Modeling of Between- and Within-Subject Variances using Mixed Effects Location Scale Models for Intensive Longitudinal Data

Donald Hedeker
University of Chicago

hedeker@uchicago.edu

https://hedeker-sites.uchicago.edu/

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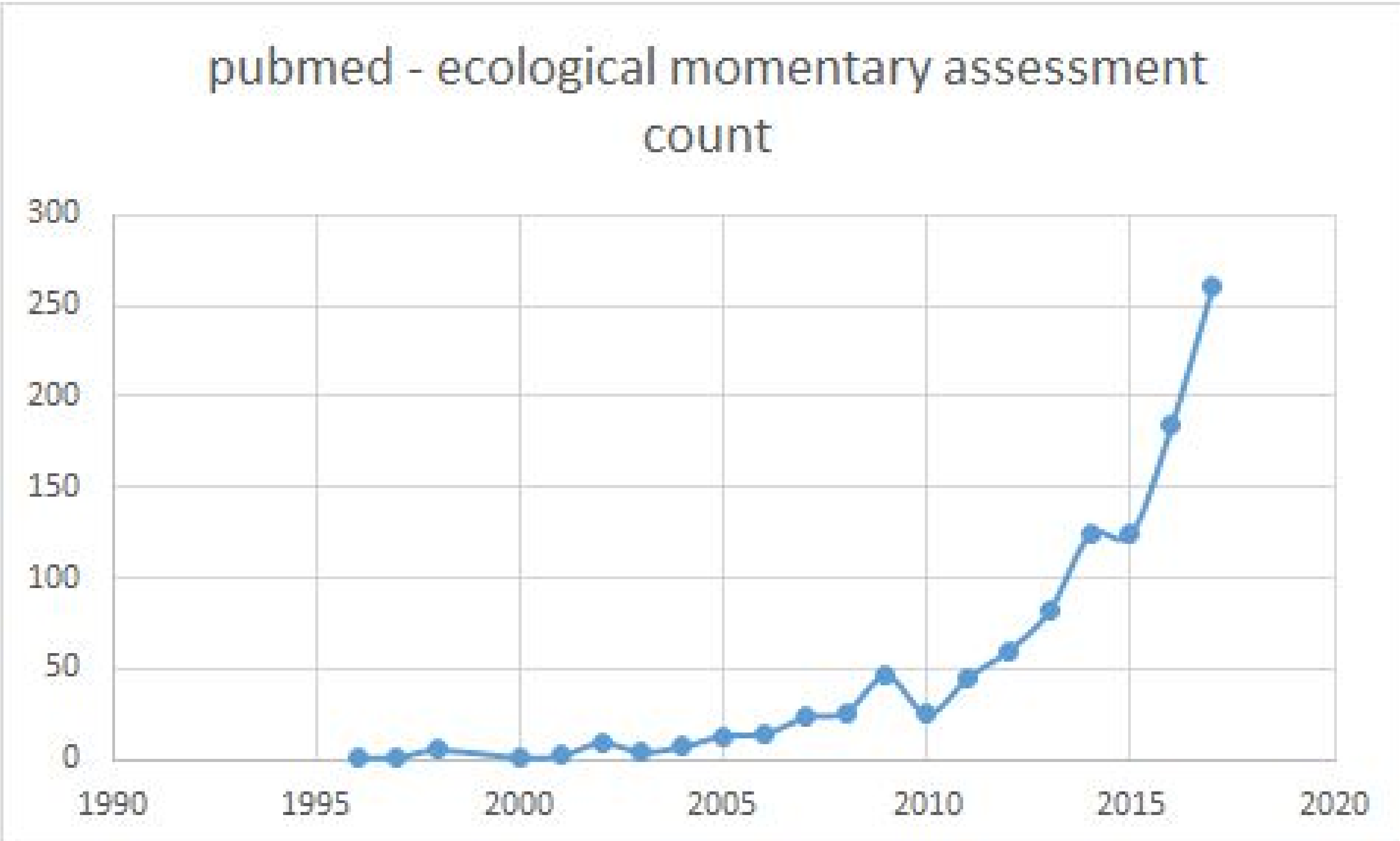
Ecological Momentary Assessment (EMA) data

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
count
300
250
200
150
100
50
0
1990
1995
2000
2005
2010
2015
2020

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?

