Methodological Advances in Individual Participant Data Meta-Analysis with Zero-altered Addictions Outcomes:

An Illustration with College Drinking Interventions

David Huh, Ph.D.
David C. Atkins, Ph.D.

Society for Prevention Research 27th Annual Meeting, San Francisco, CA, USA
May 31, 2019

Supported by NIH/NIAAA grant
R01 AA019511

UNIVERSITY *of* WASHINGTON

One-step meta-analysis using individual participant data (IPD)

- We walk through a **one-step IPD meta-analysis** using data from Project INTEGRATE[1], where observation-level data from multiple studies is combined and analyzed in a single statistical model.

- The approach[2,3] we detail accommodates common features of prevention trial data, including:
  - Skewed outcomes with many zeroes
  - Varying numbers of intervention conditions (two-arm and multi-arm studies)
  - Differing number and timing of follow-up assessments

[1]Mun et al. (2014); [2]Huh et al (2014); [3]Huh, Mun, Walters, Zhou, & Atkins (in press)

One-step meta-analysis using IPD (cont.)

- More analytic flexibility with one-step IPD meta-analysis versus meta-analysis using aggregate data
  - Able to control for participant-level factors as covariates
  - Model can be extended to evaluate moderators of treatment effects
  - Distribution-appropriate analysis

Outline

- The illustrative data from Project INTEGRATE
- Modeling zero-altered count outcomes from intervention trials
- Combining data from two-arm and multi-arm trials
- Conducting a one-step IPD meta-analysis with a Bayesian hurdle model
- Conclusions

Illustrative data from Project INTEGRATE 1.0

- A meta-analysis project of 24 studies evaluating brief motivational interventions (BMIs) for college drinking.[1]
- The example IPD[3] includes a total of **13,534 assessments** from **5,952 individuals** across **15 studies**.
  - 12 two-arm trials, 2 three-arm trials, 1 four-arm trial
- We focus on 15 randomized control trials that evaluated one of three BMIs:
  - Individual Motivational Interview with Personalized Feedback (MI+PF)
  - Standalone Personalized Feedback (PF)
  - Group Motivational Interview (GMI)

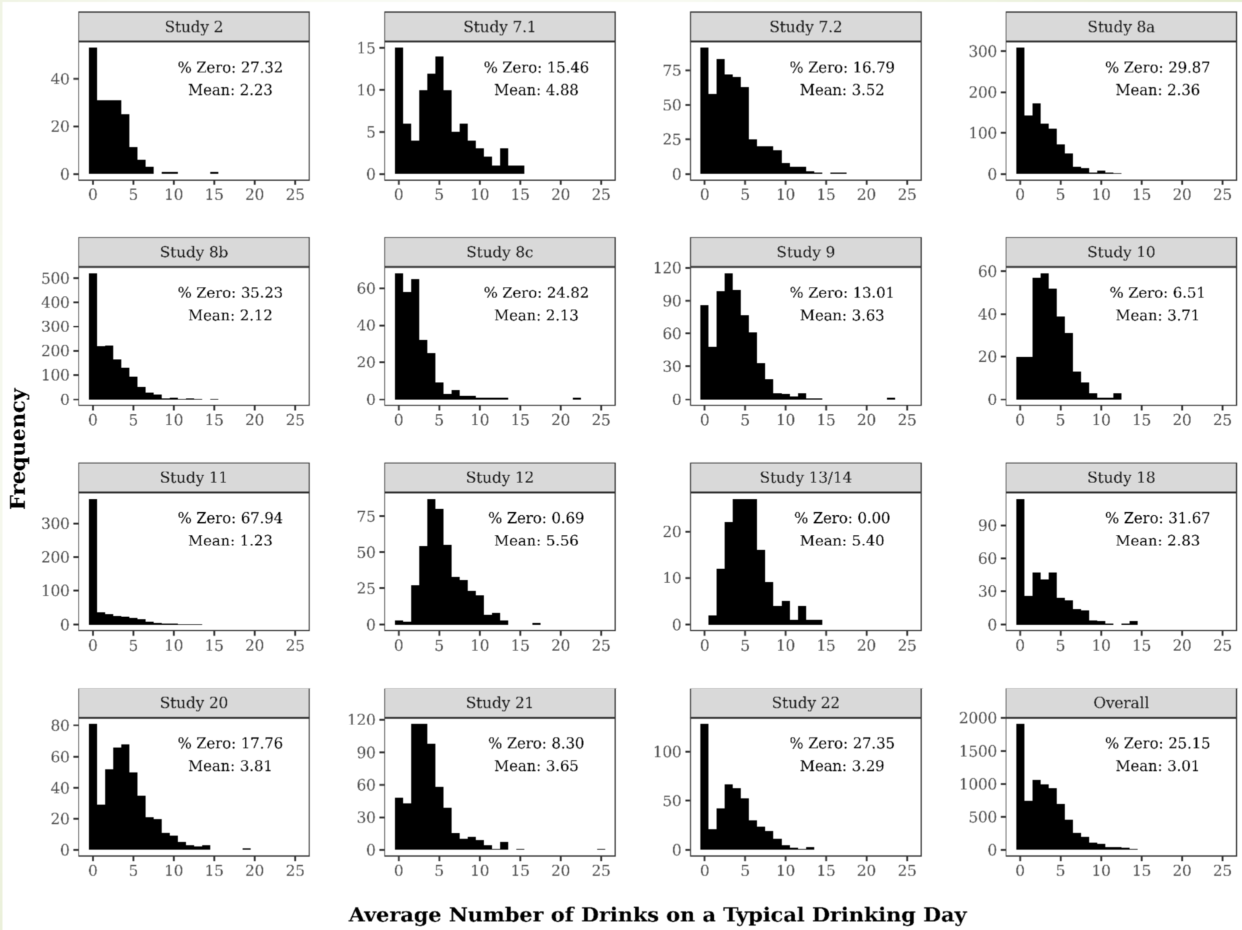
[1]Mun et al. (2014); [3]Huh et al. (in press)

