Methods for Synthesizing Findings across Randomized Trials: Opportunities and Challenges for LGBT Preventive Intervention Research

C Hendricks Brown
University of Miami School of Medicine
Northwestern University Feinberg School of Medicine

Objectives

- To discuss the feasibility of synthesizing data sets across prevention intervention studies with outcomes in adolescence and young adulthood to examine drug use and abuse, HRSB related to HIV/AIDS and other important mental, emotional and behavioral (MEB) outcomes for LGBT youth,
- To determine methodologic steps necessary to accomplish synthesis of data sets and analysis of data with considerations related to small or selected samples, harmonization of measures
- To discuss and problem solve potential barriers including sharing of research data
- Concept of “Scientific Equity” to Address Health Disparities

NIDA Supplement to Compare US-EU School-Based Drug Prevention
C Hendricks Brown/Zili Sloboda

Collaborative Data Synthesis Methodology :
NIMH R01MH040859-25

Examine shared and unique mediator and moderator effects across multiple randomized trials

George Howe, George Washington University
Tatiana Perrino, University of Miami
David MacKinnon, Arizona State University

Hilda Pantin, University of Miami
Getachew Dagne, University of South Florida
Juned Siddique, Northwestern University
Ahnalee Brincks, University of Miami
Gracelyn Cruden, University of Miami

Irwin Sandler, ASU
Bill Beardslee, Harvard
Guillermo Bernal, UPR
Velma Murry, Vanderbilt
David Brent, U Pitt

MILLER SCHOOL OF MEDICINE UNIVERSITY OF MIAMI

NORTHWESTERN UNIVERSITY

THE GEORGE WASHINGTON UNIVERSITY WASHINGTON DC

USF UNIVERSITY OF SOUTH FLORIDA

How do we build a knowledge base for Preventing Adverse Outcomes for LGBT Youth Based on Randomized Trials?

Findings from a Single, <u>Generic</u> Randomized Trial

Powered for Main Effect of Intervention

Underpowered for Most Subgroup, Moderator/Mediator Analyses

National Data

Same Sex Sexual Behavior [1]

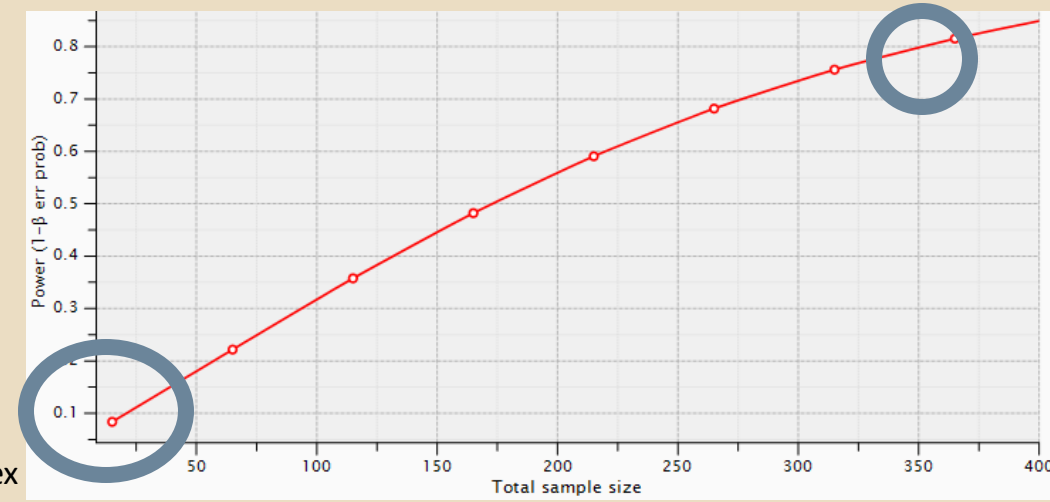
Males 15-19: 2.5%

Females 15-19: 11.0%

Sexual Identity: Homosexual/bisexual [1]

Males 18-19: 2.7%

Females 18-19: 7.7%



Local Data

4-10% of Familias Unidas interventions report same sex sexual behavior

Conclusion: Single Generic Randomized Trials are Completely Underpowered to Examine Impact on an LGBT Subset.

