Methods: Mind the Gap

Webinar Series

Modern Meta-Analytic Methods for Prevention Science

Presented by:

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Modern Meta-Analytic Methods for Prevention Science

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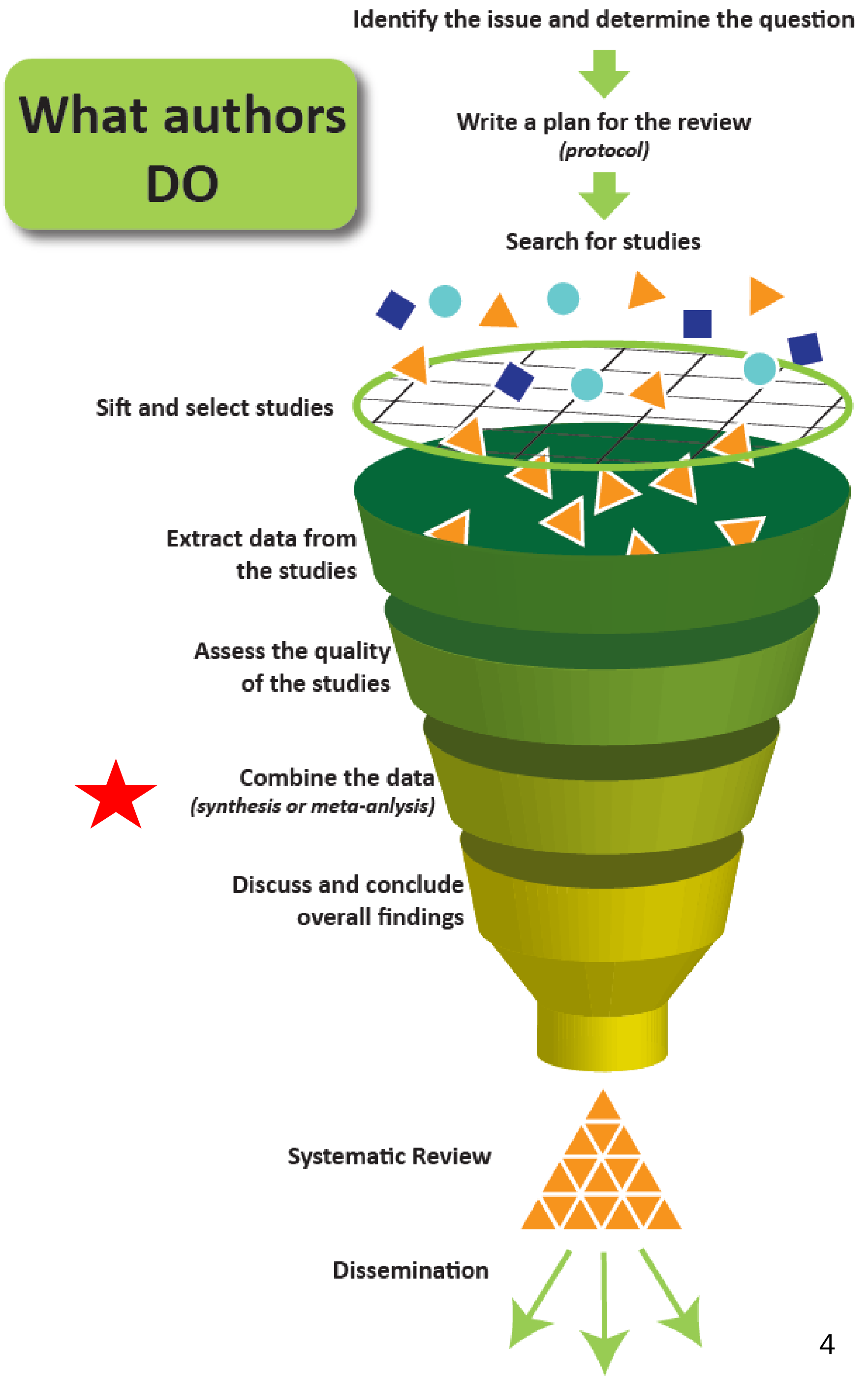
Outline

What is Meta-Analysis?