Illustrative data from Project INTEGRATE 1.0 (cont.)

- **Outcome:** Average number of drinks on a typical drinking day
  - Assessed using the Daily Drinking Questionnaire (DDQ)[4]
- Each participant had a baseline assessment and 1 to 3 follow-up assessments, up to 12 months post-baseline.

[4]Collins, Parks, & Marlatt, 1985

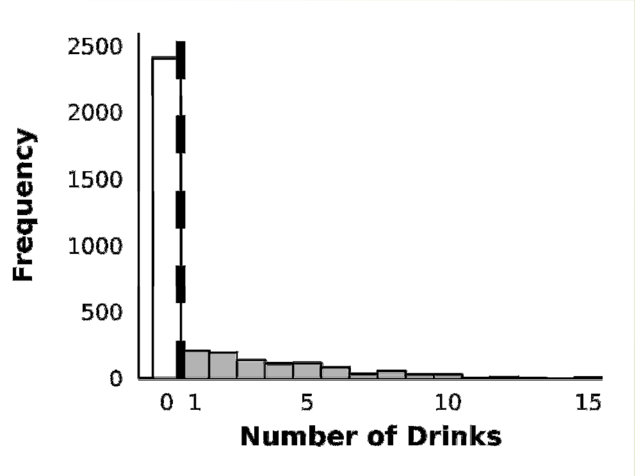
Distribution of drinking data across studies



Important to attend to excess zeroes…

- Behavioral outcomes in prevention research frequently contain many zeroes. Examples include…
  - Alcohol and other drug use (AOD)
  - Sexual risk behaviors
  - Suicide-related behaviors

- **Zeroes may be a key feature of the outcome and not just a nuisance in the data…**



Important to attend to excess zeroes… (cont.)