Source: [1] Chandra et al., National Health Statistics Reports 2011

Source: [2] Personal communication, Prado & Pantin

How do we build a knowledge base for Preventing Adverse Outcomes for LGBT Youth Based on Randomized Trials?

Single Site Randomized Preventive Trial for LGBT Youth
- Early self identification, stigmatizing
- Conclusion:

Science Builds on Replication: Shared vs Unique Findings

Multicenter Randomized Trial of all Youth, including LGBT
- Strategic, Same Protocol, (NIDA CTN, PODS, TADS)
- Variation in Impact as Function of Social Context

Replicate Trial
- Expensive, not Innovative

Literature Review / Meta-Analysis of Existing Trials
- Inexpensive
- Limited to What's Published

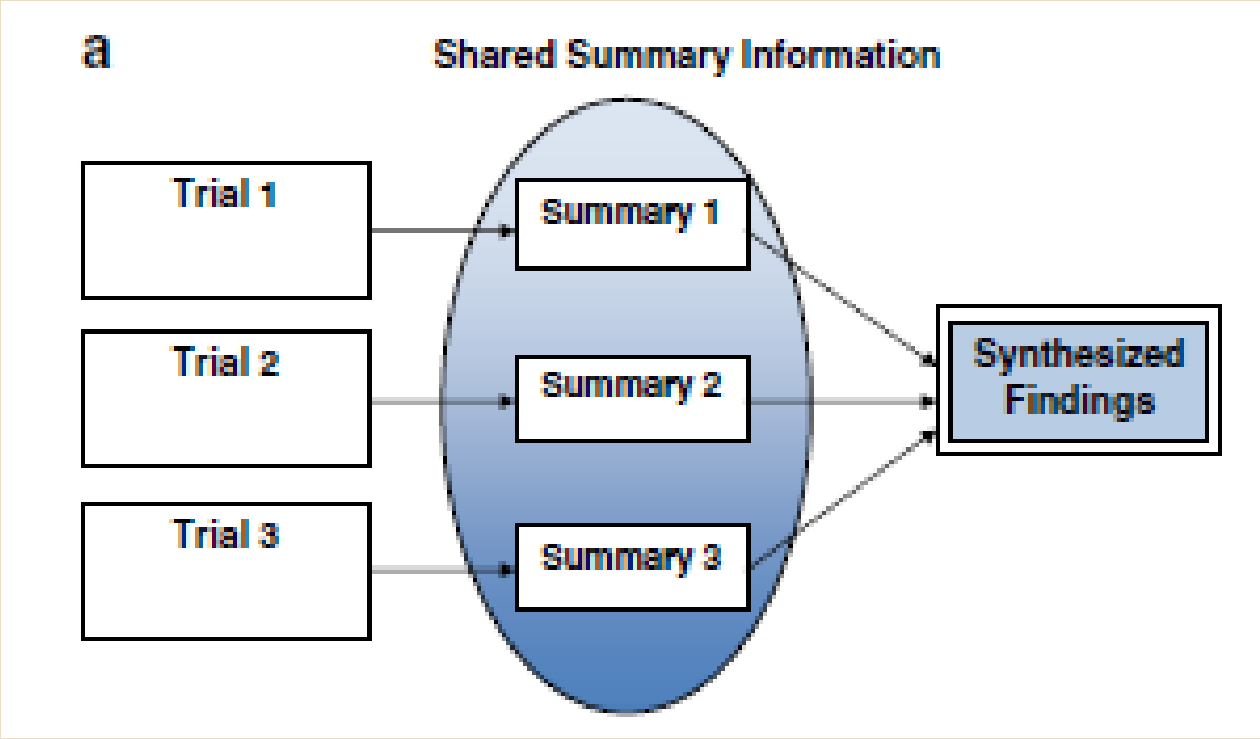
Synthesis of Individual Level Data Analysis Across Multiple Trials
- Relatively Inexpensive
- Full multilevel, multisite analysis