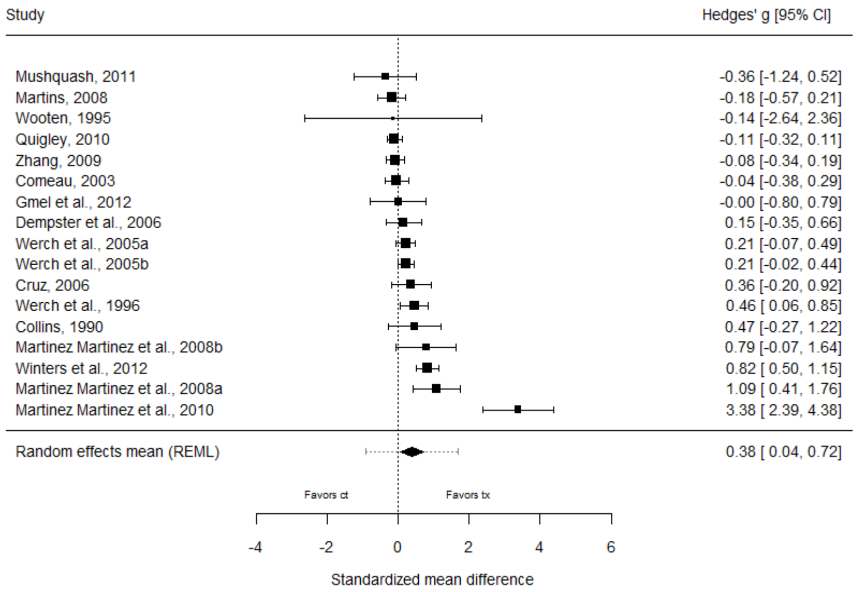
- Meta-analysis refers to the statistical synthesis of quantitative findings from two or more empirical research studies
- The research studies included in a meta-analysis are often identified as part of a systematic review
- The outcomes/findings from research studies are encoded as effect sizes (e.g., mean difference, standardized mean difference, risk ratio, hazard ratio, proportion, correlation coefficient)

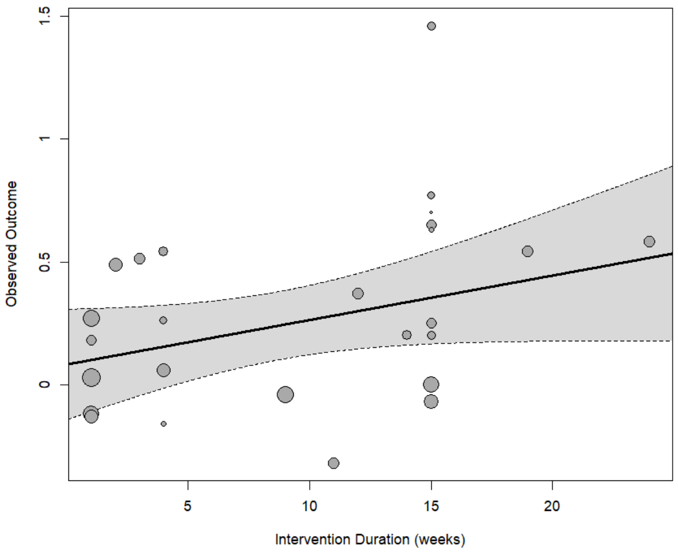


The Value of Meta-Analysis

- Results can provide cumulative summaries of the current, best available research evidence relevant to a specific question
- Permits examination of research questions that may be difficult to address in an individual primary study
  - Replicability of empirical findings
  - Variation in effects across populations, settings, methods, study design features

Univariate Meta-Regression Approach





Weighted least squares estimator

$$\hat{\beta} = (\mathbf{X}'\mathbf{W}\mathbf{X})^{-1}(\mathbf{X}'\mathbf{W}\mathbf{Y})$$

$$\mathrm{V}(\hat{\beta}) = (\mathbf{X}'\mathbf{W}\mathbf{X})^{-1}(\mathbf{X}'\mathbf{W}\boldsymbol{\Sigma}\mathbf{W}\mathbf{X})(\mathbf{X}'\mathbf{W}\mathbf{X})^{-1}$$