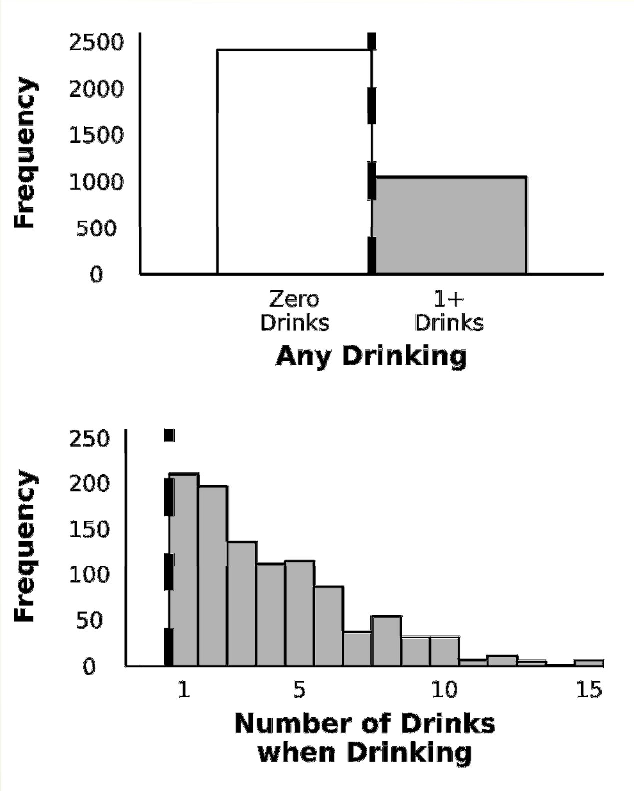
- An intervention may have an effect on either:
  - The decision to drink vs. not to drink (0 vs. 1 or more)
  - The number of drinks when drinking is non-zero (1, 2, 3, …)

Accounting for zero-altered outcomes using a hurdle model…

- Hurdle models, a type of two-part model, are appropriate for zero-inflated count data, such as number of drinks.[5,6]

- A threshold must be crossed from zero into positive counts.

- The outcome is effectively divided into two parts
  - No drinking vs. any drinking
    - Logistic regression
  - Amount of drinking when drinking:
    - Zero-truncated count regression (Poisson or negative binomial)



[5]Atkins, Baldwin, Zheng, Gallop, & Neighbors (2013); [6]Huh, Kaysen, & Atkins (2014)

Combining studies with differing numbers of treatment conditions.

- The majority of randomized trials (>78%) are two-arm studies,[7] however, multiple-arm trials are not uncommon.
  - In Project INTEGRATE 1.0, one in five studies evaluated multiple treatments.

- A common challenge is how to combine studies with varying numbers of arms.[8]

[7]Hopewell, Dutton, Yu, Chan & Altman (2010); [8]Gleser & Olkin (2009)

Is a multilevel model (MLM) with study at the highest level the logical choice?

- The motivating example data from Project INTEGRATE 1.0 could be modeled in a 3-level model…
  - Assessments (Level 1) nested within
  - Participants (Level 2), which are nested within
  - Studies (Level 3)

- Average treatment effects can be included as predictors (fixed effects), with unique treatment effects for each study.
  - i.e., a “random slope” for treatment

A one-step IPD meta-analysis using a 3-level MLM

Outcome at baseline

Additional covariate(s)

$$\text{Hurdle}(\text{OUTCOME}_{t>0,is}) =$$
$$b_0 + b_1\text{OUTCOME}_{t=0,is} + b_2\text{COVARIATE}_{is} +$$
$$b_3\text{MI\_PF}_{is} + b_4\text{PF}_{is} + b_5\text{GMI}_{is} +$$
$$u_{0s} +$$
$$u_{1s}\text{MI\_PF}_s + u_{2s}\text{PF}_{is} + u_{3s}\text{GMI}_{is} +$$
$$r_{0is}$$

Post-baseline values of the outcome

Average intervention effect sizes of MI+PF, PF, and GMI

The deviations of each study from the average intervention effect (study-specific slopes for each treatment type vs. control)

Study-specific intercept for variability across studies

Participant-specific intercept for variability across individuals

t = time point of assessment
i = individual
s = study

The previous model is rank deficient as not all treatment types were evaluated in all studies…

Studies (15)

Treatment Types (3)