$\Rightarrow$ Modeling of the WS variance alllows examination of these questions

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

$$y_{ij} \;=\; \boldsymbol{x}'_{ij}\boldsymbol{\beta} + \upsilon_i + \epsilon_{ij}$$

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

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

$\upsilon_i \sim N(0, \sigma^2_\upsilon)$ BS variance; how homogeneous/heterogeneous are subjects?

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

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

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

  $\Rightarrow$ magnitude of σ_υ^2 indicates how different subjects are from each other (homogeneity/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 (consistency/erraticism)

Log-linear models for variances

$$\text{BS variance} \qquad \sigma^2_{\upsilon_{ij}} \;=\; \exp(\boldsymbol{u}'_{ij}\boldsymbol{\alpha}) \qquad \text{or} \quad \log(\sigma^2_{\upsilon_{ij}}) \;=\; \boldsymbol{u}'_{ij}\boldsymbol{\alpha}$$

$$\text{WS variance} \qquad \sigma^2_{\epsilon_{ij}} \;=\; \exp(\boldsymbol{w}'_{ij}\boldsymbol{\tau}) \qquad \text{or} \quad \log(\sigma^2_{\epsilon_{ij}}) \;=\; \boldsymbol{w}'_{ij}\boldsymbol{\tau}$$

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

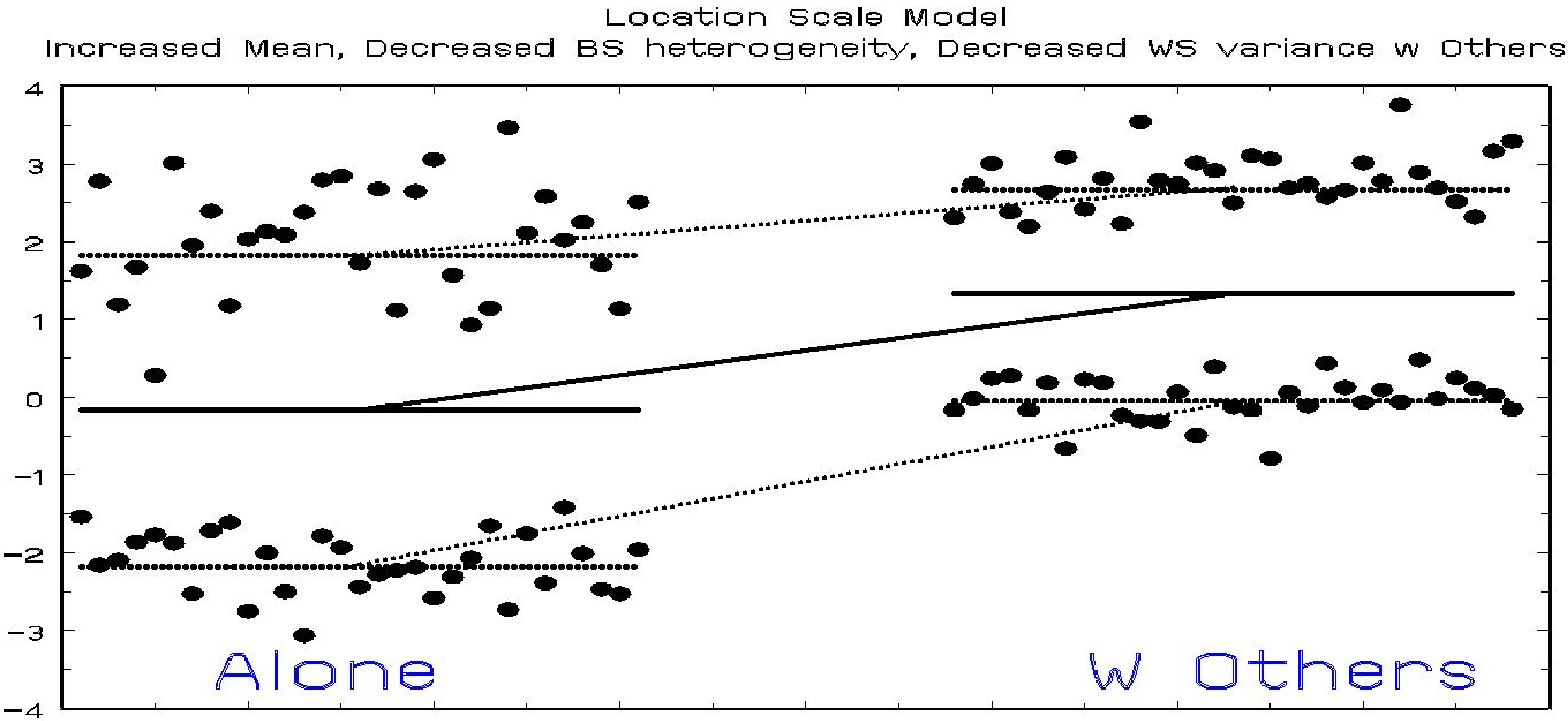
How can WS variables influence BS variance?