Three Alternatives for Combining Findings Across Trials

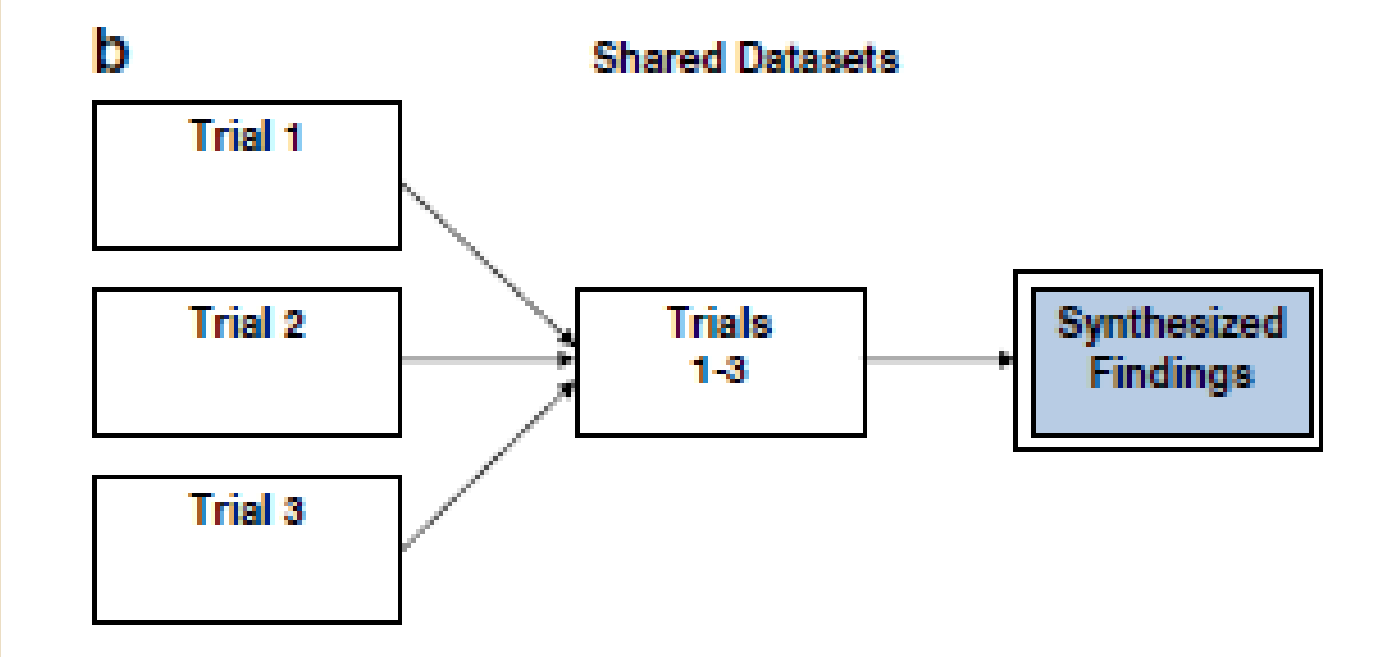
- Meta-Analysis
- Integrative Data Analysis
- Parallel Analysis

Brown CH, Sloboda Z, Faggiano F, Teasdale B, Keller F, Burkhart G et al. (2013). Methods for Synthesizing Findings on Moderation Effects Across Multiple Randomized Trials. *Prevention Science* 8 Prev S 14: 144-156, DOI 10.1007/s11121-011-0207-8

