How do we combine two treatment arm trials with multiple arms trials in IPD meta-analysis?

An Illustration with College Drinking Interventions

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IPD opens the door to new possibilities…

- Meta-analysis of individual participant-level data (IPD) opens the door to a greater variety of research hypotheses that can be tested, yet it's rarely done in the social sciences.

- Provides a means of combining information across studies more accurately.
  - Compared with traditional methods based on summary statistics, IPD-based meta-analysis can be more flexibility tailored to the characteristics of the data and study designs.

- A challenge in meta-analysis†, including with IPD:

  How to combine studies with varying numbers of treatments.
  - Most randomized trials (> 78%) are two arm studies‡, however, multiple arm trials are not uncommon.
  - Little discussion in the IPD meta-analysis literature about how to combine studies with varying numbers of arms.

†Gleser & Olkin, 2009; ‡ Hopewell, Dutton, Yu, Chan & Altman, 2010

IPD meta-analysis can accommodate varying arms and other data characteristics

- The appropriate combination of studies with varying numbers of arms was a key consideration in an IPD meta-analysis that our research group (Project INTEGRATE)† undertook of college drinking interventions.

- Other important analytic issues:
  - Differing number of assessments
  - Confounders and moderators of intervention outcome
  - Normally-distributed and zero-inflated count outcomes

- Ultimately settled a novel formulation of a Bayesian multilevel model that retained all the available data and accommodated differing numbers of treatment groups.

† Mun et al., 2014

A real-world application with drinking interventions

- For over two decades, brief motivational interventions (BMIs) have been implemented on college campuses to reduce heavy drinking and related negative consequences.
  - Recommended as a prevention strategy by the National Institute on Alcohol Abuse and Alcoholism (NIAAA).†
- Such interventions include:
  - In-person motivational interviews with personalized feedback (MI+PF)
  - Group motivational interviews (GMI)
  - Stand-alone PF interventions delivered via mail, computer, or the Web.
- Meta-analytic reviews using aggregate data from published studies suggest their short-term efficacy, but the effects vary.
  - Carey and colleagues‡ found that across 62 studies, 50% of tests of intervention outcomes were statistically significant.
  - Significant findings were associated with small effect sizes.

† NIAAA, 2002; ‡ Carey , Scott-Sheldon, Carey, DeMartini, 2007

Building on previous systematic reviews with IPD meta-analysis

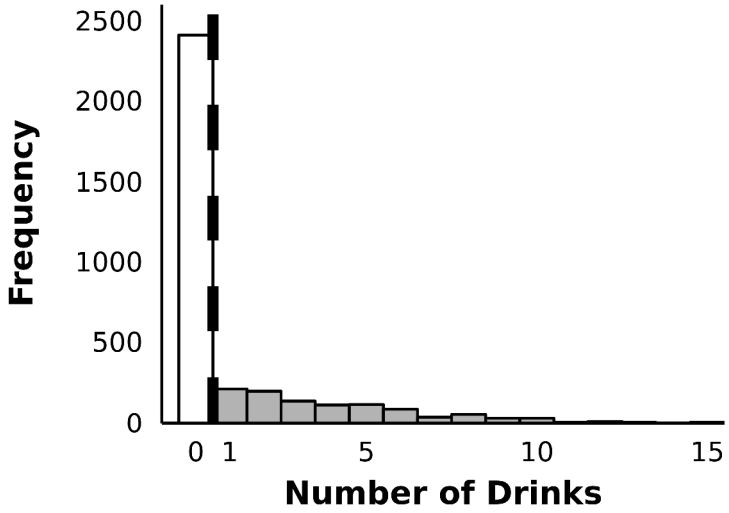
- Systematic reviews to-date have limitations
  - Effects at different time-points evaluated with different subsets of studies.
  - Moderators evaluated at the study-level (e.g., % female vs. male).
  - Alcohol outcomes are often highly skewed with many zeroes.
    - Both Gaussian and traditional count models under-represent the actual frequency of zeroes.†

- More analytic options with IPD compared with classical meta-analysis using aggregate data.
  - Ability to control for participant-level covariates.
  - Model can be easily extended to evaluate individual-level moderators.
  - Distribution-appropriate analysis

† Atkins, Baldwin, Zheng, Gallop, & Neighbors, 2013

Important to attend to excess zeroes…

- Distribution of the data is another important consideration.
  - Behavioral outcomes assessing short intervals will often contain a lot of zeroes.
    - Substance use
    - Sexual behavior



- Zeroes may be a key feature of the outcome and not just a nuisance of the data.
  - An intervention may have an effect on either:
    - **The decision to drink (zero drinks vs. 1 or more drinks)**
    - **The number of drinks once started (1, 2, 3, …)**

What IPD meta-analysis options are available?