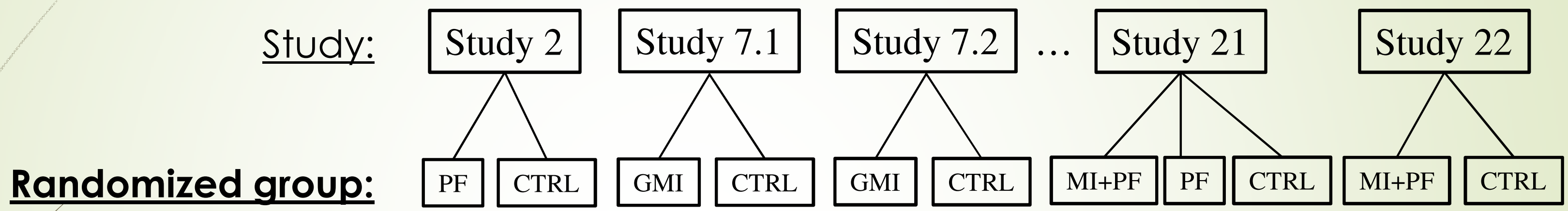
	2	7.1	7.2	8a	8b	8c	9	10	11	12	13/14	18	20	21	22
MI+PF	×	×	×	×	×	×	✓	✓	×	✓	✓	×	✓	✓	✓
PF	✓	×	×	✓	✓	✓	✓	×	✓	×	✓	✓	×	✓	×
GMI	×	✓	✓	×	×	×	✓	×	×	×	×	×	×	×	×

- 45 possible study by treatment combinations
  - But 26 combinations (58%) don’t exist.
  - Not possible to calculate a treatment effect in studies that did not evaluate a particular treatment, without a methodological intervention.

What are our options?

- Pool active intervention conditions within a study or keep only 1 active treatment?
  - Reduces each study to a 2-arm RCT design.
  - Loss of information → not ideal
- Apply parameter constraints to the model?
  - May not be ideal either…
- **Exclude the non-existent study by treatment combinations** that are making the model rank deficient.

Defining “randomized group” at the highest level of an MLM



- The highest level of the model is the unique randomized group rather than study.
  - This is analogous to converting a two-way ANOVA to an equivalent one-way ANOVA, where each study by treatment combination is defined as a separate group
    - Missing study by treatment combinations are excluded.
- There is no fixed effect for treatment.
  - Intervention effect sizes are calculated from the random effect coefficients.

A multilevel hurdle model with randomized group at the highest level: logistic portion

The probability of participant ***i*** in randomized group ***g*** drinking at assessment ***t***

Unique randomized group effect

$$\log\left(\frac{\Pr[\mathrm{DRINKS}_{t>0,ig}>0]}{\Pr[\mathrm{DRINKS}_{t>0,ig}=0]}\right) =$$

$$b_{0(B)} + b_1\mathrm{OUTCOME}_{t=0,ig(B)} + b_2\mathrm{COVARIATE}_{ig(B)} + u_{0g(B)} + r_{0ig(B)}$$

t = repeated measure
i = participant
g = unique randomization group

A multilevel hurdle model with randomized group at the highest level: negative binomial portion

The expected number of drinks when drinking was non-zero for participant ***i*** in randomized group ***g*** drinking at assessment ***t***

↓

- $\log(\mathrm{E}[\mathrm{DRINKS}_{t>0,ig}] | \mathrm{DRINKS}_{t>0,ig} > 0) =$

$$b_{0(C)} + b_1\mathrm{OUTCOME}_{t=0,ig} + b_{2(C)}\mathrm{COVARIATE}_{ig} + u_{0g(C)} + r_{0ig(C)}$$

The negative binomial portion is essentially the same, except that it focuses on drinking quantity when non-zero.