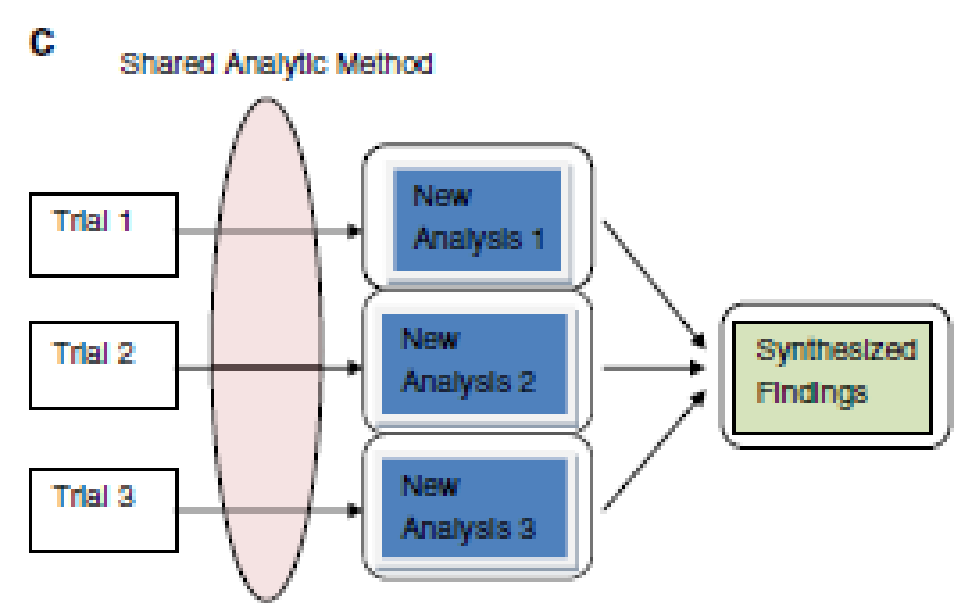
Meta-Analysis



Combining Data in a Single Analysis
Integrative Data Analysis,
Patient Level Meta-Analysis



Parallel Data Analysis



When Is Synthesis of Multiple Trials Useful for a Subgroup Analysis (LGBT)?

- Has to do better than a subgroup analysis in a single trial

Effect on Statistical Power

Positive: Added sample size

Negative: Heterogeneity across trials

- Population (and Context)
- Intervention
- Design

Qualitative Result

A synthesis will have increased precision over that of a single trial when

- the between variance is small, or
- the number of trials relative to number of subjects is large.

Quantitative Result

- ICC < 4 (#Trials -1) / Avg Trial Sample Size

  4 Trials: Virtually Guaranteed if N < 240 s's

Conclusion: Very likely to improve precision by combining data from similar trials.

Brown et al., (2013).

But will synthesis succeed in obtaining sufficient statistical power?

Illustration from prevention trials for youth

5 Familias Unidas Trials

Trial Name	Same Sex	Percent	Total N
Effectiveness	30	4.69%	640
CDC	6	4.08%	147
Hepi-1	8	3.86%	207
Hepi-2	15	9.87%	152
DJJ	22	9.87%	223
N	**81**	**5.90%**	**1369**

Power for Detecting Impact on Total N and LGBT

Sample	Low (.25)	Med (.5)	High (.75)
All (N=1369)	0.75	0.99	0.99
Same Sex(N=81)	0.15	0.4	0.7

But will synthesis succeed in obtaining sufficient statistical power?

Illustration from prevention trials for youth

9 Prevention Trials measuring

Same Sex Sexual Behavior

Power for Detecting Impact on Total N and LGBT

Sample	Low (.25)	Med (.5)	High (.75)
All (N=4498)	0.88	0.99	0.99
Same Sex (N=271)	0.21	0.65	0.9

Suggested Conclusion

- Enough data are now available to conduct a meaningful synthesis of the effects of existing prevention programs on drug and sex risk behavior among those engaged in same sex sexual behavior.
- Likely would require combining data from heterogeneous interventions

Some Examples of Integrative Data Analysis: Antidepressants (Fluoxetine) and Suicide in Youth

4 Youth Trials N = 708, Measures = 2536

- Depression Remission Rates for Youth 46% Fluoxetine, 16% Placebo
- For Youth and Adults, Suicide Symptoms Decreases over time for both Fluox & Placebo
- For Adults, Fluox decreased Suicide Sx faster than Placebo did, and mediated by Depressive Sx
- For Youth, Fluox did not decrease Suicide Sx faster than Placebo.