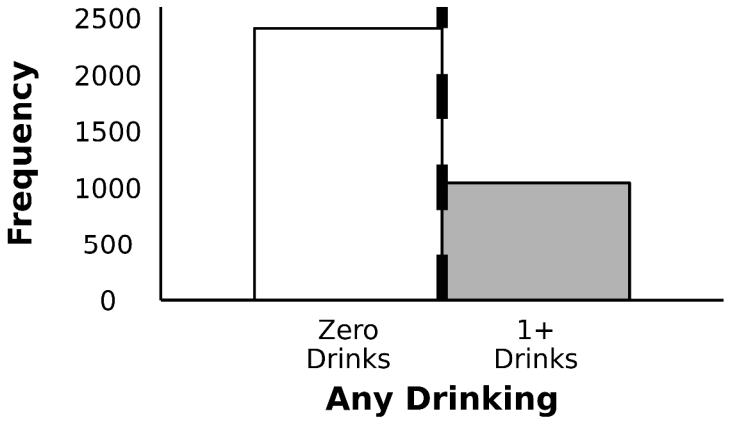
- Two-stage IPD meta-analysis
  - The most common†
  - Raw data are converted into standardized effect sizes.
    - For continuous data (*d* and *g*)
    - For dichotomous and count data (*OR*, *RR*)
  - Standardized effect sizes are pooled.

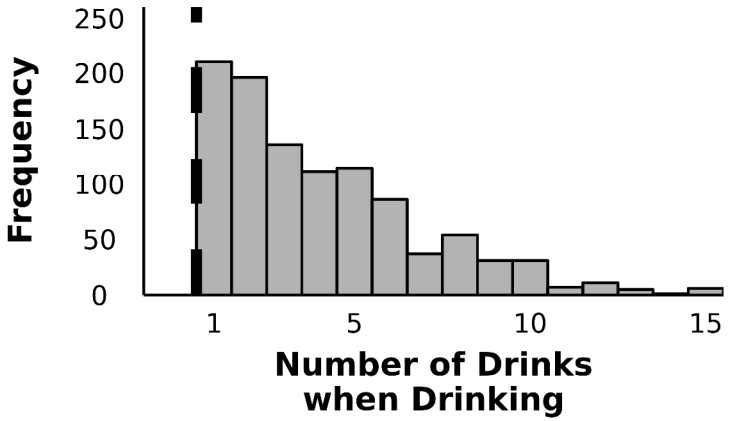
- Single-stage IPD meta-analysis
  - We have the raw data, why not use it?
    - Less variation in IPD-generated estimates, thus greater power.
    - Participant-level covariates can be incorporated.
  - Greater variety of statistical models at our disposal.

† Cooper & Patall, 2009

Accounting for zero-inflated outcomes using a hurdle model

- Hurdle models, a type of two-part model are appropriate for zero-inflated count data, such as drinking.†
- 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 Poisson or Negative binomial regression





† Huh, Kaysen, & Atkins, 2014

An example with longitudinal IPD

- Project INTEGRATE
  - One of the largest IPD meta-analysis projects to-date evaluating brief motivational interventions for college drinking.†,‡
  - Focused on randomized controlled studies evaluating one or more BMIs:
    - Individual Motivational Interview with Personalized Feedback
    - Standalone Personalized Feedback
    - Group Motivational Interview
  - IPD sample included 17 studies of 8,275 individuals
    - 14 two-arm studies
    - 2 three-arm studies
    - 1 four-arm study
  - 2 – 5 repeated measures up to 12 months post-baseline

