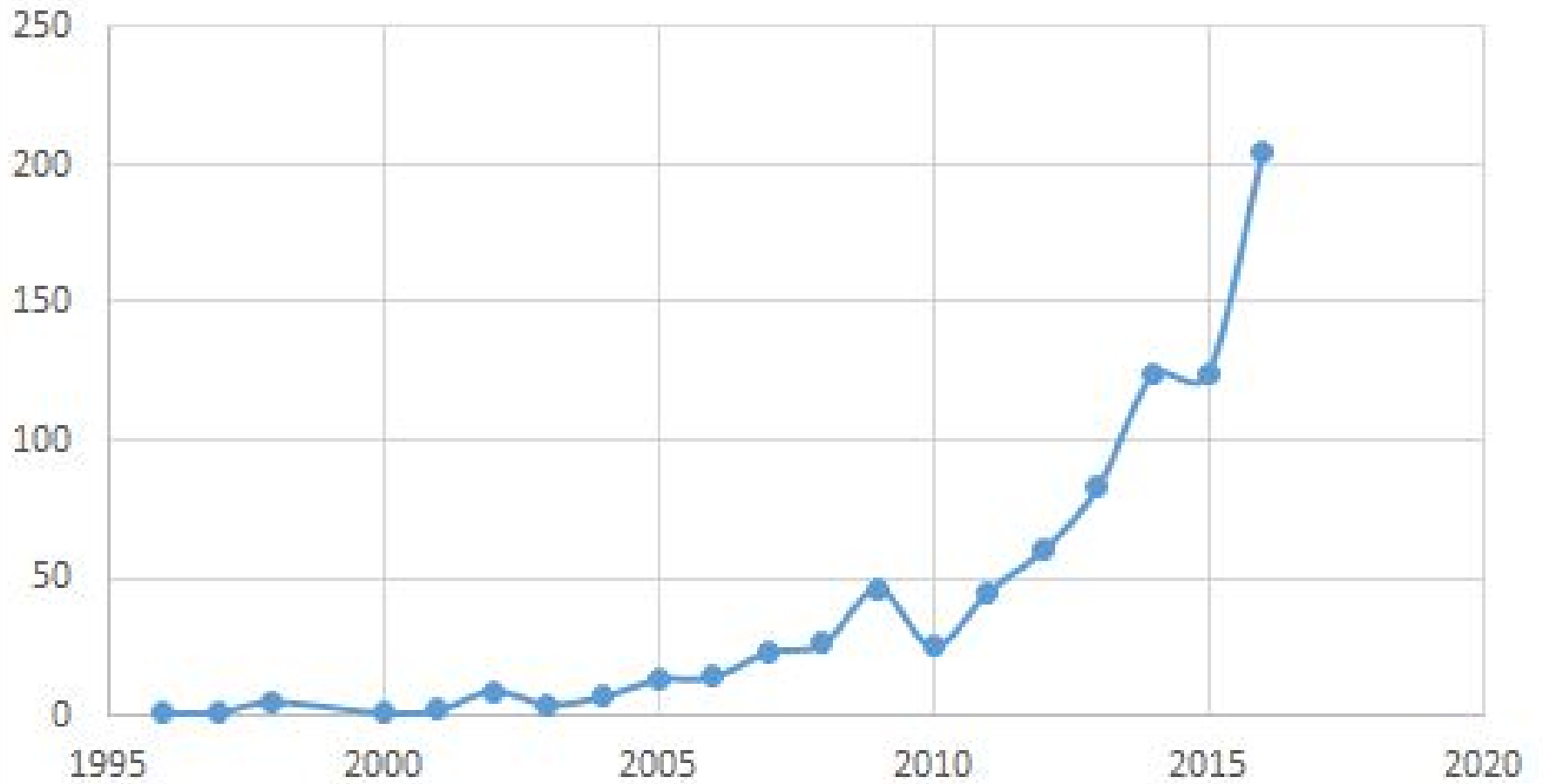
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Ecological Momentary Assessment (EMA) data

experience sampling and diary methods, intensive longitudinal data

- Subjects provide frequent reports on events and experiences of their daily lives (*e.g.*, 30-40 responses per subject collected over the course of a week or so)
 - electronic diaries: palm pilots, personal digital assistants (PDAs), smart phones
- Capture particulars of experience in a way not possible with more traditional designs
e.g., allow investigation of phenomena as they happen over time
- Reports could be time-based, following a fixed-schedule, randomly triggered, event-triggered

pubmed - ecological momentary assessment



Data are rich and offer many modeling possibilities!

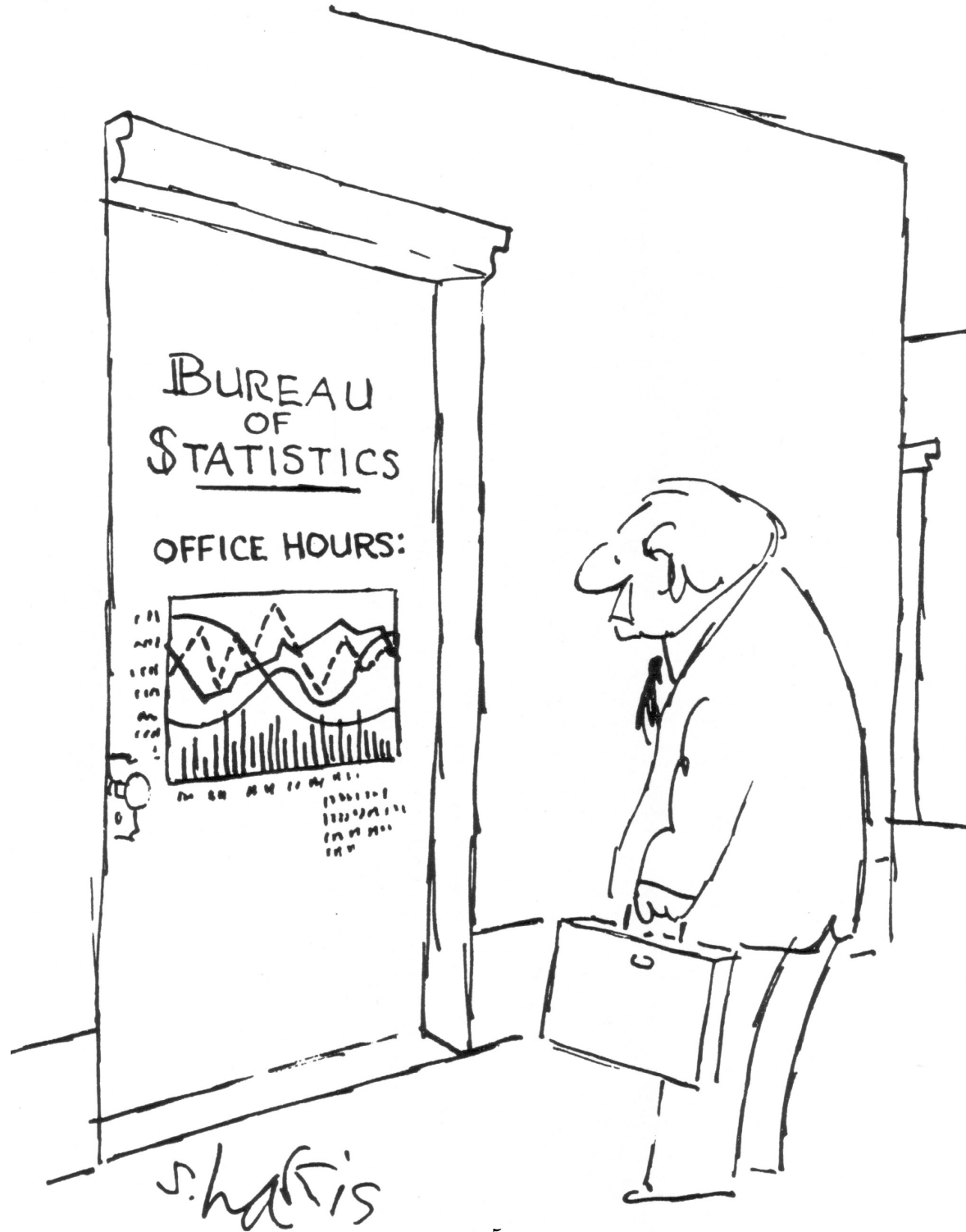
- person-level and occasion-level determinants of occasion-level responses \Rightarrow potential influence of context and/or environment
e.g., subject response might vary when alone vs with others
- allows examination of why subjects differ in variability rather than just mean level
 - between-subjects (BS) variance
e.g., subject heterogeneity could vary by gender or age
 - within-subjects (WS) variance
e.g., subject degree of stability could vary by gender or age

Carroll (2003) Variances are not always nuisance parameters,
Biometrics.

Smoking and Mood Regulation

- Mood regulation is thought to be related to smoking
- Mood regulation does not seem to necessarily be about better mood, but rather more consistent mood
- Do more frequent smokers experience mood stabilization?
- As a person increases their level of smoking across time, does their mood response to smoking get more consistent?

⇒ Modeling of the WS variance allows examination of these questions



Multilevel (mixed-effects regression) model for measurement y of subject i ($i = 1, 2, \dots, N$) on occasion j ($j = 1, 2, \dots, n_i$)

$$y_{ij} = \mathbf{x}'_{ij}\boldsymbol{\beta} + v_i + \epsilon_{ij}$$

$\mathbf{x}_{ij} = p \times 1$ vector of regressors (including a column of ones)

$\boldsymbol{\beta} = p \times 1$ vector of regression coefficients

$v_i \sim N(0, \sigma_v^2)$ BS variance; how homogeneous/heterogeneous are subjects?

$\epsilon_{ij} \sim N(0, \sigma_\epsilon^2)$ WS variance; how consistent/erratic are the data within subjects?