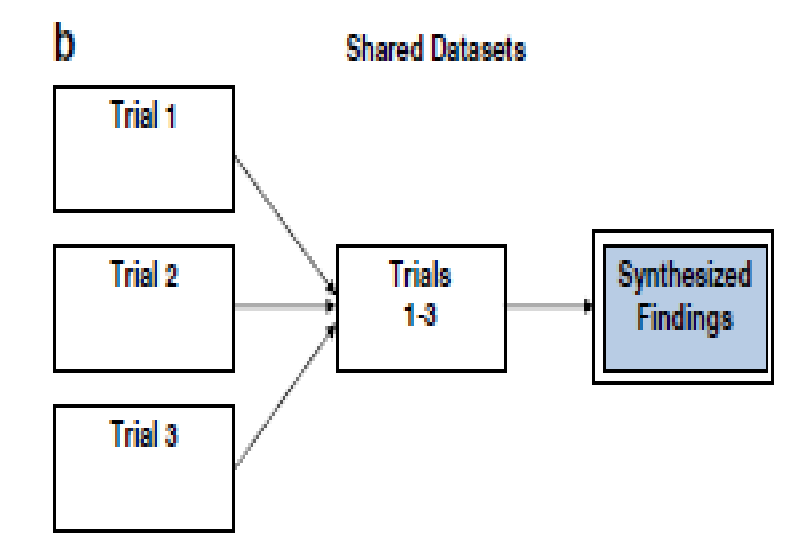
(Gibbons, Brown et al., 2012 a,b JAMA Psychiatry)

What are the technical challenges in synthesizing findings across randomized trials at the individual level?

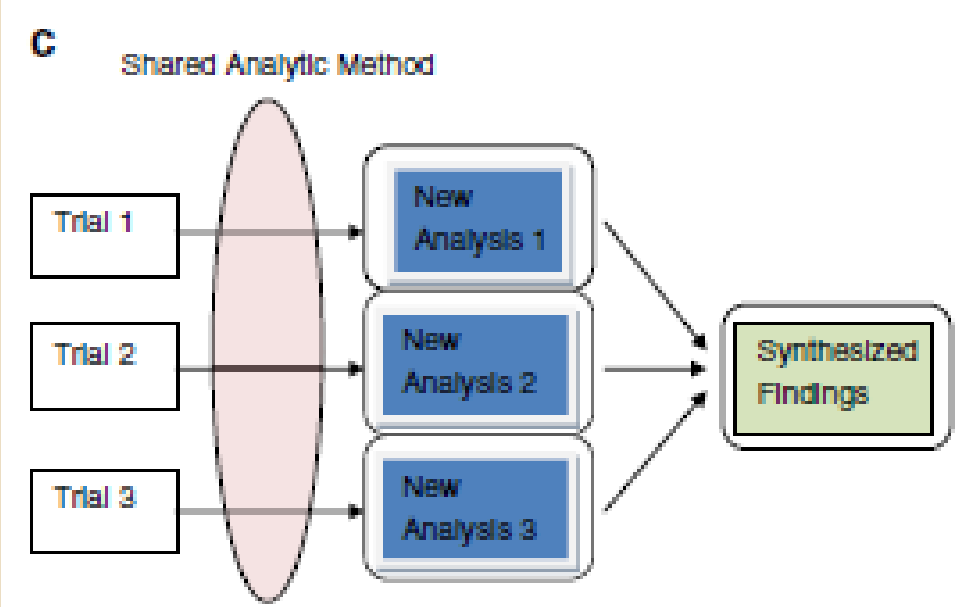
1. Obtaining/Sharing the data – Tatiana Perrino
2. Handling differences in the studies
   - Population
   - Intervention
   - Design
     - Harmonizing different measures
     - -- George Howe
3. Statistical Analysis
   - Mediation – Dave MacKinnon

Obtaining/Sharing the Data

Integrative Data Analysis



Parallel Data Analysis



Parallel Data Analysis

- Use when it is not possible to obtain all datasets,
- For “Holdout” datasets, the trialists are still willing to conduct their own analyses on their data
- Specify exactly how the statistical analysis needs to be done on “Holdout” datasets
- Obtain summary results from these “Holdout” datasets
- Synthesize these summaries together in a combined analysis, accounting for heterogeneity

How can we best handle differences in populations, interventions, and trial designs, as well as limitations of dealing with small sample sizes?