$$\sigma^2_{\upsilon_{ij}} = \exp(\boldsymbol{u}'_{ij}\boldsymbol{\alpha})$$

- 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

$\Rightarrow$ being alone increases subject heterogeneity (or, subjects report more similar mood when with 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

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

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

- 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
- υ_i are "location" random effects - how does a subject differ in terms of the mean of their data

Multilevel model of WS variance

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

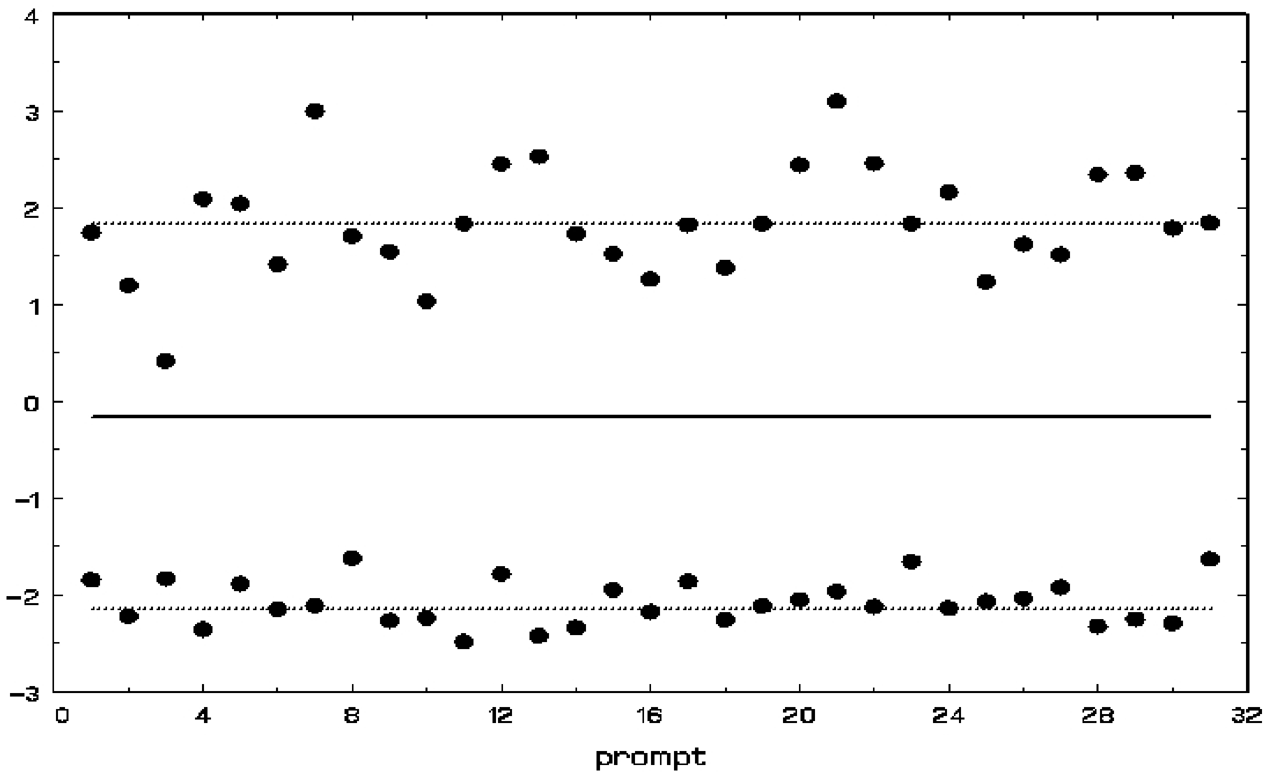
Why not use some summary statistic per subject (say, calculated subject standard deviation S_{y_i}) in a second-stage model?