Model with no covariates: $y_{ij} = \beta_0 + v_i + \epsilon_{ij}$

- v_i is subject's mean (deviation from β_0)
 - if subjects are alike, $v_i \approx 0$ and σ_v^2 will approach 0
 - if subjects are different, $v_i \neq 0$ and σ_v^2 will increase from 0

\Rightarrow magnitude of σ_v^2 indicates how different subjects are from each other (heterogeneity)
- ϵ_{ij} is subject i 's error at time j (deviations from their mean)
 - if subjects are all well-fit, $\epsilon_{ij} \approx 0$ and σ_ϵ^2 will approach 0
 - if subjects are not well-fit, $\epsilon_{ij} \neq 0$ and σ_ϵ^2 will increase from 0

\Rightarrow magnitude of σ_ϵ^2 indicates how data vary within subjects (erraticism)

Log-linear models for variances

BS variance $\sigma_{v_{ij}}^2 = \exp(\mathbf{u}'_{ij}\boldsymbol{\alpha})$ or $\log(\sigma_{v_{ij}}^2) = \mathbf{u}'_{ij}\boldsymbol{\alpha}$

WS variance $\sigma_{\epsilon_{ij}}^2 = \exp(\mathbf{w}'_{ij}\boldsymbol{\tau})$ or $\log(\sigma_{\epsilon_{ij}}^2) = \mathbf{w}'_{ij}\boldsymbol{\tau}$

- \mathbf{u}_{ij} and \mathbf{w}_{ij} include covariates (and $\mathbf{1}$)
- subscripts i and j on variances indicate that these change depending on covariates \mathbf{u}_{ij} and \mathbf{w}_{ij} (and their coefficients)
- exp function ensures a positive multiplicative factor, and so resulting variances are positive

How can WS variables influence BS variance?

$$\sigma_{v_{ij}}^2 = \exp(\mathbf{u}'_{ij}\boldsymbol{\alpha})$$

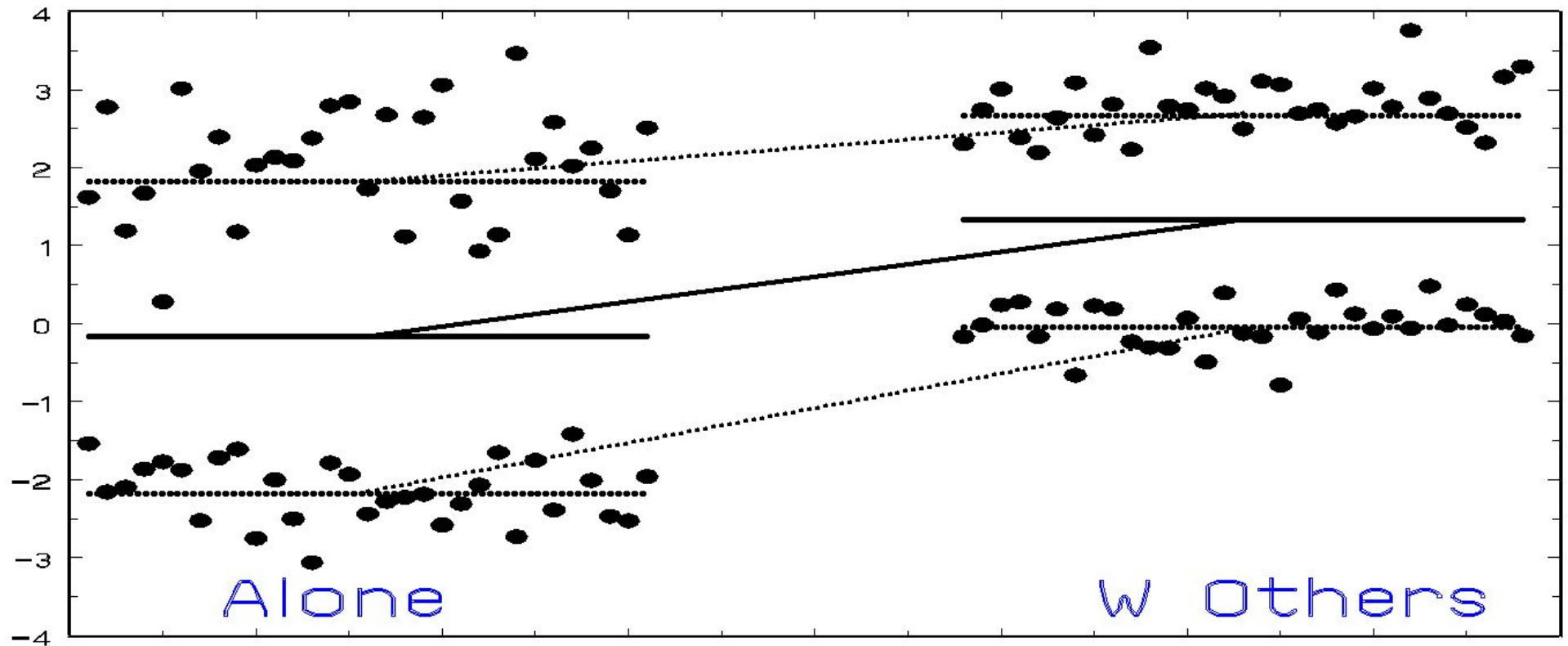
- Do rainy days and Mondays get everyone down?
- Is Tuesday just as bad as Stormy Monday for all?
- Are all kids happy on the last day of school?

Example: strong positive effect of being alone on BS variance of positive and negative mood

⇒ being alone increases subject heterogeneity (or, subjects report more similar mood when with others)

Location Scale Model

Increased Mean, Decreased BS heterogeneity, Decreased WS variance w Others



- Means are increased with others
- Subjects are more similar to each other when with others (BS var)
- Within-subject data are more consistent with others (WS var)

WS variance varies across subjects

$$\sigma_{\epsilon_{ij}}^2 = \exp(\mathbf{w}'_{ij}\boldsymbol{\tau} + \omega_i) \quad \text{where} \quad \omega_i \sim N(0, \sigma_{\omega}^2)$$

$$\log(\sigma_{\epsilon_{ij}}^2) = \mathbf{w}'_{ij}\boldsymbol{\tau} + \omega_i$$

- ω_i are log-normal subject-specific perturbations of WS variance
- ω_i are “scale” random effects - how does a subject differ in terms of the variation in their data
- v_i are “location” random effects - how does a subject differ in terms of the mean of their data

Multilevel model of WS variance

$$\log(\sigma_{\epsilon_{ij}}^2) = \mathbf{w}'_{ij}\boldsymbol{\tau} + \omega_i$$

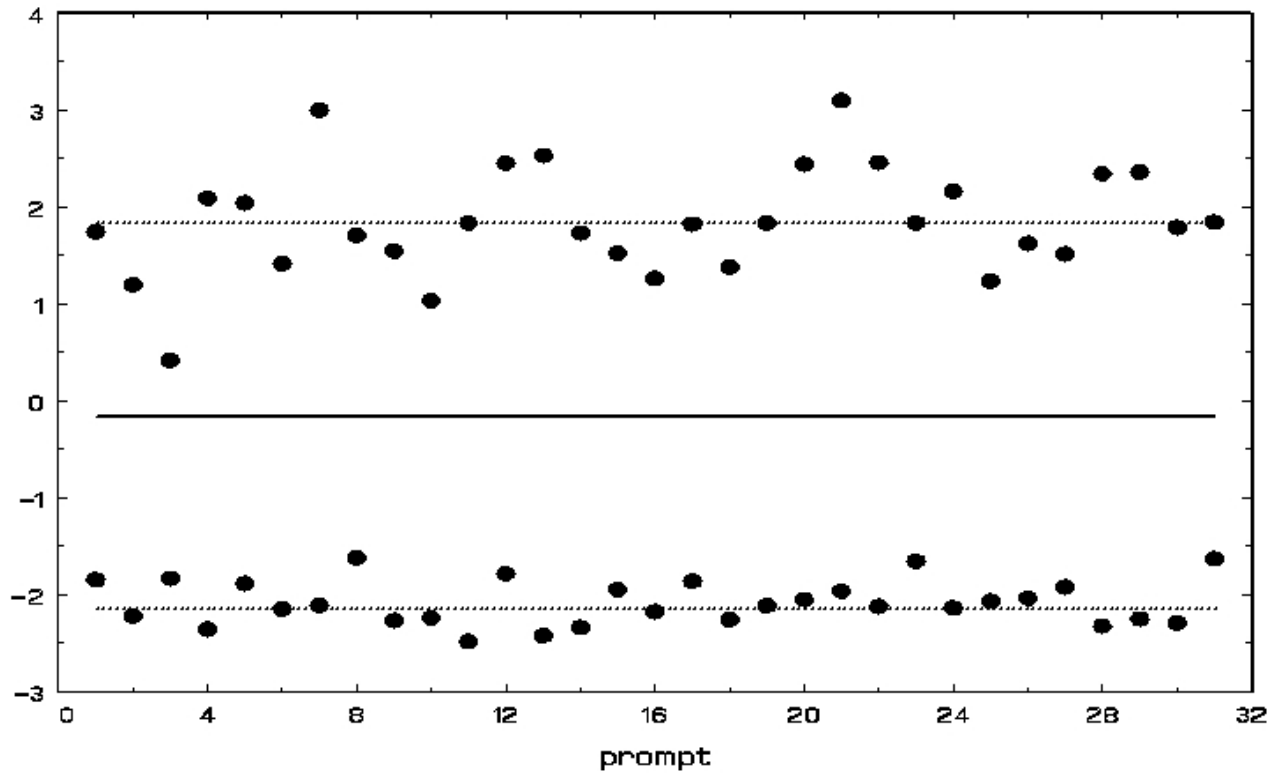
Why not use some summary statistic per subject (say, calculated subject standard deviation S_{y_i}) in a second-stage model?

$$S_{y_i} = \mathbf{x}'_i\boldsymbol{\beta} + \epsilon_i$$

latter approach

- treats all standard deviations as if they are equally precise (but some might be based on 2 prompts or 40 prompts)
- does not recognize that these are estimated quantities (underestimation of sources of variation)
- does not allow occasion-varying predictors

⇒ We use multilevel models for mean response, why not for variance?



Model allows covariates to influence

- mean: level of solid line
- BS variance: dispersion of dotted lines
- WS variance: dispersion of points

additional random subject effects on: mean and WS variance

Estimation

- SAS PROC NLMIXED (slow and must provide starting values)

Hedeker, D., Mermelstein, R.J., & Demirtas, H. (2008). An application of a mixed-effects location scale model for analysis of Ecological Momentary Assessment (EMA) data. *Biometrics*, 64, 627-634, *Supplemental Materials*.