† Mun et al., 2014; Huh et al., 2014

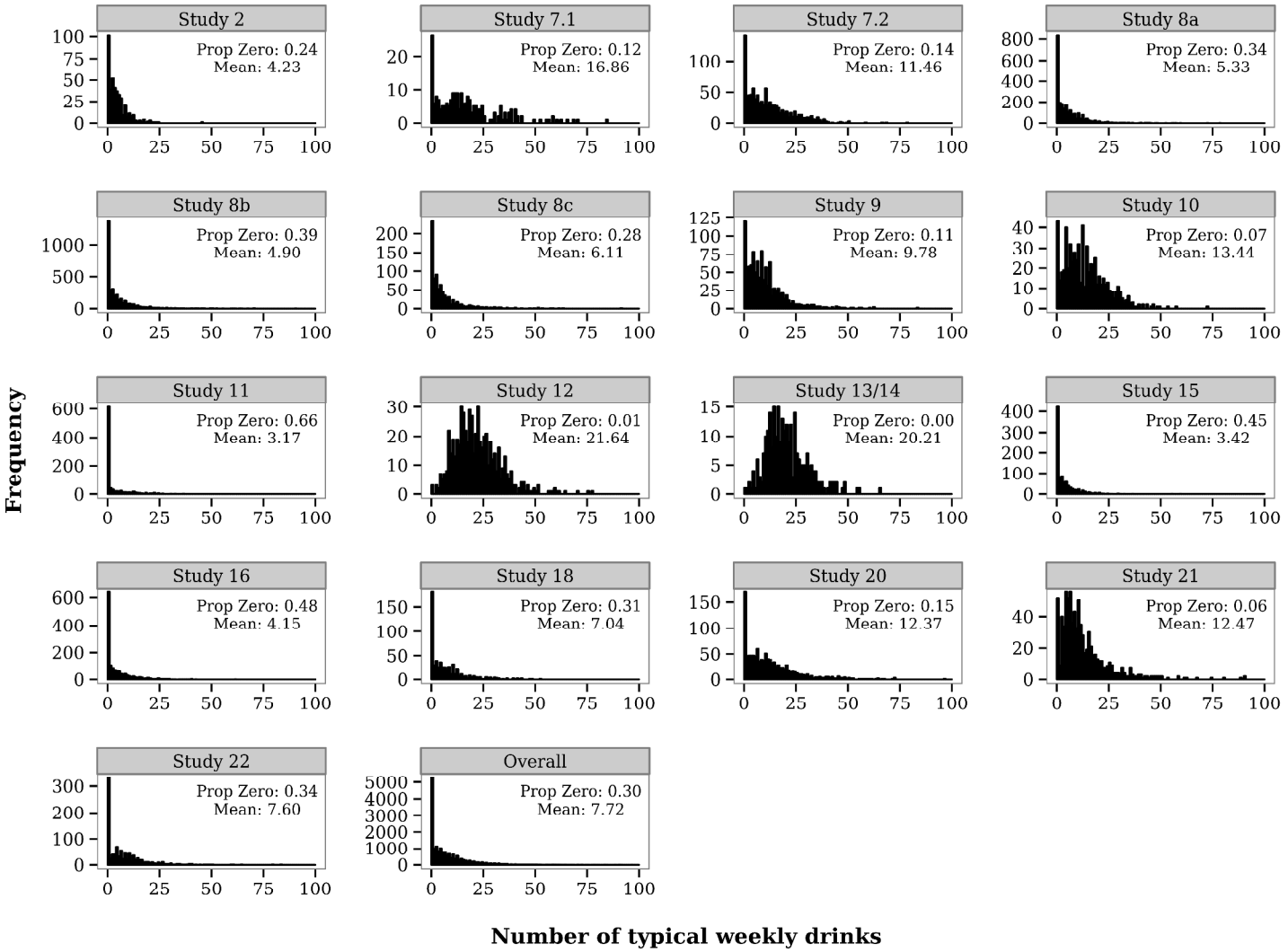
The longitudinal drinking outcomes

- **Total drinks in a typical week**
  - Daily Drinking Questionnaire (DDQ)†
  - Zero-inflated count variable.

- **Alcohol Problems**
  - Six questionnaires used to derive latent trait scores.
    - E.g., Rutgers Alcohol Problem Index (RAPI), Alcohol Use Disorders Identification Test (AUDIT)
  - Relatively normally-distributed outcome

† Collins et al., 1985

Frequencies of Drinks per Week by Study



The Analytic Approach Used…

- Bayesian Multilevel Modeling (MLM)†
  - Markov-chain Monte Carlo estimation
    - MCMCglmm package in R‡,*
  - Permitted distribution-appropriate analysis
    - Hurdle Poisson model for zero-inflated drinking outcome
      - Logistic regression
        - No drinking vs. any drinking
      - Truncated Poisson regression
        - Number of drinks when drinking
    - Gaussian Model for alcohol problems outcome
      - Relatively normally-distributed

† Gelman & Hill, 2006; ‡ Hadfield, 2010; * R Core Team, 2013

Why Bayesian and not maximum likelihood estimation?