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

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

$\Rightarrow$ 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://hedeker-sites.uchicago.edu

  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)

- $\Sigma_i^N n_i = 14,105$ total number of observations

Outcomes: positive and negative affect

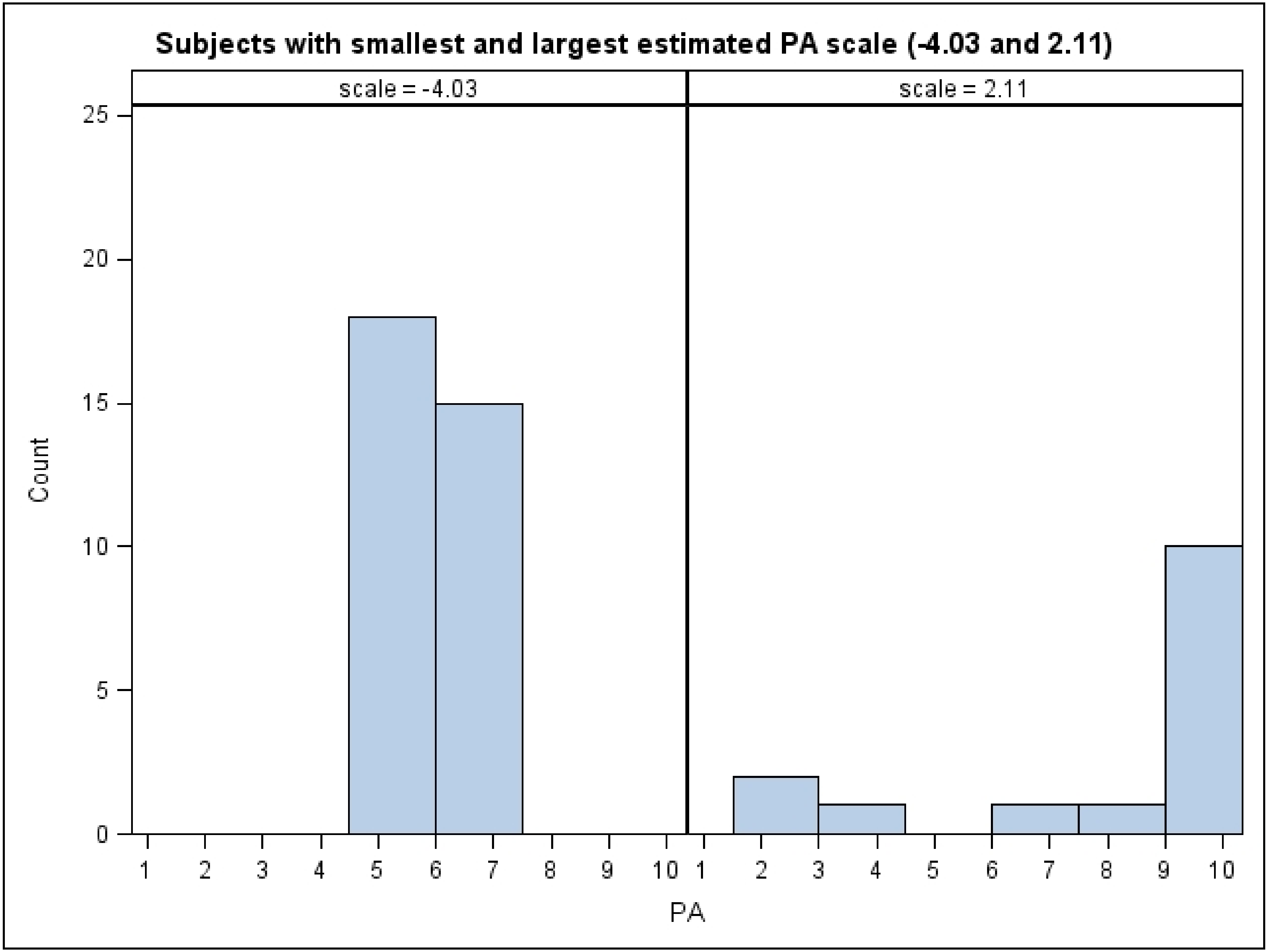
Interest: characterizing determinants of affect level, as well as BS and WS affect heterogeneity