- MIXREGLS freeware (faster and no starting values); also DLL is accessible via R - <https://www.jstatsoft.org/article/view/v052i12>

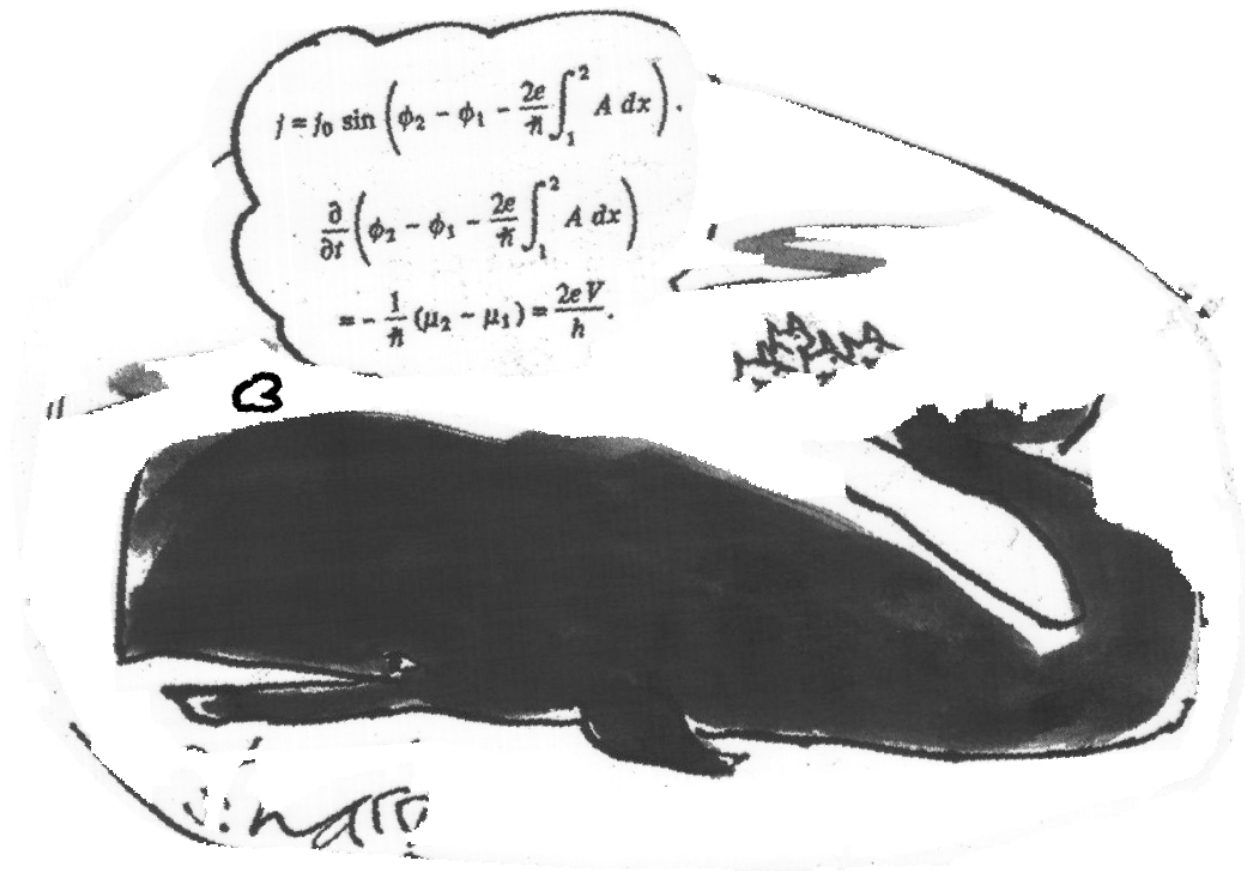
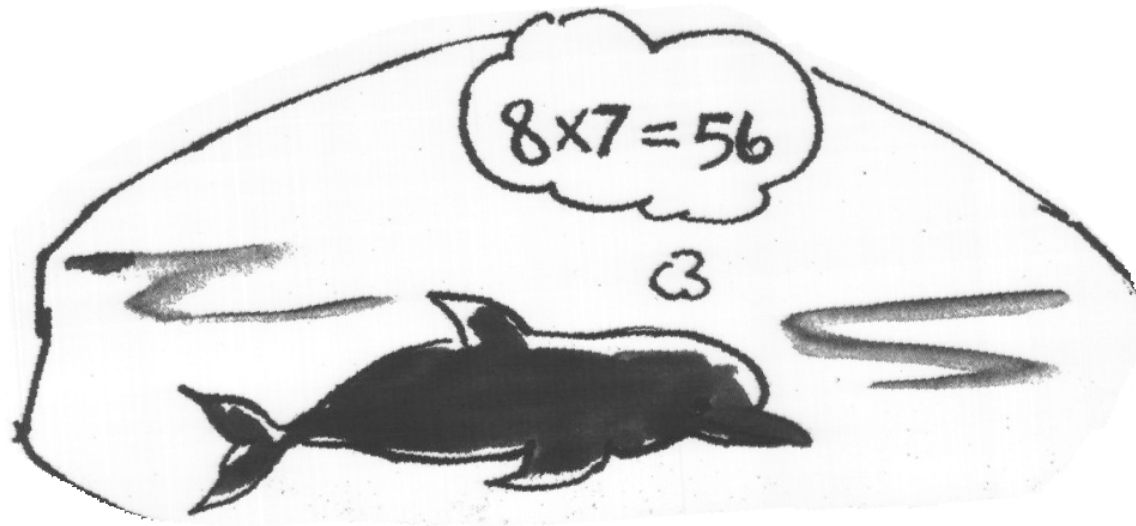
Hedeker, D. & Nordgren, R. (2013). MIXREGLS: A program for mixed-effects location scale analysis. *Journal of Statistical Software*, 52(12), 1-38.

- MIXREGLS via STATA - <https://www.jstatsoft.org/article/view/v059c02/0>

Leckie, G.(2014). runmixregls: A program to run the MIXREGLS mixed-effects location scale software from within Stata. *Journal of Statistical Software*, 59; *Code Snippet 2*, 1-41.

- Bayesian approach using WinBUGS or JAGS

Rast, P., Hofer, S. M., & Sparks, C. (2012). Modeling individual differences in within-person variation of negative and positive affect in a mixed effects location scale model using BUGS/JAGS. *Multivariate Behavioral Research*, 47, 177-200.



Ecological Momentary Assessment (EMA) Study of Adolescent Smokers (Mermelstein)

- 461 adolescents (9th and 10th graders); former and current smoking experimenters, and regular smokers
- Carry PDA for a week, answer questions when prompted
average = 30 answered prompts (range = 7 to 71)
- $\sum_i^N n_i = 14,105$ total number of observations

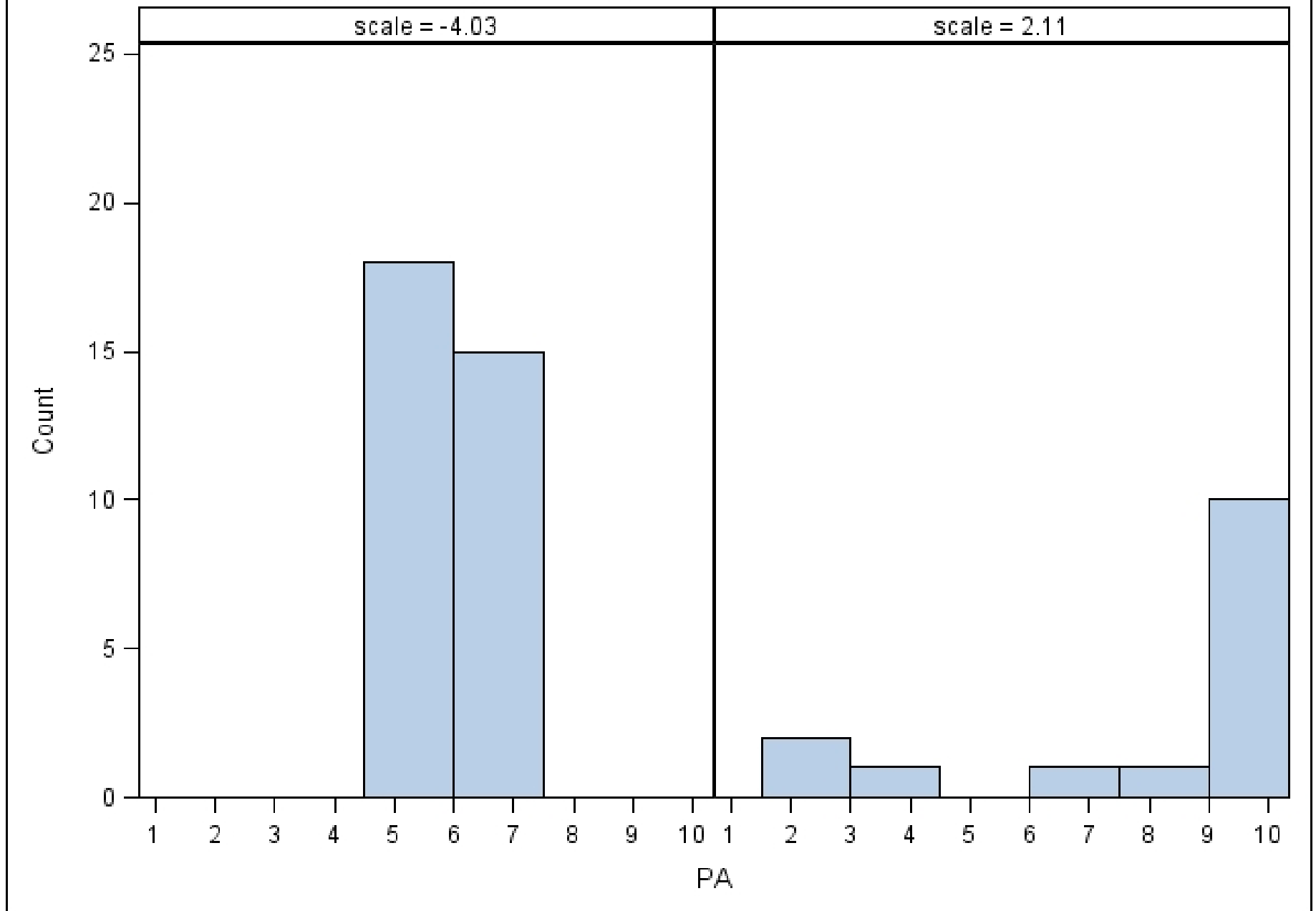
Outcomes: positive and negative affect

Interest: characterizing determinants of affect level, as well as BS and WS affect heterogeneity