- MCMC sampling yields a complete distribution of the regression coefficients and random effects, rather than a single point estimate for each parameter in an ML (frequentist) model.
  - Why this is important:

    Random effects for each treatment group can be estimated with uncertainty (i.e., confidence intervals).

The first model attempted: A 3-level model (3: Study → 2: Participant → 1: Observation)

$$\begin{aligned}\text{OUTCOME}_{t>0,ig} = \\ b_0 + b_1\text{OUTCOME}_{t=0,ig} + b_2\text{COVARIATE}_{ig} + b_3\text{MI\_PFP}_g \\ + b_4\text{PFP}_g + b_5\text{GMI}_g + u_{0g} + u_{1g}\text{MI\_PFP}_g + u_{2g}\text{PFP}_g \\ + u_{3g}\text{GMI}_g + r_{0ig} + e_{tig}\end{aligned}$$

- Study is the highest level of the model.
- Study-specific treatment effects (random slopes) are included for each distinct intervention type.
- This model has intuitive appeal.

Illustrating with Project INTEGRATE

Studies (17)

Treatment Types (3)

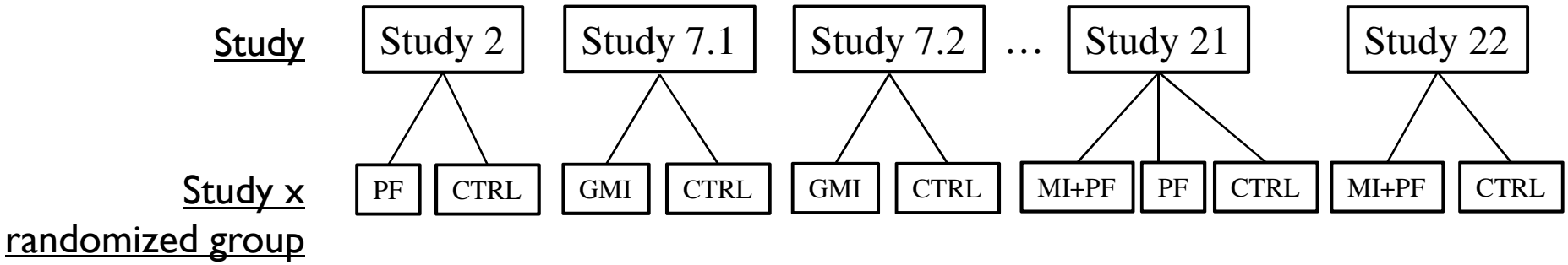
	2	7.1	7.2	8a	8b	8c	9	10	11	12	13/14	15	16	18	20	21	22
MI+PF	×	×	×	×	×	×	✓	✓	×	✓	✓	×	×	×	✓	✓	✓
PF	✓	×	×	✓	✓	✓	✓	×	✓	×	✓	×	×	✓	×	✓	×
GMI	×	✓	✓	×	×	×	✓	×	×	×	×	✓	✓	×	×	×	×

- Problem: Not all treatments evaluated in each study, so the resulting model is rank deficient.
  - 51 possible treatment by study combinations
    - 30 combinations (59%) don't exist.
- Model does not converge using diffuse default priors.

The model with study at the highest level doesn't work, what are our options?

- Keep the model as-is, but use a more informative prior for the random effects.
  - Is it worth that much effort to get the model to work?
  - Informative priors have their critiques and drawbacks.
- Pool active intervention conditions within a study or remove one or more conditions.
  - Reduces each study to a 2-arm RCT design.
  - Potential loss of information
- **Exclude the non-existent study by treatment combinations that are making the model rank deficient.**

Defining study × randomized group at the highest level



- The highest level of the model is study by randomized group rather than study.
  - Preserves the randomization within studies in the model.
- There is no fixed effect for treatment.
  - Intervention effect sizes are calculated from the posterior distribution of the randomization group random effects.