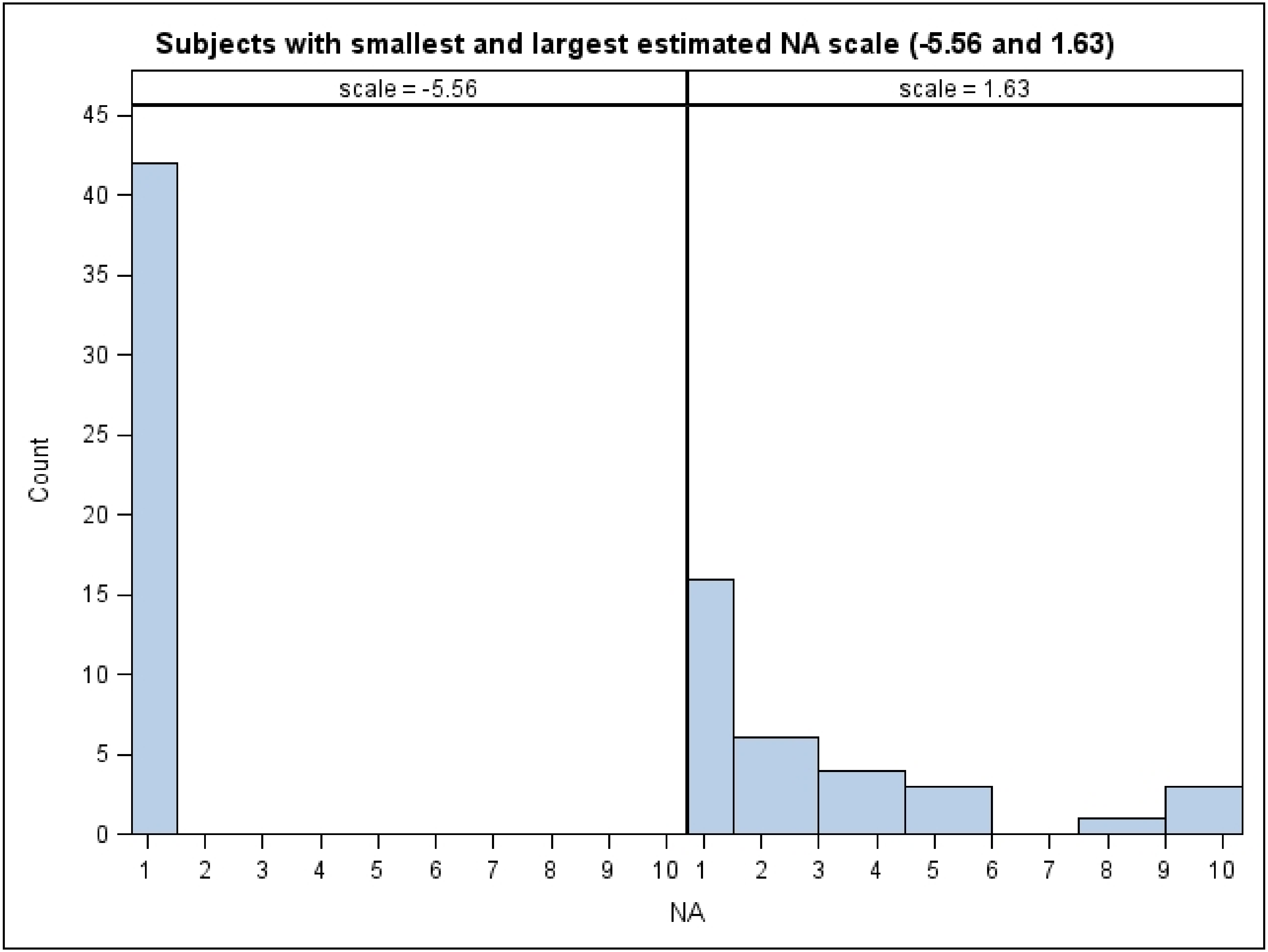
Dependent Variables

- 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

$\Rightarrow$ items rated on 1 (not al all) to 10 (very much) scale


Subjects with smallest and largest estimated PA scale (-4.03 and 2.11)
scale = -4.03
scale = 2.11
Count
0
5
10
15
20
25
1 2 3 4 5 6 7 8 9 10
1 2 3 4 5 6 7 8 9 10
PA


Subjects with smallest and largest estimated NA scale (-5.56 and 1.63)
scale = -5.56
scale = 1.63