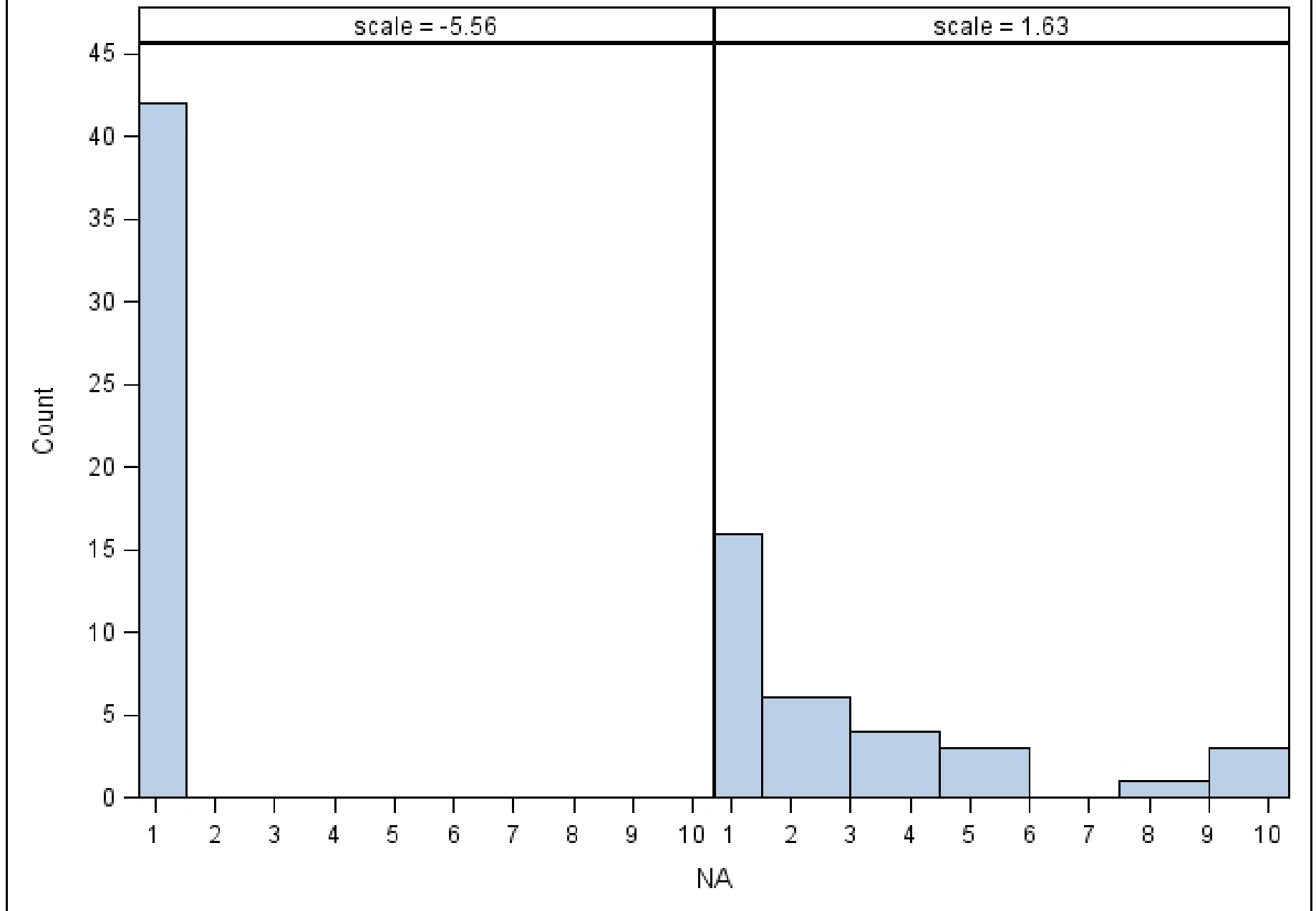
Dependent Variables

- Positive Affect mood scale (mean=6.797 and sd=1.935)
 - Before signal: I felt Happy
 - Before signal: I felt Relaxed
 - Before signal: I felt Cheerful
 - Before signal: I felt Confident
 - Before signal: I felt Accepted by Others
 - Negative Affect mood scale (mean=3.455 and sd=2.253)
 - Before signal: I felt Sad
 - Before signal: I felt Stressed
 - Before signal: I felt Angry
 - Before signal: I felt Frustrated
 - Before signal: I felt Irritable
- ⇒ items rated on 1 (not at all) to 10 (very much) scale

Subjects with smallest and largest estimated PA scale (-4.03 and 2.11)



Subjects with smallest and largest estimated NA scale (-5.56 and 1.63)



Subject-level Independent Variables

	mean	std dev	min	max
Smoker	.508	.500	0	1
Male	.449	.498	0	1

- **Smoker**: gave at least one report of a smoking event in the week of EMA measurement (about half of the subjects)
- **Male**: a bit more females than males in this sample

parameter	Positive Affect			Negative Affect		
	estimate	se	$p <$	estimate	se	$p <$
<u>Mean</u>						
Intercept β_0	6.743	.095	.001	3.608	.121	.001
Male β_1	.298	.114	.01	-.611	.137	.001
Smoker β_2	-.197	.115	.09	.292	.136	.032
<u>WS variance</u>						
Intercept τ_0	.706	.060	.001	.824	.077	.001
Male τ_1	-.279	.072	.001	-.453	.093	.001
Smoker τ_2	.081	.071	.26	.238	.092	.01
<u>BS variance</u>						
Intercept α_0	.320	.110	.004	.891	.112	.001
Male α_1	-.180	.136	.19	-.465	.131	.001
Smoker α_2	.215	.135	.11	.104	.130	.43
<u>Scale</u>						
standard deviation σ_ω	.642	.025	.001	.820	.031	.001
covariance $\sigma_{v\omega}$	-.308	.035	.001	.485	.044	.001

Variance model coefficients

$$\sigma_{BS}^2 = \exp(\tau_0 + \tau_1 \mathbf{Male} + \tau_2 \mathbf{Smoker})$$

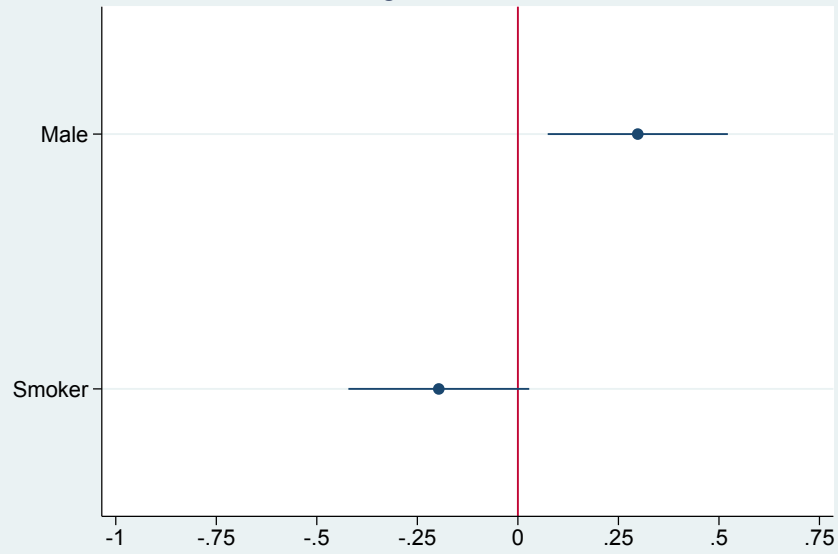
Holding **Smoker** constant, BS variance equals:

females: $\exp(\tau_0)$ males: $\exp(\tau_0 + \tau_1)$

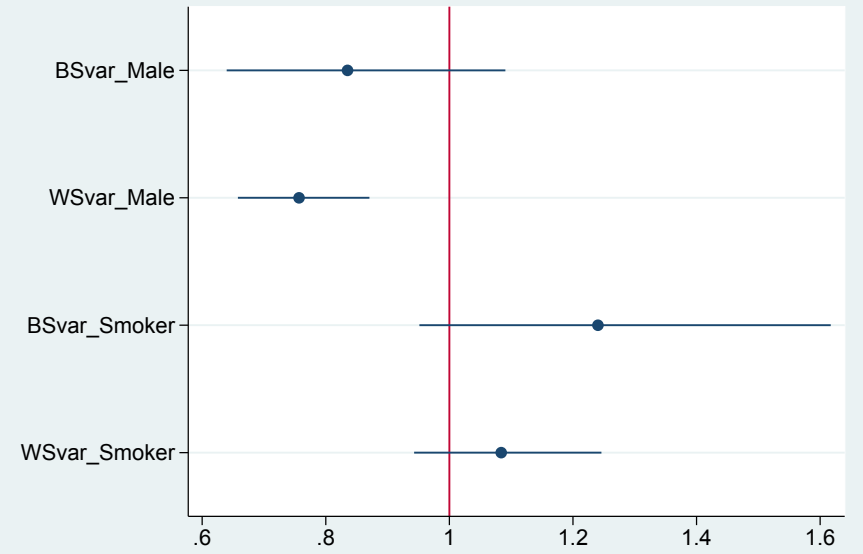
$$\Rightarrow \text{male to female BS variance ratio} = \frac{\exp(\tau_0 + \tau_1)}{\exp(\tau_0)} = \exp(\tau_1)$$

- $\exp \tau_j$ = variance ratio of σ_{BS}^2 for a unit change in x_j
- $\exp \alpha_j$ = variance ratio of σ_{WS}^2 for a unit change in x_j