The Basic Model: Similar to an ANCOVA

Post-baseline values of the outcome

Unique randomization group random effect

Residual error

$$\text{OUTCOME}_{t>0,ig} = b_0 + b_1\text{OUTCOME}_{t=0,ig} + b_2\text{COVARIATE}_{ig} + u_{0g} + r_{0ig} + e_{tig}$$

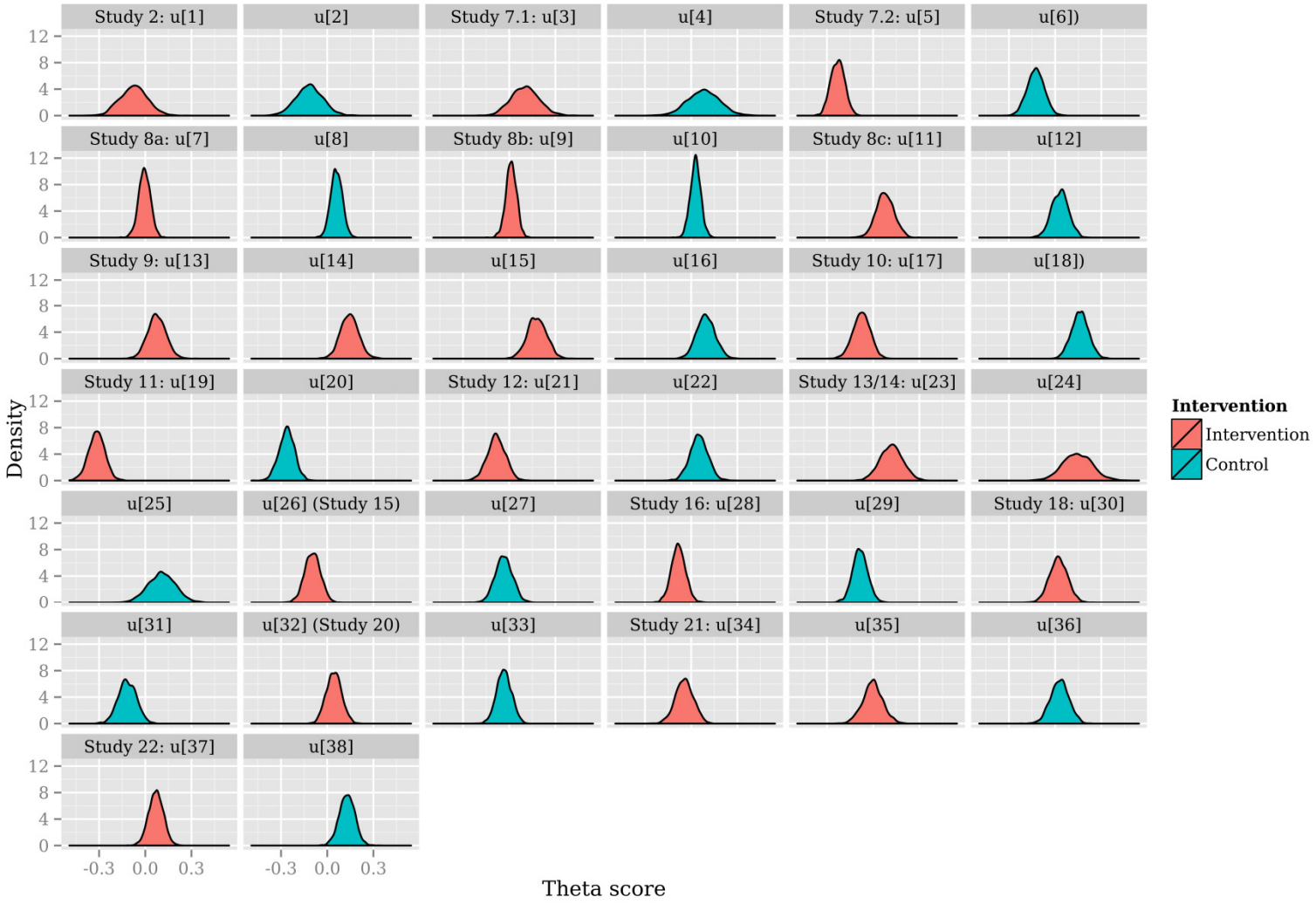
Baseline value of the outcome

Additional covariate(s)

Participant random effect

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

Unique randomization group random effects includes intervention and control groups



Calculating the intervention effect

- The key estimates of interest are the samples from the posterior distributions of the random effects for randomization group.
  - Each random effect has its' own distribution of samples.