Count
NA
0
5
10
15
20
25
30
35
40
45
1 2 3 4 5 6 7 8 9 10
1 2 3 4 5 6 7 8 9 10

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

	Positive Affect			Negative Affect		
parameter	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 $\sigma_{\upsilon\omega}$	-.308	.035	.001	.485	.044	.001

Variance model coefficients

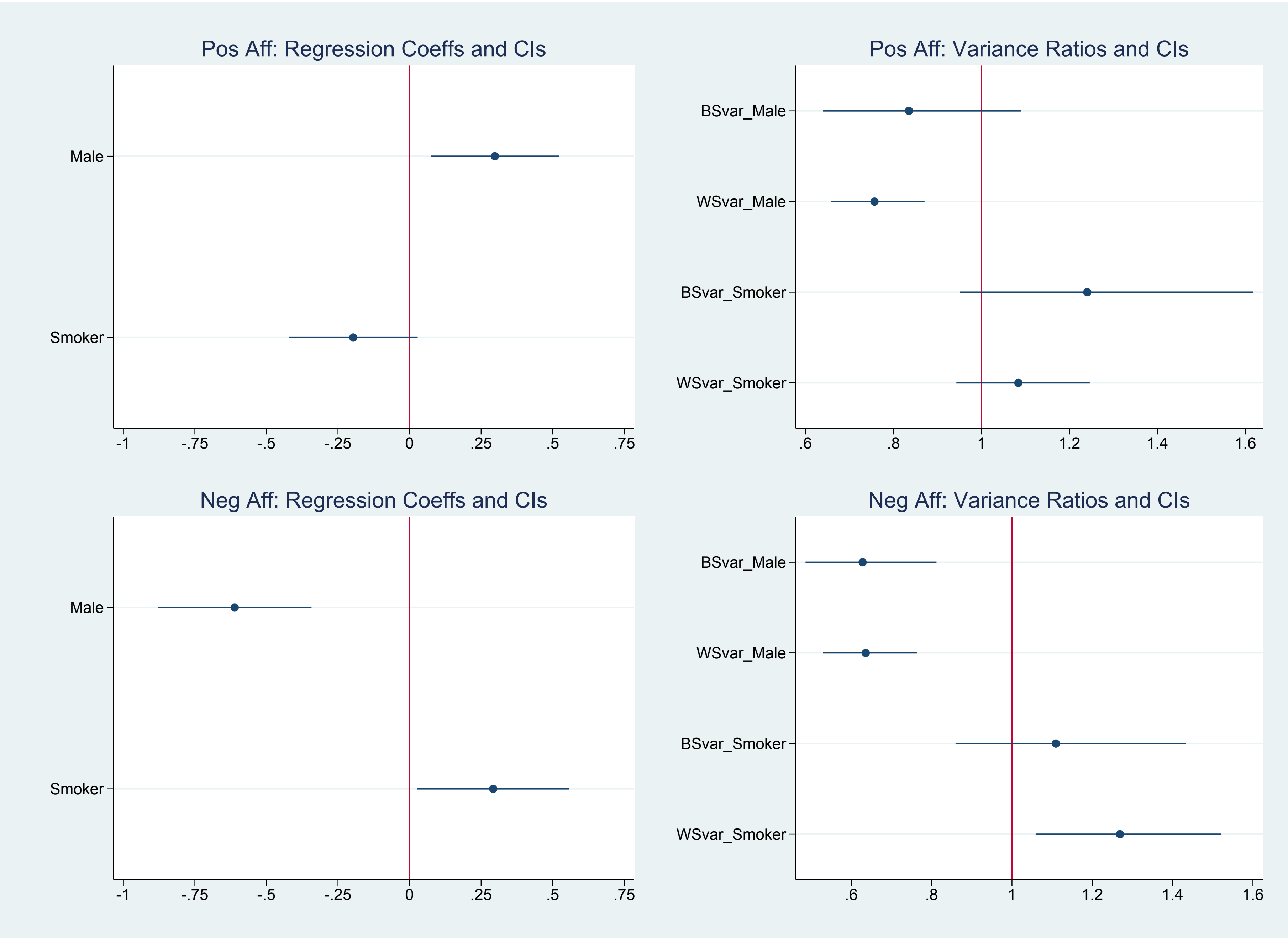
$$\sigma^2_{BS} = \exp(\tau_0 + \tau_1 \texttt{Male} + \tau_2 \texttt{Smoker})$$