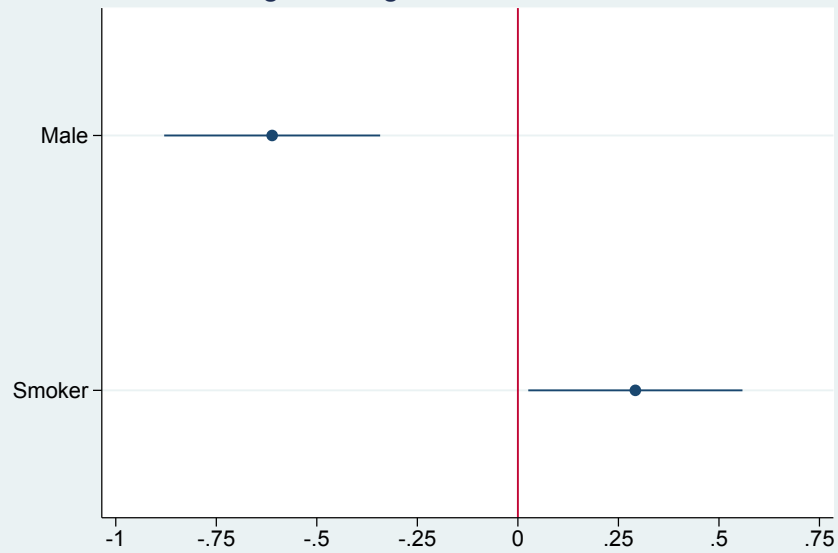
Pos Aff: Regression Coeffs and CIs



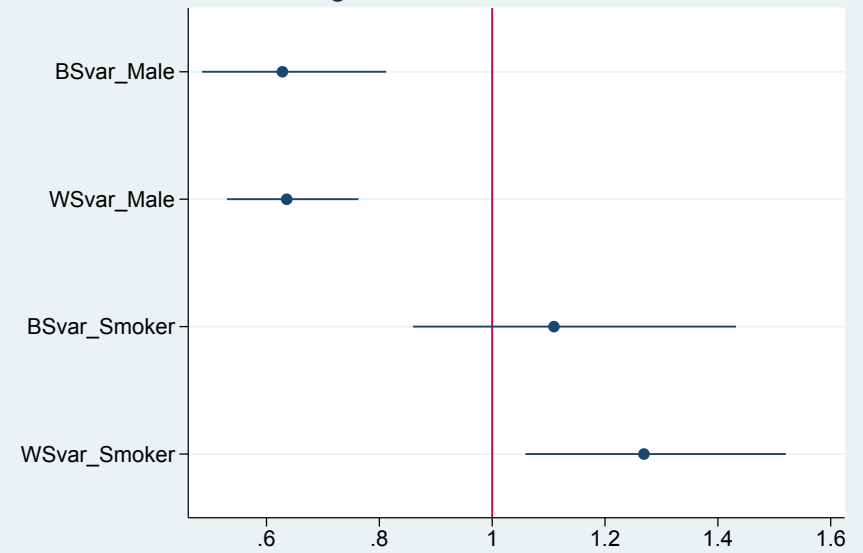
Pos Aff: Variance Ratios and CIs



Neg Aff: Regression Coeffs and CIs



Neg Aff: Variance Ratios and CIs





What about smoking?

- **Smoker** does not consider smoking level (just whether or not a subject provided at least one smoking event)
- 234 with smoking events: average=5, median=3, range = 1 to 42
- Perhaps, smoking level needs to be considered
- **PropSmk** = proportion of occasions (both random prompts and smoking events) that were smoking events

$$\text{PropSmk} = n_{\text{smk}} / (n_{\text{smk}} + n_{\text{random}})$$

Model with Smoker and Psmk

$$\text{PropSmk} = n_smk / (n_smk + n_random)$$

N=234 with $n_smk > 0$ (and **Smoker** = 1)

min = .014, 25% quartile = .05, median = .08, 75% quartile = .18

$$\text{Psmk} = 10 \times (\text{PropSmk} - \min(\text{PropSmk}))$$

$$\text{Model: } \text{Mood}_{ij} = \beta_0 + \beta_1 \text{Smoker} + \beta_2 \text{Psmk} + \dots + v_i + \epsilon_{ij}$$

subject	Smoker	PropSmk	Psmk	mean
non-smoker	0	0	0	β_0
min smoker	1	.014	0	$\beta_0 + \beta_1$
light smoker	1	.05	0.36	$\beta_0 + \beta_1 + 0.36\beta_2$
medium smoker	1	.08	0.66	$\beta_0 + \beta_1 + 0.66\beta_2$
high smoker	1	.18	1.66	$\beta_0 + \beta_1 + 1.66\beta_2$

⇒ piecewise linear model for means

Similar models for BS and WS variance

BS Variance Model: $\exp(\alpha_0 + \alpha_1 \mathbf{Smoker} + \alpha_2 \mathbf{Psmk} + \dots)$

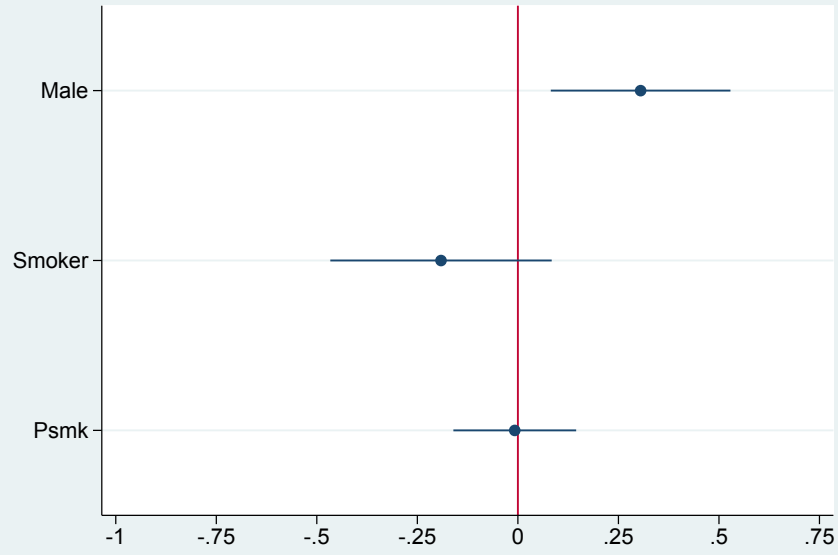
WS Variance Model: $\exp(\tau_0 + \tau_1 \mathbf{Smoker} + \tau_2 \mathbf{Psmk} + \dots + \omega_i)$

subject	Smoker	Psmk	BS variance	WS variance
non-smoker	0	0	$\exp(\alpha_0)$	$\exp(\tau_0 + \omega_i)$
min smoker	1	0	$\exp(\alpha_0 + \alpha_1)$	$\exp(\tau_0 + \tau_1 + \omega_i)$
light smoker	1	0.36	$\exp(\alpha_0 + \alpha_1 + 0.36\alpha_2)$	$\exp(\tau_0 + \tau_1 + 0.36\tau_2 + \omega_i)$
med smoker	1	0.66	$\exp(\alpha_0 + \alpha_1 + 0.66\alpha_2)$	$\exp(\tau_0 + \tau_1 + 0.66\tau_2 + \omega_i)$
high smoker	1	1.66	$\exp(\alpha_0 + \alpha_1 + 1.66\alpha_2)$	$\exp(\tau_0 + \tau_1 + 1.66\tau_2 + \omega_i)$

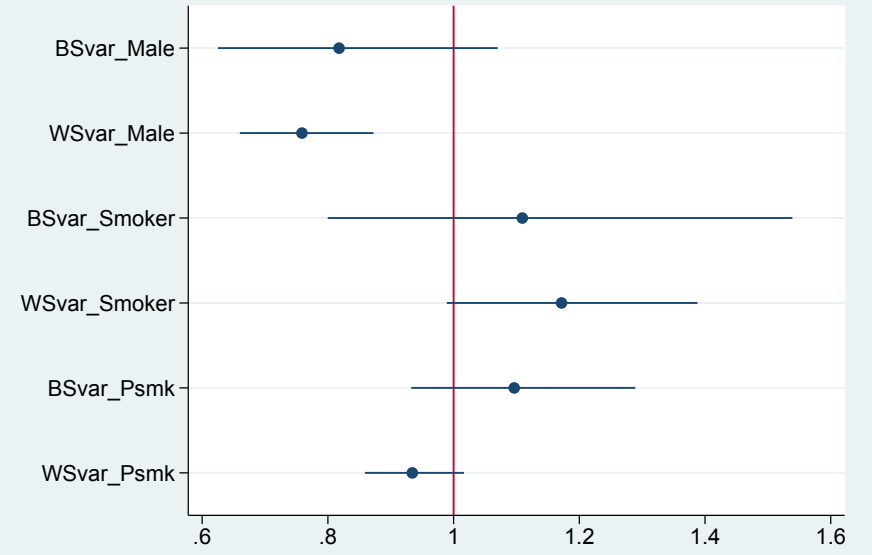
Note: other covariates set to zero

parameter	Positive Affect			Negative Affect		
	estimate	se	$p <$	estimate	se	$p <$
<u>Mean</u>						
Intercept β_0	6.741	.095	.001	3.605	.121	.001
Male β_1	.305	.114	.01	-.606	.137	.001
Smoker β_2	-.191	.140	.18	.474	.169	.005
PSmk β_3	-.008	.077	.93	-.154	.079	.05
<u>WS variance</u>						
Intercept τ_0	.705	.059	.001	.820	.077	.001
Male τ_1	-.276	.071	.001	-.444	.092	.001
Smoker τ_2	.159	.086	.07	.410	.112	.001
Psmk τ_3	-.068	.043	.11	-.148	.055	.008
<u>BS variance</u>						
Intercept α_0	.326	.111	.004	.890	.112	.001
Male α_1	-.201	.137	.15	-.469	.131	.001
Smoker α_2	.104	.167	.54	.187	.159	.24
Psmk α_3	.092	.083	.27	-.074	.075	.32
<u>Scale</u>						
standard deviation σ_ω	.640	.025	.001	.814	.031	.001
covariance $\sigma_{\nu\omega}$	-.304	.035	.001	.481	.044	.001