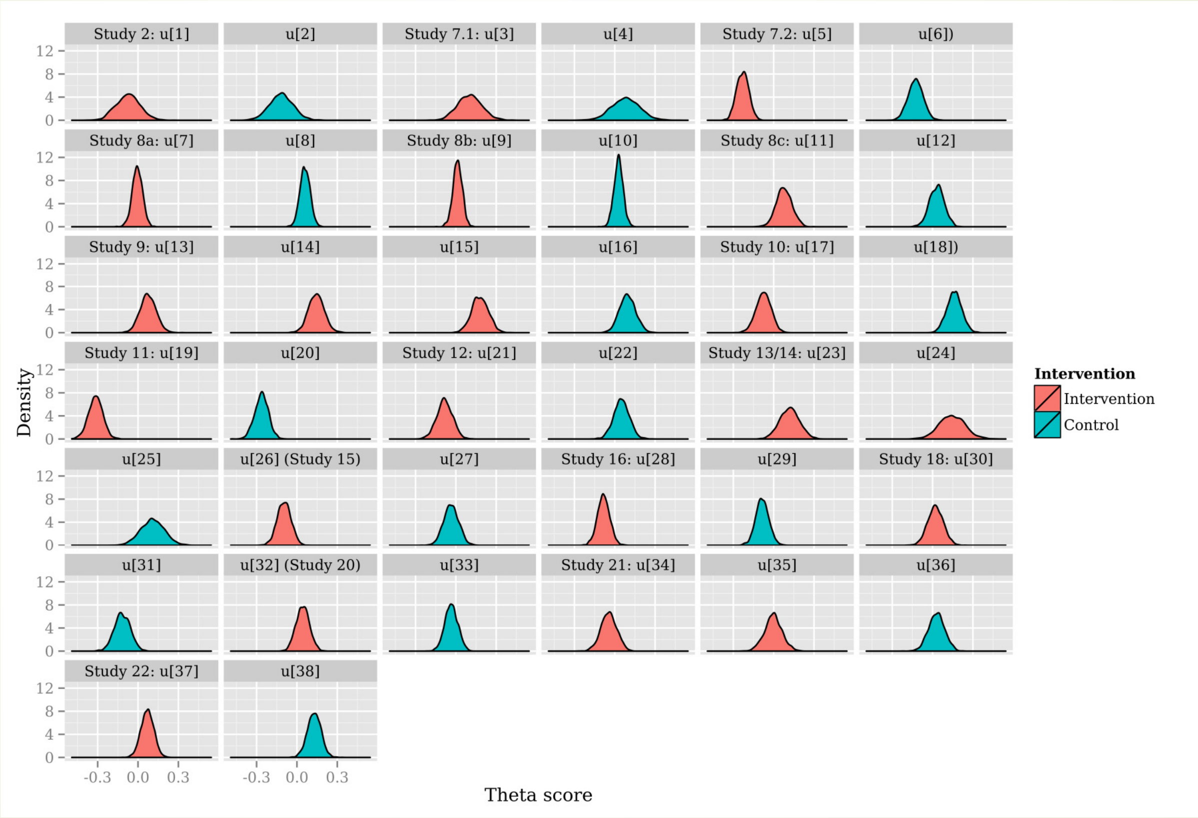
t = repeated measure
i = participant
g = unique randomization group

Using a Bayesian approach to estimate the meta-analysis model…

- To calculate a treatment effect using the model described, a full statistical distribution for each unique randomized group is needed.
  - MLMs are commonly estimated using restricted maximum likelihood (REML), but this does not provide the necessary information.
- A Bayesian approach to MLM using Markov Chain Monte Carlo (MCMC) estimation can simulate the distribution for all parameters in the model, <u>including</u> the random effects.
  - A key feature of Bayesian estimation is specifying a prior distribution.
  - We used minimally informative priors which yield results comparable to those obtained from REML.

[7]Hopewell, Dutton, Yu, Chan & Altman (2010); [8]Gleser & Olkin (2009)