Holding `Smoker` constant, BS variance equals:

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

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

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


Pos Aff: Regression Coeffs and CIs
Male
Smoker
-1 -.75 -.5 -.25 0 .25 .5 .75
Pos Aff: Variance Ratios and CIs
BSvar_Male
WSvar_Male
BSvar_Smoker
WSvar_Smoker
.6 .8 1 1.2 1.4 1.6
Neg Aff: Regression Coeffs and CIs
Male
Smoker
-1 -.75 -.5 -.25 0 .25 .5 .75
Neg Aff: Variance Ratios and CIs
BSvar_Male
WSvar_Male
BSvar_Smoker
WSvar_Smoker
.6 .8 1 1.2 1.4 1.6

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

`PropSmk` = n_smk / (n_smk + n_random)

Model with `Smoker` and `Psmk`

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

N=234 with n_smk > 0 (and $\texttt{Smoker} = 1$)

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

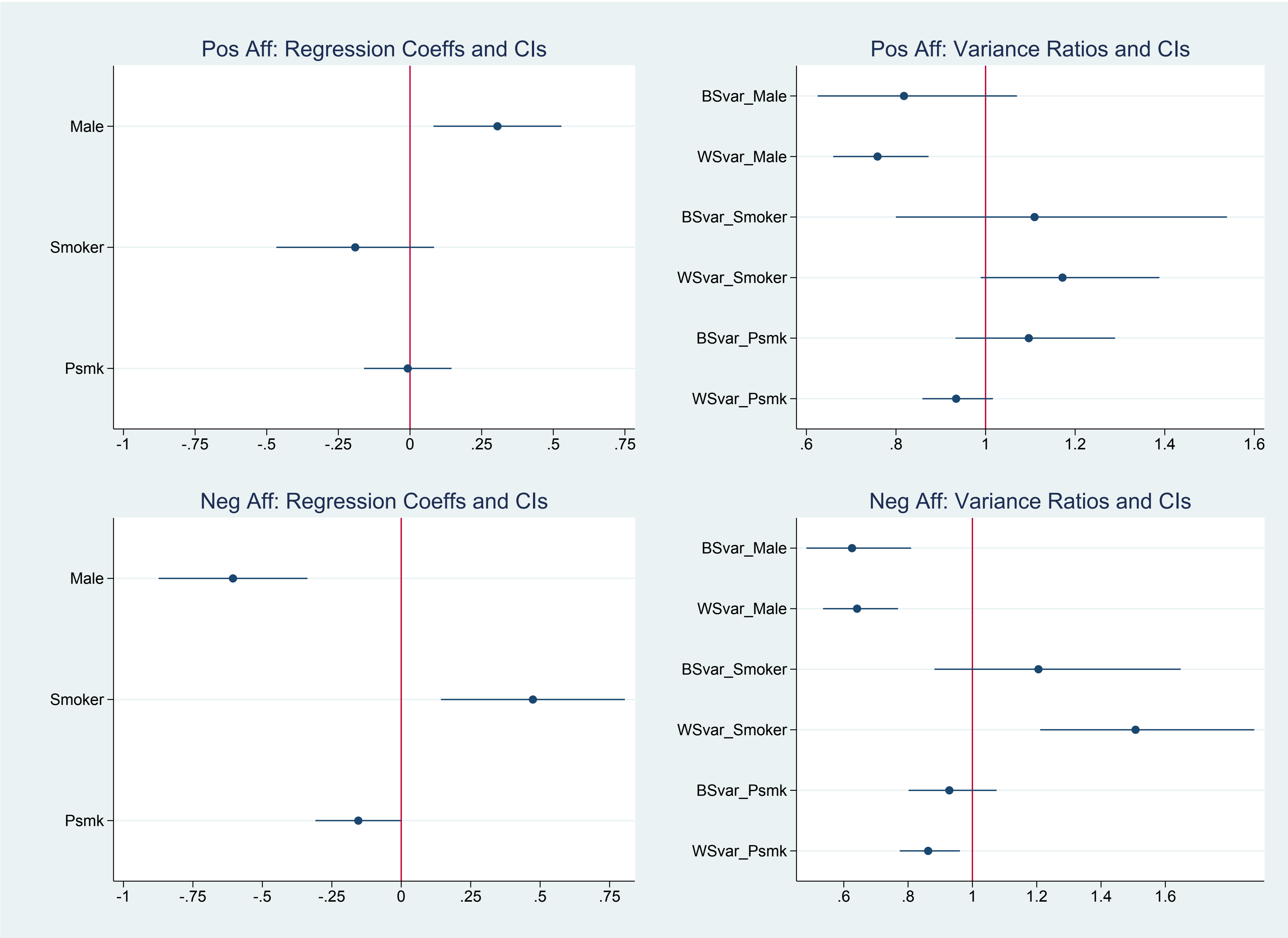
$\texttt{Psmk} = 10 \times (\texttt{PropSmk} - \min(\texttt{PropSmk}))$

Model: $\texttt{Mood}_{ij} = \beta_0 + \beta_1 \texttt{Smoker} + \beta_2 \texttt{Psmk} + \ \ldots \ + \upsilon_i + \epsilon_{ij}$

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	$\beta_0 + \beta_1 + 1.66\beta_2$

$\Rightarrow$ piecewise linear model for means; same for BS and WS variance models