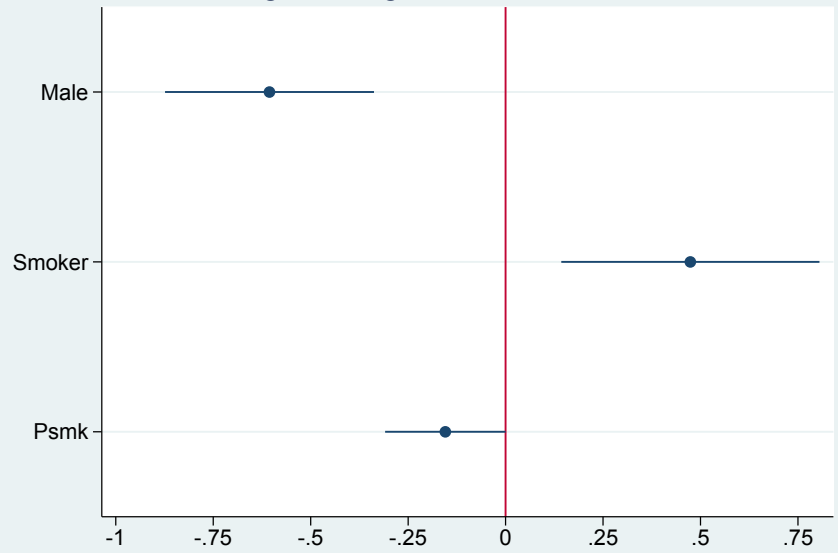
Pos Aff: Regression Coeffs and CIs



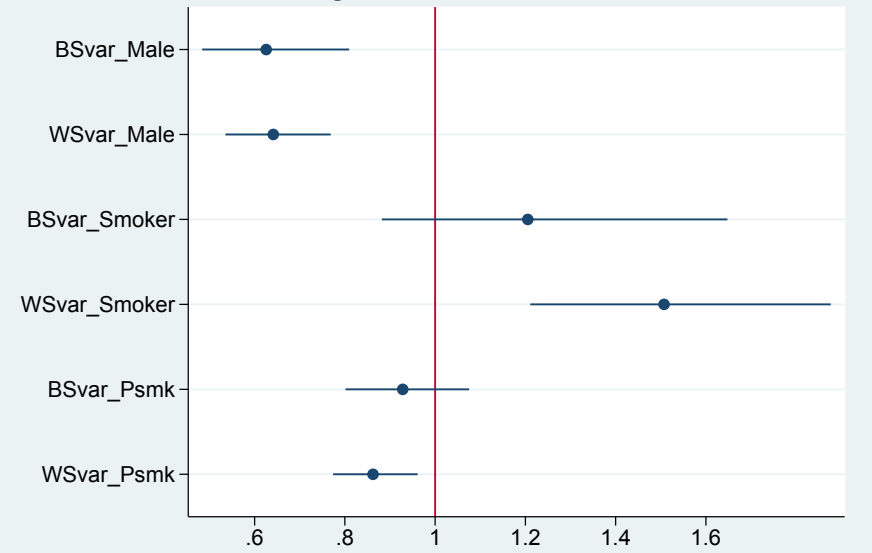
Pos Aff: Variance Ratios and CIs



Neg Aff: Regression Coeffs and CIs



Neg Aff: Variance Ratios and CIs



- These analyses focused on one measurement wave and the effect of smoking level on mood variance from random prompts (between-subjects or cross-sectional effect)
- What about as subjects change their own level of smoking? (within-subjects or longitudinal effect)
- What about smoking-attributable change in mood? (mood responses from smoking events)

EMA Study of Adolescents (Mermelstein, NCI)

- 461 adolescents (9th and 10th graders; 55% female); former and current smoking experimenters, and regular smokers
- Carry PDA for a week, answer questions when randomly prompted, or event-record when smoking (mutually exclusive)
- baseline, 6-month, 15-month, 2-year, and 5-year follow-ups

Interest: characterizing determinants of change in positive and negative affect associated with smoking events, especially across time

⇒ analysis of 158 subjects with two or more waves, where at each wave subject had two or more smoking events

158 subjects with two or more waves

at each wave subject had two or more smoking events

- total of 4,727 smoking events
- 65, 30, 33, 30 subjects had data at two, three, four and five waves
- number of subjects across waves:
126 (baseline), 93 (6 mo), 95 (15 mo), 101 (2 yr), and 87 (5 yr)
- average number of smoking events across waves:
6.90 (range = 2 to 42)
7.53 (2 to 32)
9.74 (2 to 43)
10.14 (2 to 49)
13.90 (2 to 64)

Dependent Variables - mood reports for smoking events

- Positive Affect (PA) mood scale (5 items)
 - Before smoking I felt: Happy, Relaxed, Cheerful, Confident, Accepted by Others
- Negative Affect (NA) mood scale (5 items)
 - Before smoking I felt: Sad, Stressed, Angry, Frustrated, Irritable
- items rated on 1 (not at all) to 10 (very much) scale
- also rated for “Now after smoking: I feel”
- difference (now-before) is measure of reported mood change associated with smoking
- PA mood change averages = .75, .54, .34, .41, .41 across waves
- NA mood change averages = -.46, -.45, -.33, -.44, -.32 across waves

Mixed Model for the mood y of subject i ($i = 1, 2, \dots, N$ subjects) at occasion j ($j = 1, 2, \dots, n_i$ smoking events):

$$y_{ij} = (\beta_0 + v_{0i}) + (\beta_1 + v_{1i})\text{Wave}_j + \beta_2\text{Male}_i \\ + \beta_3\text{AvgRate}_i + \beta_4\text{DevRate}_{ij} + \epsilon_{ij}$$

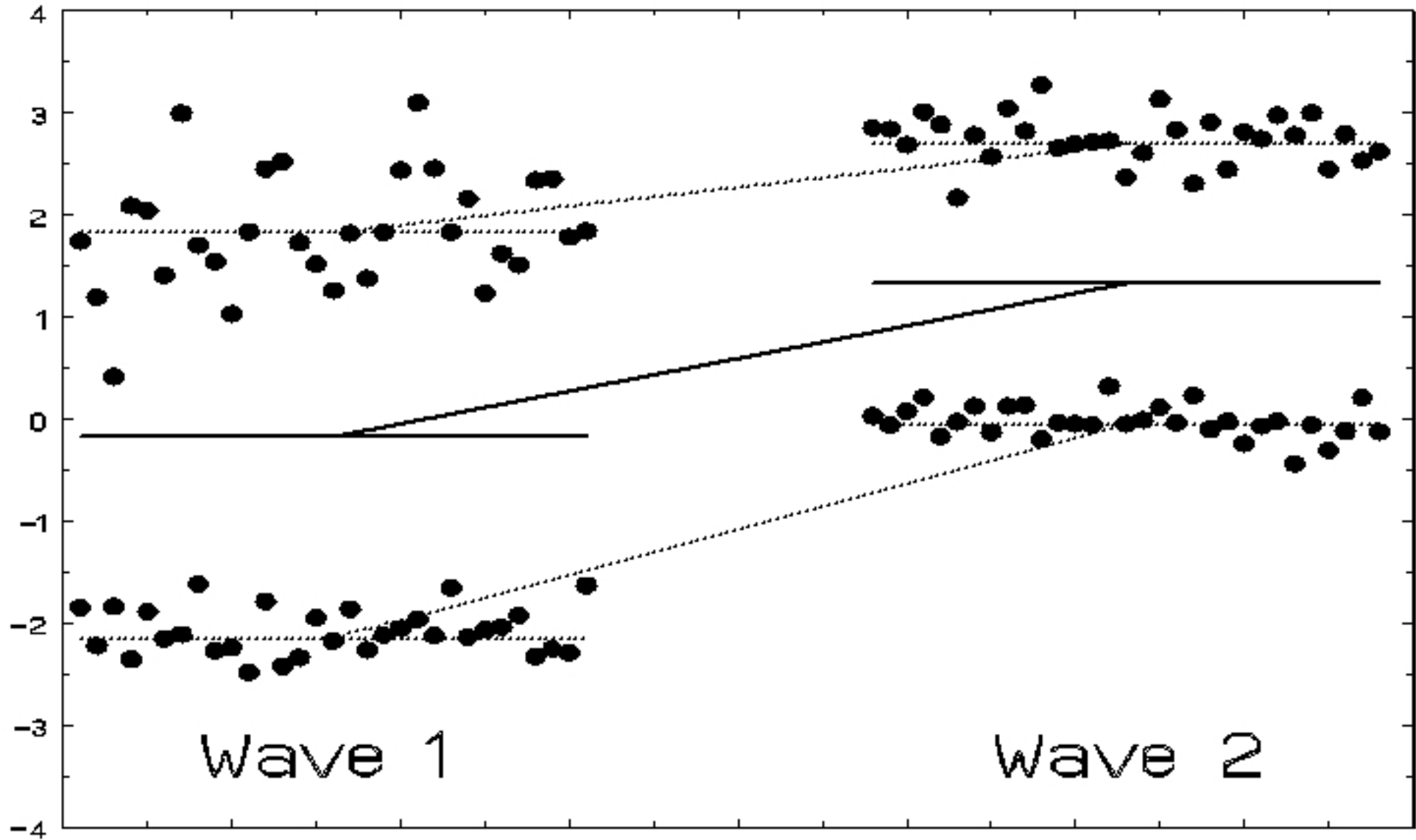
- Wave_j (0=baseline, .5=6 mos, 1.25=15 mos, 2=2yrs, 5=5yrs)
- Male_i (0=female, 1=male)
- Smoking level
 - * SmkRate_{ij} = per wave daily smoking rate (ln units)
 - * BS version AvgRate_i = subject average of SmkRate_{ij}
 - * WS version $\text{DevRate}_{ij} = (\text{SmkRate}_{ij} - \text{AvgRate}_i)$
= per wave deviation in the daily smoking rate

Error variance model $\epsilon_{ij} \sim N(0, \sigma_\epsilon^2)$ WS variance

$$\log(\sigma_{\epsilon_{ij}}^2) = \tau_0 + \tau_1 \text{Wave}_j + \tau_2 \text{Male}_i + \tau_3 \text{AvgRate}_i + \tau_4 \text{DevRate}_{ij} + \omega_i$$

log-linear model of within-subject variance, with subject-specific perturbation $\omega_i \sim N(0, \sigma_\omega^2)$

- WS variance follow a log-normal distribution at the subject level
- skewed nonnegative nature of log-normal makes it a reasonable choice for representing variances
- random scale effect ω_i allowed to be correlated with random intercept v_{0i} and trend v_{1i}