The model produces a distribution for each randomized group…



Example intervention effect calculation for Study 2

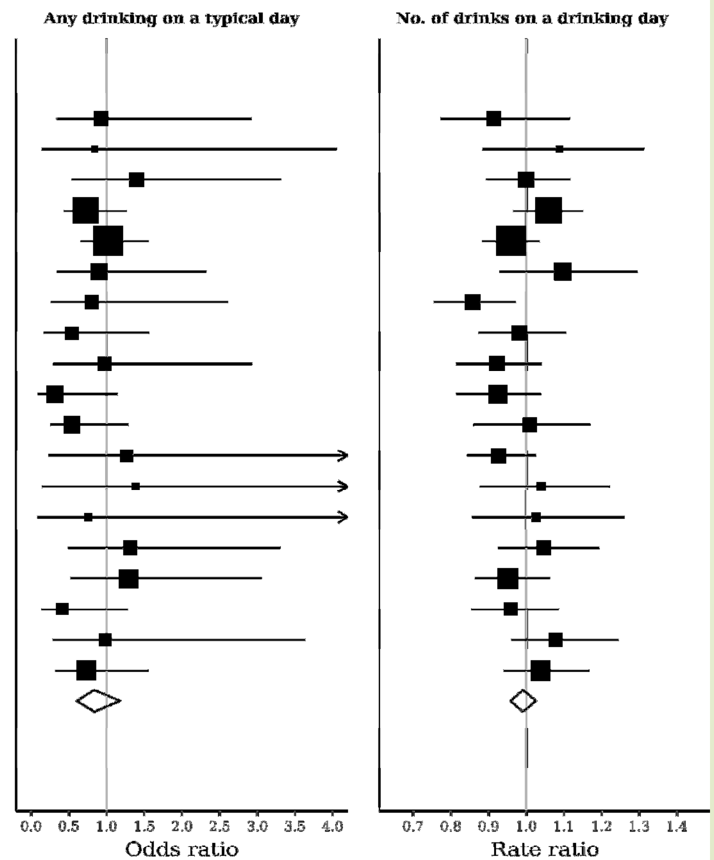
- Three steps to calculating the effect size for a treatment group
  1. Identify the posterior draws from the random effect for an intervention group and its' corresponding control group.
  2. Take the difference ($u_{intervention} - u_{control}$).
  3. Calculate the mean and 95% confidence interval of that difference.

- Repeat for all other intervention groups.

	Study 2		
	PF	Control	Effect Size
(Sample)	U_1	U_2	$U_1 - U_2$
1	-0.036	-0.037	0.010
2	-0.167	-0.191	0.240
3	-0.001	0.100	-0.999
⋮	⋮	⋮	⋮
2000	-0.145	-0.023	-0.122

One-Step IPD Meta-Analysis Results

Study	Intervention	Any drinking OR [95% CI]	No. of drinks RR [95% CI]
2	PF	0.93 [0.34, 2.92]	0.91 [0.77, 1.12]
7.1	GMI	0.84 [0.14, 4.05]	1.09 [0.88, 1.31]
7.2	GMI	1.40 [0.54, 3.31]	1.00 [0.89, 1.12]
8a	PF	0.72 [0.43, 1.26]	1.06 [0.96, 1.15]
8b	PF	1.02 [0.65, 1.56]	0.96 [0.88, 1.04]
8c	PF	0.90 [0.34, 2.33]	1.10 [0.93, 1.30]
9	MI+PF	0.81 [0.25, 2.61]	0.86 [0.75, 0.97]
	PF	0.54 [0.17, 1.57]	0.98 [0.87, 1.11]
	GMI	0.97 [0.29, 2.93]	0.92 [0.81, 1.04]
10	MI+PF	0.32 [0.09, 1.15]	0.93 [0.81, 1.04]
11	PF	0.54 [0.26, 1.29]	1.01 [0.86, 1.17]
12	MI+PF	1.27 [0.23, 6.75]	0.93 [0.84, 1.03]
13/14	MI+PF	1.39 [0.14, 9.06]	1.04 [0.88, 1.22]
	PF	0.76 [0.08, 6.66]	1.03 [0.86, 1.26]
18	PF	1.31 [0.48, 3.30]	1.05 [0.92, 1.19]
20	MI+PF	1.30 [0.52, 3.06]	0.95 [0.86, 1.06]
21	MI+PF	0.41 [0.14, 1.28]	0.96 [0.85, 1.09]
	PF	0.99 [0.28, 3.64]	1.08 [0.96, 1.25]
22	MI+PF	0.73 [0.31, 1.55]	1.04 [0.94, 1.17]
Overall		0.84 [0.61, 1.18]	0.99 [0.96, 1.03]
MI+PF only		0.93 [0.61, 1.36]	0.99 [0.94, 1.05]
PF only		0.88 [0.56, 1.32]	0.98 [0.94, 1.04]
GMI only		1.03 [0.50, 2.04]	1.00 [0.90, 1.10]



Conclusions

- The approach detailed is a feasible method for combining data from heterogeneous studies while accounting for other important characteristics of addictions data, such as nested data and zero-altered outcomes.