	Positive Affect			Negative Affect		
parameter	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 $\sigma_{\upsilon\,\omega}$	-.304	.035	.001	.481	.044	.001


Pos Aff: Regression Coeffs and CIs
Male
Smoker
Psmk
-1
-.75
-.5
-.25
0
.25
.5
.75
Pos Aff: Variance Ratios and CIs
BSvar_Male
WSvar_Male
BSvar_Smoker
WSvar_Smoker
BSvar_Psmk
WSvar_Psmk
.6
.8
1
1.2
1.4
1.6
Neg Aff: Regression Coeffs and CIs
Male
Smoker
Psmk
-1
-.75
-.5
-.25
0
.25
.5
.75
Neg Aff: Variance Ratios and CIs
BSvar_Male
WSvar_Male
BSvar_Smoker
WSvar_Smoker
BSvar_Psmk
WSvar_Psmk
.6
.8
1
1.2
1.4
1.6

Summary - https://hedeker-sites.uchicago.edu/page/mixregls-program-estimating-mixed-effects-location-scale-models

- More applications where interest is on modeling variance

Cursio, J.F., Mermelstein, R.J., & Hedeker, D. (under review). Latent trait shared-parameter mixed-models for missing Ecological Momentary Assessment data.

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.

Lin, X., Mermelstein, R.J., & Hedeker, D. (under review). A three-level Bayesian mixed-effects location scale model with an application to Ecological Momentary Assessment data.

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)*