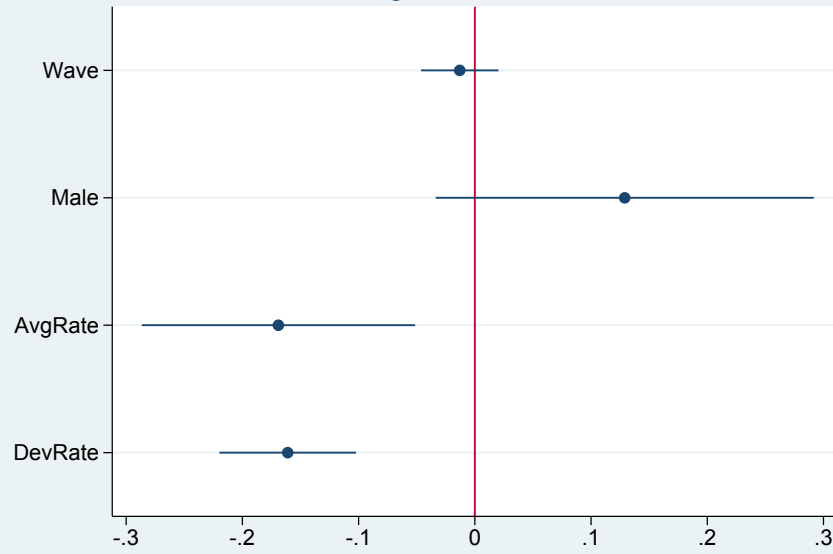


- population intercept and trend (solid line)
- random intercept and trend for 2 subjects (dotted lines)
- error variance varies across time and subjects (random scale)

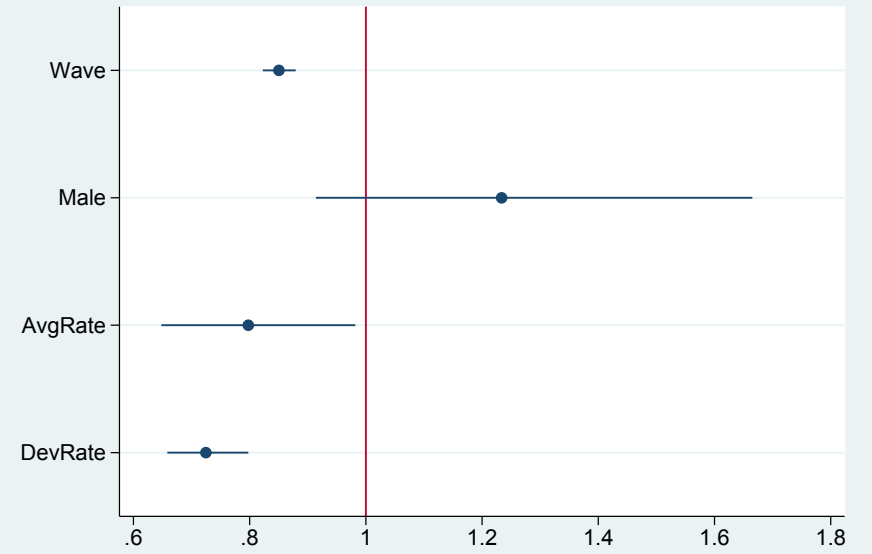
Smoking-related Positive and Negative Affect Change estimates, standard errors (se), and p -values

<i>Mean Model</i>	Positive Affect			Negative Affect		
	est	se	$p <$	est	se	$p <$
Intercept β_0	.691	.110	.001	-.432	.093	.001
Wave β_1	-.013	.017	.44	.004	.013	.78
Male β_2	.129	.083	.13	-.057	.070	.41
AvgRate β_3	-.169	.060	.006	.071	.053	.19
DevRate β_4	-.161	.030	.001	.059	.027	.03
<i>Error Var Model</i>	est	se	$p <$	est	se	$p <$
Intercept τ_0	.921	.172	.001	1.043	.210	.001
Wave τ_1	-.162	.017	.001	-.121	.018	.001
Male τ_2	.210	.153	.172	.215	.193	.27
AvgRate τ_3	-.226	.106	.034	-.337	.133	.012
DevRate τ_4	-.322	.049	.001	-.319	.055	.001

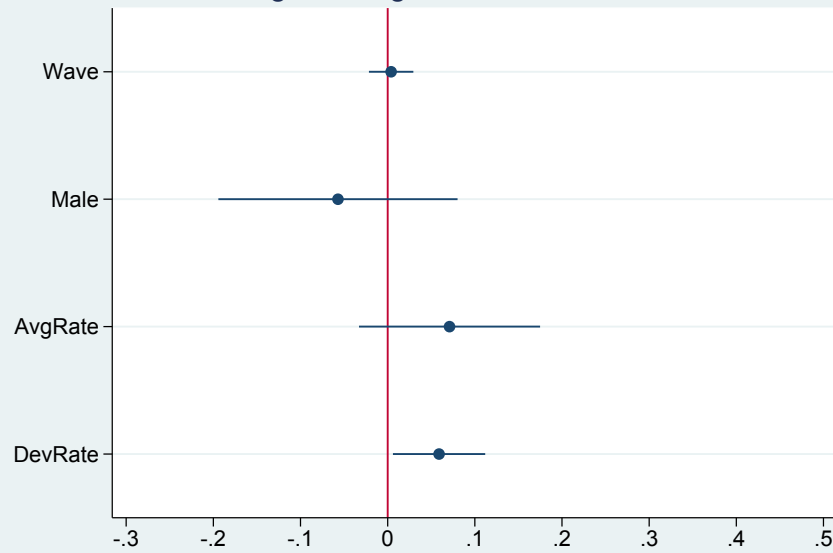
Pos Aff: Regression Coeffs and CIs



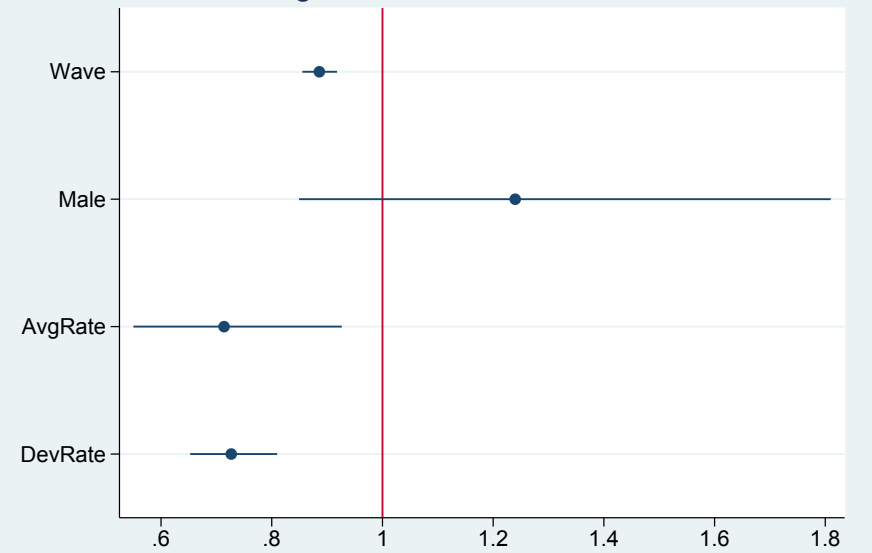
Pos Aff: Variance Ratios and CIs



Neg Aff: Regression Coeffs and CIs



Neg Aff: Variance Ratios and CIs



Smoking-related Positive and Negative Affect Change

estimates, standard errors (se), and p -values

<i>Random effect (co)variances</i>	Positive Affect			Negative Affect		
	est	se	$p <$	est	se	$p <$
Intercept $\sigma_{v_0}^2$.284	.062	.001	.125	.040	.002
Wave $\sigma_{v_1}^2$.014	.004	.001	.003	.002	.12
Scale σ_{ω}^2	.752	.103	.001	1.26	.167	.001
Int, Wave $\sigma_{v_0 v_1}$	-.043	.014	.003	-.010	.007	.18
Int, Scale $\sigma_{v_0 \omega}$.213	.057	.001	-.208	.052	.001
Wave, Scale $\sigma_{v_1 \omega}$	-.004	.015	.77	.011	.013	.39

Second or third thoughts?

- analysis treats observations (level-1) within subjects (level-2)

$$y_{ij} = (\beta_0 + v_{0i}) + (\beta_1 + v_{1i})\text{Wave}_j + \beta_2\text{Male}_i + \beta_3\text{AvgRate}_i + \beta_4\text{DevRate}_{ij} + \epsilon_{ij}$$

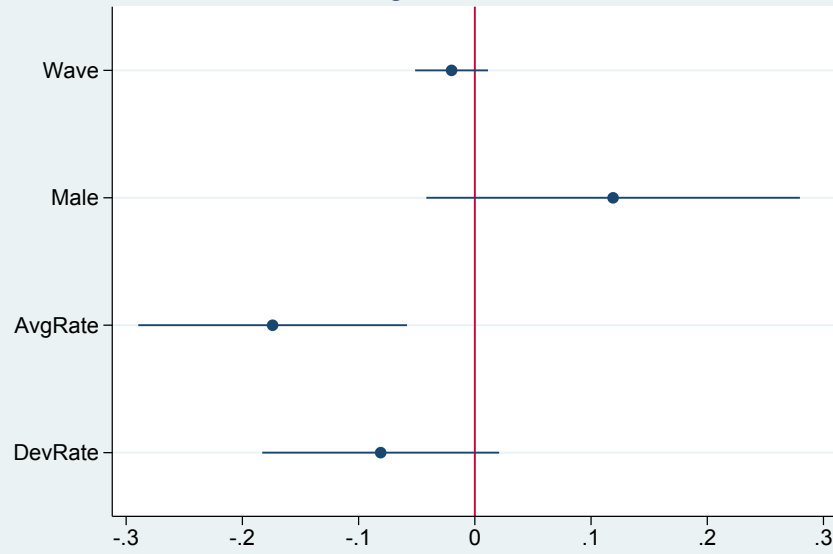
$$\sigma_{\epsilon_{ij}}^2 = (\tau_0 + \tau_1\text{Wave}_j + \tau_2\text{Male}_i + \tau_3\text{AvgRate}_i + \tau_4\text{DevRate}_{ij} + \omega_i)$$

- however, observations (level-1) are nested within waves (level-2) within subjects (level-3)