- A minor drawback: Bayesian estimation is more computationally intensive than models estimated via REML
  - ~2 hours in our example analysis

Future directions for IPD meta-analysis…

- Additional outcome distributions
- Extending one-step IPD meta-analysis models to accommodate both IPD and AD simultaneously.
  - One of the aims of Project INTEGRATE 2.0

Tutorial walkthrough, R code, and example data available online…

- **Tutorial walkthrough of this approach**:

  Huh, D., Mun, E.-Y., Walters, S. T., Zhou, Z., & Atkins, D. C. (2019). A tutorial on individual participant data meta-analysis using Bayesian multilevel modeling to estimate alcohol intervention effects across heterogeneous studies. *Addictive Behaviors, 94*, 162-170. https://doi.org/10.1016/j.addbeh.2019.01.032

- **R code** and **example data** available through *Mendeley Data*:
  - https://doi.org/10.17632/4dw4kn97fz.2

Contact Information

David Huh, Ph.D.
Director of the Methods Division
Indigenous Wellness Research Institute
University of Washington School of Social Work
dhuh@uw.edu

References

1. Mun, E.-Y., de la Torre, J., Atkins, D. C., White, H. R., Ray, A. E., Kim, S.-Y., … the Project INTEGRATE Team. (2014). *Project INTEGRATE: An integrative study of brief alcohol intervention trials for college students. Psychology of Addictive Behaviors, 29,* 34-48. https://doi.org/10.1037/adb0000047
2. Huh, D., Mun, E.-Y., Larimer, M. E., White, H. R., Ray, A. E., Rhew, I. C., . . . Atkins, D. C. (2014). *Brief motivational interventions for college student drinking may not be as powerful as we think: An individual participant-level data meta-analysis. Alcoholism: Clinical and Experimental Research, 39,* 919-931. https://doi.org/10.1111/acer.12714
3. Huh, D., Mun, E.-Y., Walters, S. T., Zhou, Z., & Atkins, D. C. (2019). A tutorial on individual participant data meta-analysis using Bayesian multilevel modeling to estimate alcohol intervention effects across heterogeneous studies. *Addictive Behaviors, 94*, 162-170. https://doi.org/10.1016/j.addbeh.2019.01.032
4. Collins, R. L., Parks, G. A., & Marlatt, G. A. (1985). Social determinants of alcohol consumption: The effects of social interaction and model status on the self-administration of alcohol. *Journal of Consulting and Clinical Psychology, 53,* 189–200. https://doi.org/10.1037/0022-006X.53.2.189
5. Atkins, D. C., Baldwin, S. A., Zheng, C., Gallop, R. J., & Neighbors, C. (2013). A tutorial on count regression and zero-altered count models for longitudinal substance use data. *Psychology of Addictive Behaviors, 27,* 166–177. https://doi.org/10.1037/a0029508
6. Huh, D., Kaysen, D., & Atkins, D. C. (2014). *Modeling cyclical patterns in daily college drinking data with many zeroes. Multivariate Behavioral Research, 50,* 184-196. https://doi.org/10.1080/00273171.2014.977433
7. Hopewell, S., Dutton, S., Yu, L.-M., Chan, A.-W., & Altman, D. G. (2010). The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. *BMJ (Clinical Research Ed.), 340*, c723.
8. Gleser, L. J., & Olkin, I. (2009). Stochastically dependent effect sizes. In H. Cooper, L. V. Hedges, & J. C. Valentine (Eds.), *The handbook of research synthesis and meta-analysis* (2nd ed., pp. 357–376). New York, NY: Russell Sage Foundation.

Assumptions of the approach…

- Study by treatment combinations that were not observed are missing by design and missing at random, and do not bias the findings.
- Using randomized groups as the highest data level assumes that the groups are independent within study due to randomization.
- Outcomes, interventions, and comparison groups are equivalent across studies.
  - In INTEGRATE 1.0, measures were similar across studies and intervention groups were carefully selected for equivalency.