	Fixed effects		Randomization group effects					
			Study 2		…	Study 21		
(Sample)	b_0	b_1	u_1	u_2	…	u_{34}	u_{35}	u_{36}
1	-0.037	0.670	-0.036	-0.037		-0.070	-0.137	-0.088
2	-0.008	0.675	-0.167	-0.191		-0.009	-0.047	-0.055
3	-0.072	0.680	-0.001	0.100		-0.050	-0.020	0.012
⋮	⋮	⋮	⋮	⋮		⋮	⋮	⋮
2000	-0.039	0.660	-0.145	-0.023		-0.019	-0.032	0.062

Intervention (PF) | Control | Intervention (MI+PF) | Intervention (PF) | Control

Calculating the intervention effect (cont.)

- Example: The intervention effect in Study 2.

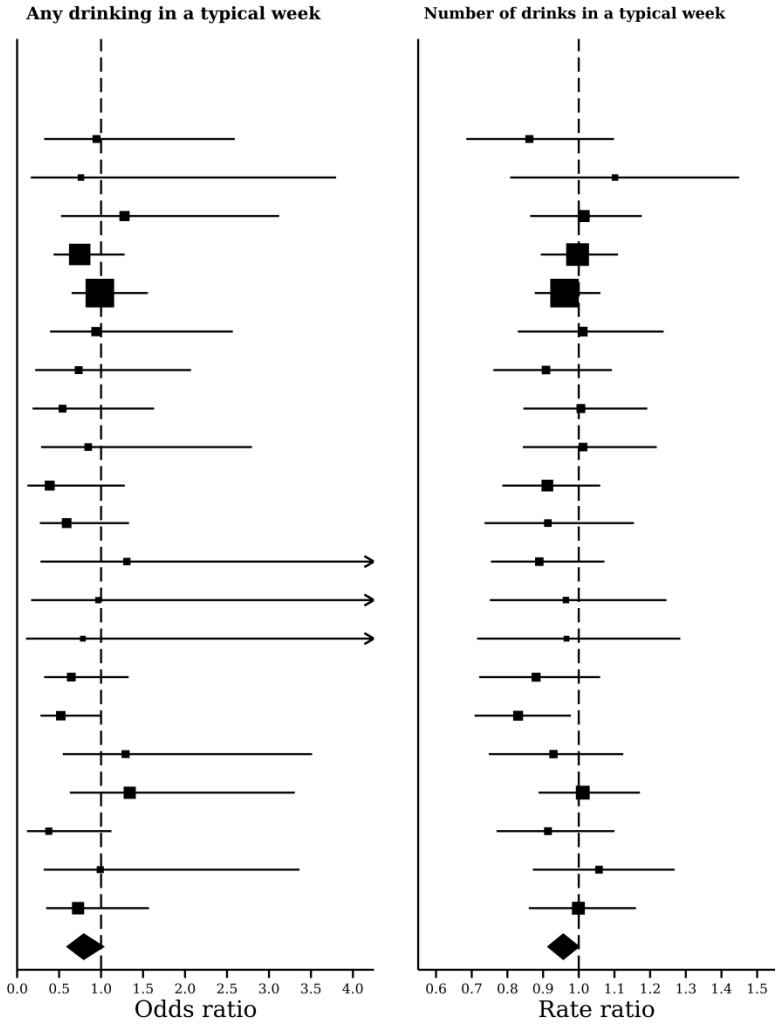
- Three steps to calculating the effect size for a treatment group
  1. Identify the posterior draws from the random effect for an intervention group and its' corresponding control group.
  2. Take the difference ($u_{\text{intervention}} - u_{\text{control}}$).
  3. Calculate the mean and 95% confidence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

- Repeat for all other intervention groups.