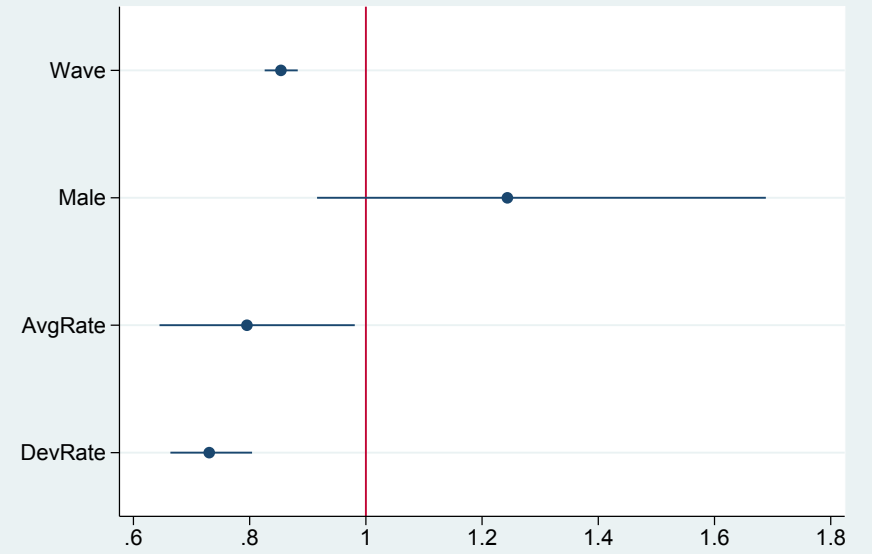
3-level Model of Smoking-related Positive and Negative Affect Change; estimates, standard errors (se), and p -values

	Positive Affect			Negative Affect		
<i>Mean Model</i>	est	se	$p <$	est	se	$p <$
Intercept β_0	.708	.106	.001	-.447	.091	.001
Wave β_1	-.020	.016	.22	.002	.013	.90
Male β_2	.119	.082	.15	-.057	.069	.41
AvgRate β_3	-.174	.059	.004	.083	.050	.10
DevRate β_4	-.081	.052	.12	.071	.039	.08
<i>Error Var Model</i>	est	se	$p <$	est	se	$p <$
Intercept τ_0	.893	.174	.001	1.048	.211	.001
Wave τ_1	-.158	.017	.001	-.117	.018	.001
Male τ_2	.218	.156	.16	.235	.193	.22
AvgRate τ_3	-.229	.107	.034	-.361	.132	.007
DevRate τ_4	-.314	.049	.001	-.321	.055	.001

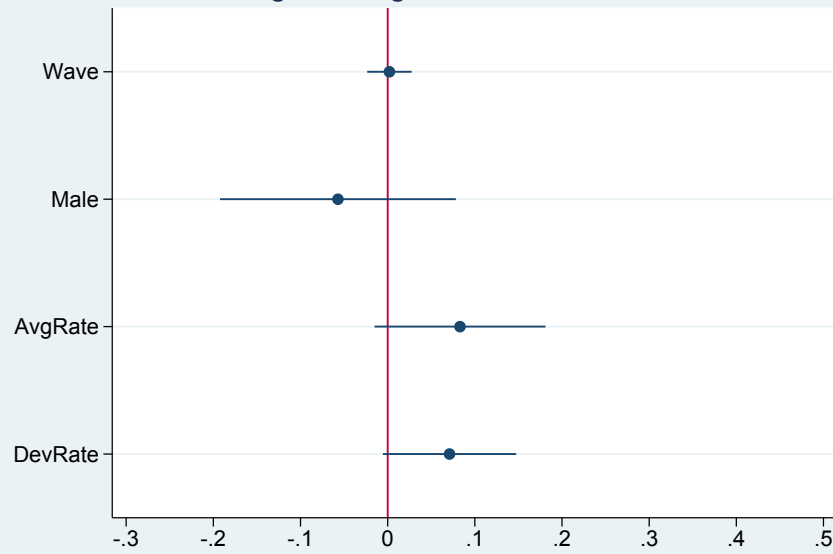
Pos Aff: Regression Coeffs and CIs



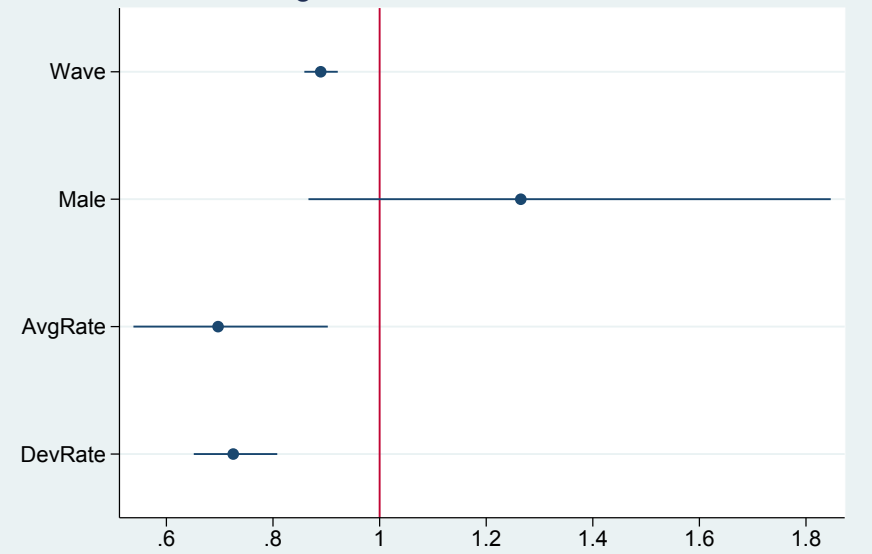
Pos Aff: Variance Ratios and CIs



Neg Aff: Regression Coeffs and CIs



Neg Aff: Variance Ratios and CIs



3-level Model of Smoking-related Positive and Negative Affect Change; estimates, standard errors (se), and *p*-values

<i>Random effect (co)variances</i>	Positive Affect			Negative Affect		
	est	se	<i>p</i> <	est	se	<i>p</i> <
<i>Subject level</i>						
Intercept $\sigma_{v(3)}^2$.130	.031	.001	.084	.023	.001
Scale σ_{ω}^2	.780	.106	.001	1.28	.166	.001
Int, Scale $\sigma_{v(3)\omega}$.186	.040	.001	-.189	.041	.001
	(r = .59)			(r = -.58)		
<i>Wave level</i>						
Intercept $\sigma_{v(2)}^2$.090	.021	.001	.028	.012	.022

Location scale analysis - example of *Golden Rule of Statistics*:
 “one person’s error term is another person’s career!”



- More applications where interest is on modeling variance

Hedeker, D. & Mermelstein, R.J. (2012). Mood changes associated with smoking in adolescents: An application of a mixed-effects location scale model for longitudinal EMA data. In G. R. Hancock & J. Harring (Eds.), *Advances in Longitudinal Methods in the Social and Behavioral Sciences* (pp. 59-79). Information Age Publishing, Charlotte, NC.

Hedeker, D., Mermelstein, R.J., & Demirtas, H. (2008). An application of a mixed-effects location scale model for analysis of Ecological Momentary Assessment (EMA) data. *Biometrics*, *64*, 627-634.

Hedeker, D., Mermelstein, R.J., & Demirtas, H. (2012). Modeling between- and within-subject variance in EMA data using mixed-effects location scale models. *Statistics in Medicine*, *31*, 3328-3336.

Hedeker, D. & Nordgren, R. (2013). MIXREGLS: A program for mixed-effects location scale analysis. *Journal of Statistical Software*, *52(12)*, 1-38.

Kapur, K., Li, X., Blood, E.A., & Hedeker, D. (2015). Bayesian mixed-effects location and scale models for multivariate longitudinal outcomes: An application to ecological momentary assessment data. *Statistics in Medicine*, *34*, 630-651.

Li, X. & Hedeker, D. (2012). A three-level mixed-effects location scale model with an application to Ecological Momentary Assessment (EMA) data. *Statistics in Medicine*, *31*, 3192-3210.

Pugach, O., Hedeker, D., Richmond, M.J., Sokolovsky, A., & Mermelstein, R.J. (2014). Modeling mood variation and covariation among adolescent smokers: Application of a bivariate location-scale mixed-effects model. *Nicotine and Tobacco Research*, *16, Supplement 2*, S151-S158.

- Ordinal outcomes

Hedeker, D., Demirtas, H., & Mermelstein, R.J. (2009). A mixed ordinal location scale model for analysis of Ecological Momentary Assessment (EMA) data. *Statistics and Its Interface*, *2*, 391-402.

Hedeker, D., Mermelstein, R.J., Demirtas, H., & Berbaum, M.L. (2016). A mixed-effects location-scale model for ordinal questionnaire data. *Health Services and Outcomes Research Methodology*, *16(3)*, 117-131.

More Examples of Variance Models in Health Studies

- Lin, Raz, & Harlow (1997) Linear mixed models with heterogeneous within-cluster variances, *Biometrics*. *Determinants of menstrual cycle length variability in women (which may be associated with fertility and long-term risk of chronic disease)*.
- Carroll (2003) Variances are not always nuisance parameters, *Biometrics*. *Drug assay validation, measurement error in nutrient intake*.
- Elliott (2007) Identifying latent clusters of variability in longitudinal data, *Biostatistics*. *Clusters based on within-subject variation in affect of recovering MI patients*.
- Elliott, Sammel, & Faul (2010) Associations between variability of risk factors and health outcomes in longitudinal studies, *Statistics in Medicine*. *Residual variability in longitudinal recall data associated with dementia risk in elderly*.
- Rast & Zimprich (2011) Modeling within-person variance in reaction time data of older adults, *Journal of Gerontopsychology and Geriatric Psychiatry*.
- Coffman, Allen, & Woolson (2012) Mixed-effects regression modeling of real-time momentary pain assessments in osteoarthritis (OA) patients, *Health Services and Outcomes Research Methodology*. *Pain variability in patients with osteoarthritis*.
- Breslin (2014) Five indices of emotion regulation in participants with a history of nonsuicidal self-injury: A daily diary study, *Behavior Therapy*.

- Need a fair amount of BS and WS data, but modern data collection procedures are good for this. Also, from analysis of Riesby depression data ($N = 66, n_i = 4$ to 6):

The data of the two highest and lowest scale estimates from analysis of the Riesby data

id	$\tilde{\theta}_{2i}$	hd0	hd1	hd2	hd3	hd4	hd5
606	1.585	19	33	12	12	3	1
505	1.532	21	11	18	0	0	4
335	-1.317	21	21	18	15	12	10
308	-1.365	22	21	18	17	12	11

- Simulations with small datasets (*e.g.*, 20 subjects with 5 obs) often leads to non-convergence; this improves dramatically as numbers increase (*e.g.*, 100 subjects with 10 obs)
- Important to include random scale for correct inference of WS variance covariates (Leckie et al., 2014, *Jrn Educ Beh Stat*)