Trial Designs: The Simple Problem

Trials have different observation times since start of trial

Trial 1: 3 months, 6 months, 12 months

Trial 2: 3 months, 9 months, 18 months

Comparable Analyses using Linear Growth Models

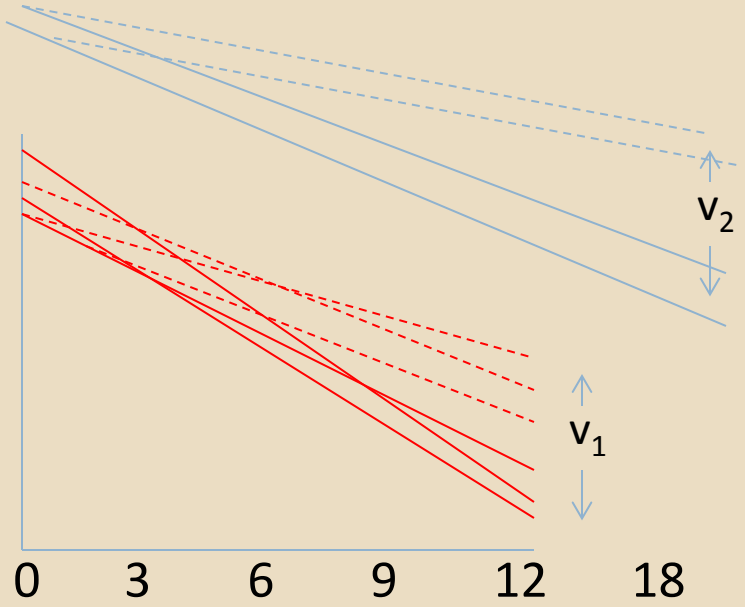
Trial 1: 0, 3 months, 6 months, 12 months