	Study 2		
	Intervention	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

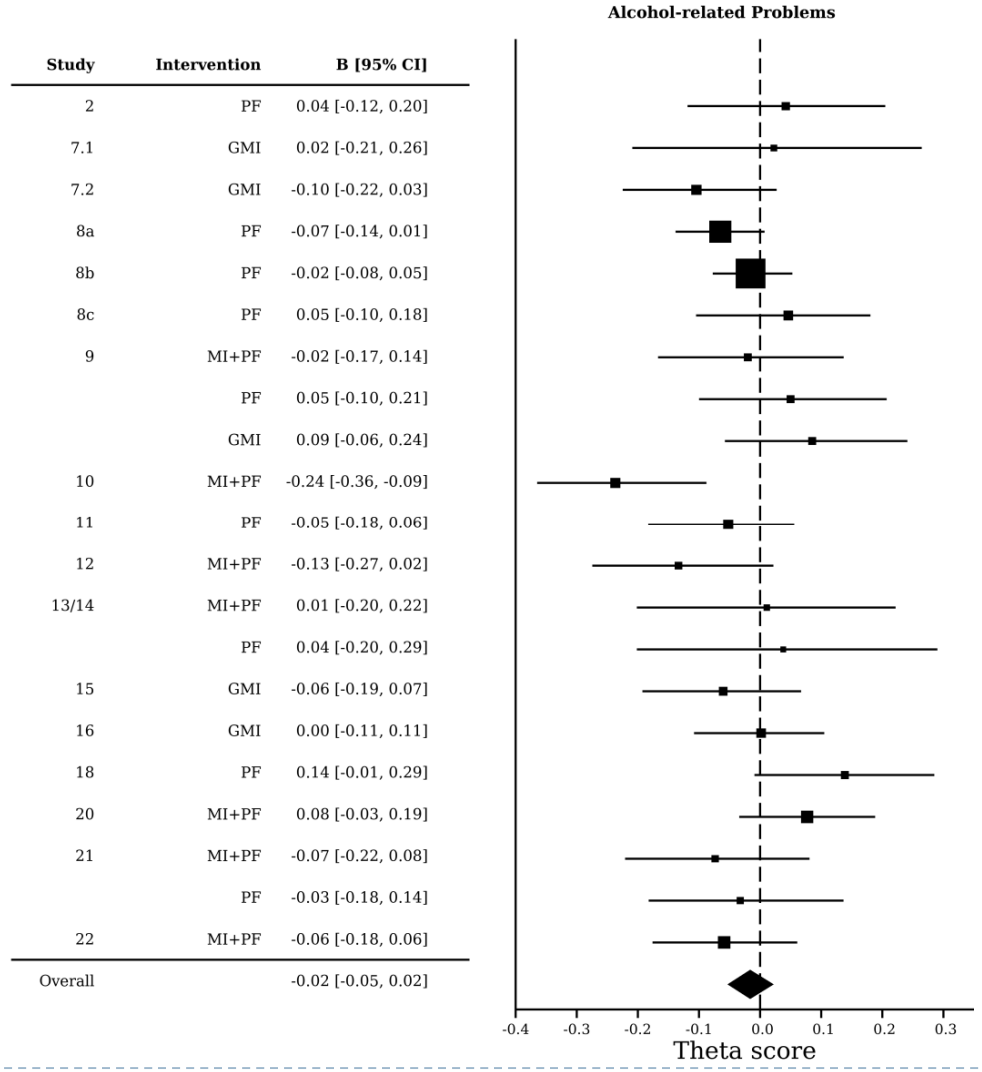
Forest Plot for Drinks per Week (Hurdle)

Study	Intervention	Any drinking OR [95% CI]	No. of drinks RR [95% CI]
2	PF	0.95 [0.32, 2.59]	0.86 [0.68, 1.10]
7.1	GMI	0.76 [0.16, 3.80]	1.10 [0.81, 1.45]
7.2	GMI	1.28 [0.52, 3.12]	1.01 [0.86, 1.18]
8a	PF	0.74 [0.43, 1.28]	1.00 [0.89, 1.11]
8b	PF	0.99 [0.65, 1.56]	0.96 [0.88, 1.06]
8c	PF	0.94 [0.39, 2.57]	1.01 [0.83, 1.24]
9	MI+PF	0.73 [0.22, 2.07]	0.91 [0.76, 1.09]
	PF	0.54 [0.18, 1.63]	1.01 [0.84, 1.19]
	GMI	0.85 [0.29, 2.80]	1.01 [0.84, 1.22]
10	MI+PF	0.39 [0.12, 1.28]	0.91 [0.79, 1.06]
11	PF	0.59 [0.27, 1.33]	0.91 [0.74, 1.15]
12	MI+PF	1.31 [0.28, 6.51]	0.89 [0.75, 1.07]
13/14	MI+PF	0.97 [0.17, 5.54]	0.96 [0.75, 1.25]
	PF	0.78 [0.11, 5.47]	0.97 [0.72, 1.28]
15	GMI	0.65 [0.32, 1.33]	0.88 [0.72, 1.06]
16	GMI	0.52 [0.28, 0.99]	0.83 [0.71, 0.98]
18	PF	1.29 [0.54, 3.51]	0.93 [0.75, 1.12]
20	MI+PF	1.34 [0.63, 3.31]	1.01 [0.89, 1.17]
21	MI+PF	0.38 [0.12, 1.12]	0.91 [0.77, 1.10]
	PF	0.99 [0.32, 3.36]	1.06 [0.87, 1.27]
22	MI+PF	0.73 [0.35, 1.57]	1.00 [0.86, 1.16]
Overall		0.79 [0.58, 1.04]	0.96 [0.91, 1.00]



- MI = Individual Motivational Interview, PF = Standalone Personalized Feedback, MI + PF = MI with Personalized Feedback, GMI = Group Motivational Interview

Forest Plot for Alcohol Problems (Gaussian)



- MI = Individual Motivational Interview, PF = Standalone Personalized Feedback, MI + PF = MI with Personalized Feedback, GMI = Group Motivational Interview

Discussion

- Wide variation of intervention effects on alcohol outcomes is generally consistent with results from meta-analyses based on summary statistics.
  - When alcohol outcomes are modeled in a distribution-appropriate analysis, intervention effects in most studies are non-significant.
  - Across studies, there are small, statistically non-significant reductions in alcohol consumption and negative consequences.

- Bayesian MLM using study by randomization group as the highest level of the model was a practical approach to combining studies with varying numbers of treatment arms.
  - Avoids the need to collapse intervention conditions or discard data.

Discussion (cont.)

- Allowed the calculation of effect sizes for:
  - Individual intervention groups
  - Across all interventions
  - For specific intervention types (not shown)

- Weighting of the intervention estimates was handled within the multilevel model.
  - The IPD is weighted within the likelihood distribution.
  - The precision of the estimates is proportional to the amount of contributing data.

- The detailed approach is generalizable to outcomes beyond alcohol use.

Analysis of non-normal outcomes not trivial…

- Bayesian MCMC estimation required a good deal of computing time, especially for the non-Gaussian model.
  - Gaussian model of alcohol problems: **< 1 hour**
  - Hurdle model of drinks per week: **36 hours**

Next steps…

- Conduct a simulation study comparing results of the Bayesian MLM approach used in the present study with summary-statistic based meta-analysis.
  - How biased are estimates using summary statistic based methods that assume normal distribution?

Questions?

- For post-conference questions, contact:
  - David Huh (dhuh@uw.edu).

References

- 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. doi:10.1037/a0029508
- Carey, K. B., Scott-Sheldon, L. A. J., Carey, M. P., & DeMartini, K. S. (2007). Individual-level interventions to reduce college student drinking: A meta-analytic review. *Addictive Behaviors, 32,* 2469–2494. doi:10.1016/j.addbeh.2007.05.004
- 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.
- Cooper, H., & Patall, E. A. (2009). The relative benefits of meta-analysis conducted with individual participant data versus aggregated data. *Psychological Methods, 14,* 165–176. doi:10.1037/a0015565
- Gelman, A., & Hill, J. (2006). *Data analysis using regression and multilevel/hierarchical models.* New York: Cambridge University.
- 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: Russell Sage Foundation.
- Hadfield, J. D. (2010). MCMC methods for multi-response generalized linear mixed models: The MCMCglmm R package. *Journal of Statistical Software, 33,* 1–22.
- 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.
- Huh, D., Kaysen, D., & Atkins, D. C. (2014). *Modeling cyclical patterns in daily college drinking data with many zeroes.* Manuscript submitted for publication.
- 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.* Manuscript submitted for publication.
- 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.* Manuscript under review.
- National Institute on Alcohol Abuse and Alcoholism (2002) *A call to action: Changing the culture of drinking at U.S. colleges* (No. 02-5010). Department of Health and Human Services, National Institutes of Health, Rockville, MD: USA.
- R Core Team (2014) *R: A language and environment for statistical computing.* R Foundation for Statistical Computing, Vienna, Austria.