Trial 2: 0, 3 months, 9 months, 18 months

$$Y_{ijt} = a_{ij} + b_{ij}\, t + \varepsilon_{ijt}$$

$$b_{ij} = u_j + v_j\, \text{Treatment}_{ij} + \delta_{ij}$$

$$v_j = \beta + \xi_j$$

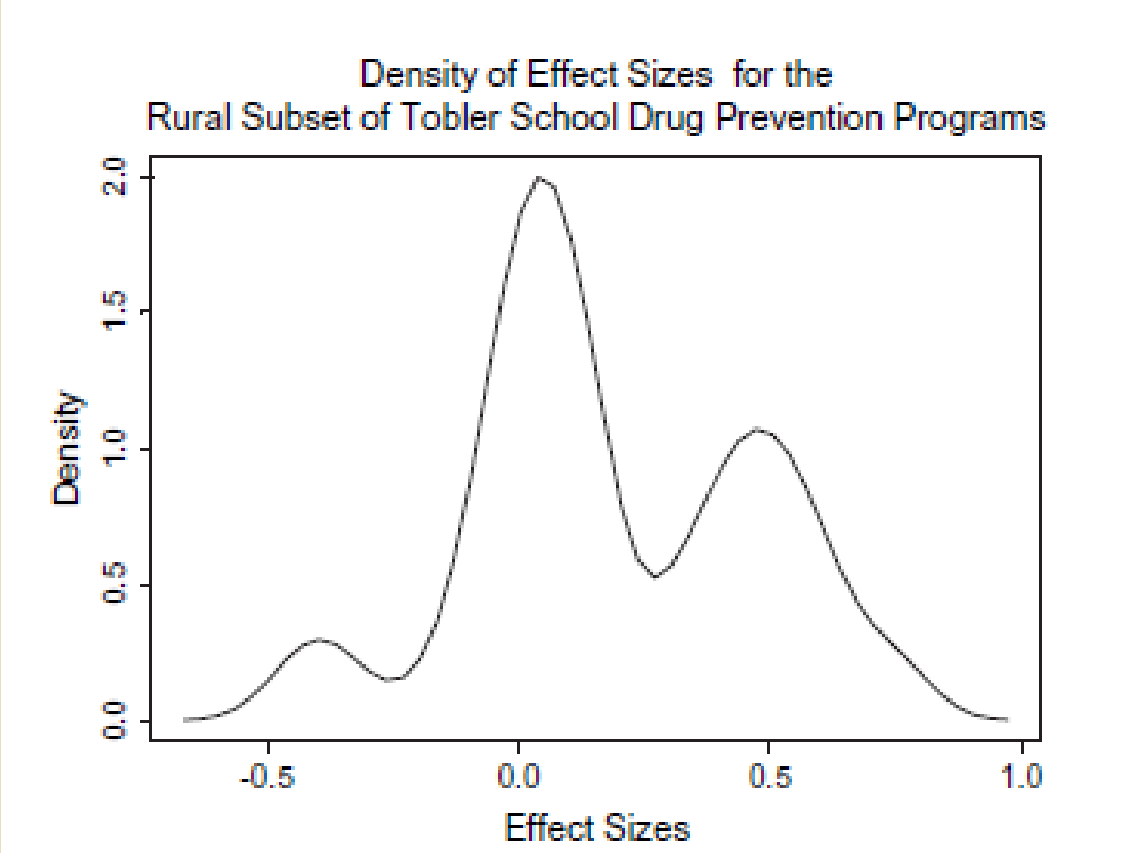


Brown et al., 2013 Prev Sci

Differences in Interventions and Populations (including Context)

- Remove Unusual or Outlying Studies
- Use trial level measures as covariates, moderators : school climate
- Model heterogeneity

Multilevel Mixture Meta-Analysis 4-10 Outcomes Per Trial



Brown CH, Wang W, Sandler I. Examining how context changes intervention impact: The use of effect sizes in multilevel mixture meta-analysis. *Child Develop Perspectives, 2,* 198-205, 2008.

"Scientific Equity"

--- Equality in the amount of scientific knowledge that is **produced** to understand both the causes and solutions to health inequities (Brown et al. In Press, 2013).

-- **Application** of knowledge to narrowing the health and health service gap between culturally and linguistically diverse disparity populations in the US.

While there is a substantial amount data to indicate that health inequities exist and that they must be addressed, we need additional research data to guide an effective strategy to achieve health equity.

Brown, C.H., et al. (In Press, 2013). JAIDS Computational Future of HIV Prevention in Minority Populations

Summary

- Learning what works for LGBT Populations Requires Scientific Equity – Strategic plan for collecting or obtaining sufficient scientific information that can inform policy and practice
- Synthesis of findings from multiple trials based on individual level data
  - Is feasible both technically and logistically
  - Is cost effective and potentially powerful enough to answer key intervention questions for LGBTQ
    - Requires a strategy to determine which studies should be included and what data management and analyses need to be done
    - Supplement longitudinal followups to collect data
    - Support data sharing, data management, and analysis
- Key issues involve determining what mediating and moderating factors affect outcomes?

NIMH Synthesis Study Team Members & Partners

Study Investigators
Hendricks Brown (PI)
George Howe (Co-I)
Hilda Pantin
Tatiana Perrino
Getachew Dagne
Juned Siddique

University of Miami Study Team
Ahnalee Brincks
Gracelyn Cruden
Ophelia Hernandez

Consultants
William Beardslee
David MacKinnon
Katherine Masyn
Bengt Muthen
Irwin Sandler

Individual Study Investigators
William Beardslee
Guillermo Bernal
Greg Clarke
Guy Diamond
Tom Dishion
Graham Emslie
Jane Gillham
Tracy Gladstone
Nancy Gonzales
Laura Mufson
Velma Murry
Hilda Pantin
Guillermo Prado
Cleve Redmond
Irwin Sandler
Richard Spoth
Beth Stormshak
Jose Szapocznik
Jenn-Yun Tein
Ben Van Voorhees
Sharlene Wolchik
Jamie Young

Investigators- Ongoing Discussions
Gene Brody
Bruce Compas
Judy Garber
There are other Investigators pending contact

Scientific Advisory Board
David Brent
Guillermo Bernal
Graham Emslie
Velma Murry

Other Partners
Anne Sperling- NIMH
David Shern- Mental Health America
Julie Totten- Families for Depression Awareness
Yanira Garcia-Barcena- Librarian

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