$$y_i = \overbrace{\mu + \delta_i}^{\theta_i} + \varepsilon_i$$

$$\delta_i \sim N(0, \tau^2)$$
$$\varepsilon_i \sim N(0, v_i)$$

$$y_i = \mu + \beta x_i + \delta_i + \varepsilon_i$$

$$\delta_i \sim N(0, \tau^2_{res})$$
$$\varepsilon_i \sim N(0, v_i)$$

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Issue editors

Emily E. Tanner-Smith, Sean P. Grant & Evan Mayo-Wilson

12 articles in this issue

Source: https://link.springer.com/journal/11121/volumes-and-issues/23-3

Robust Variance Estimation

Dependent Effect Sizes in Meta-Analysis

- Traditional univariate meta-regression assumes the effect sizes included in the model are statistically independent
- But dependent effect sizes (multivariate and/or nested effects) are common due to, e.g.:
    - Multiple measures of **outcomes** within studies
    - Multiple comparison **conditions** within studies
    - Multiple **time points** within studies
    - Multiple participant **subgroups** within studies
    - Multiple studies nested within **larger contexts**/settings
    - Multiple independent **samples** nested within studies

Handling Dependent Effect Sizes

Numerous approaches for addressing dependent effect sizes (López-López et al., 2018)

Naïve

- Ignore dependencies

Reductionist

- Separate meta-analyses
- Select one independent effect size per study per analysis (randomly, or using decision rules)
- Create a single average (synthetic) effect size per study per analysis

Integrative

- Multivariate meta-analysis
- Multi-level meta-analysis
- Robust variance estimation

Robust Variance Estimation (RVE)

- One of the most flexible methods for synthesizing dependent effect sizes (Hedges et al., 2010; Pustejovsky & Tipton, 2022; Tipton, 2015)
  - Does not require knowledge of the covariance structure between the dependent effects
  - Can be used to handle any/multiple types of dependency
- Extends the WLS estimation approach for meta-regression to include robust standard errors that account for clustered dependence structure
  - The variance-covariance matrix Σ (with unknown off-diagonal elements) is substituted with a matrix of cross-products of within-study residuals derived empirically under a working model of the covariance structure
  - Also adds a set of small sample adjustment matrices

RVE Working Models

- Analyst must choose a working model of the dependence structure to identify the weights that are expected to be approximately inverse variance (Pustejovsky & Tipton, 2022)
  - If working model is correctly specified, resulting weights are exactly inverse variance and the RVE estimator is fully efficient
  - Even if working model is misspecified, RVE estimator yields unbiased coefficient estimates and valid standard errors
- Software packages/macros available in R (`metafor`, `clubSandwich`, `robumeta`), SAS (`mvmeta`), Stata (`robumeta`)

Common working models

- Correlated effects
- Hierarchical effects
- Correlated & hierarchical effects
- Subgroup correlated effects

Cyberbullying Intervention Review (Polanin et al., 2022)

Table 2 Overall meta-analysis results

Outcome domain	Number of studies	Number of effect sizes	Average effect size (SE)	95% CI	Tau-squared (between)	I-squared (between, within)	95% PI	PPI
Cyberbullying perpetration	44	96	−0.18 (.05)	−0.28, −0.09	0.06	79.71, 9.78	−0.67, 0.30	76.08
Cyberbullying victimization	39	75	−0.13 (.04)	−0.21, −0.05	0.02	34.90, 53.77	−0.40, 0.14	72.61
Bullying perpetration	22	67	−0.18 (.05)	−0.28, −0.08	0.03	55.20, 37.44	−0.54, 0.17	77.94
Bullying victimization	24	82	−0.16 (.05)	−0.27, −0.05	0.05	63.21, 28.97	−0.59, 0.26	73.19

SE standard error, *CI* confidence interval, *PI* prediction interval, *PPI* probability of positive impact

Table 3 Confirmatory moderator analyses for cyberbullying perpetration

Variable	Number of studies	Number of effects	Coef. or mean	Standard error	95% CI—Lower	95% CI—Upper	T-statistic	*df*	p-value
Country of origin							0.87	23.28	0.39
Non-USA	30	66	−0.22	0.04	−0.31	−0.13			
USA	14	30	−0.11	0.11	−0.33	0.10			
Focus of program							−0.53	12.57	0.61
No cyber target	9	26	−0.15	0.08	−0.30	0.01			
Cyberbullying targeted	35	70	−0.20	0.06	−0.30	−0.09			
Timepoint							0.10	3.05	0.92
Posttest	42	79	−0.18	0.05	−0.28	−0.09			
Follow-up	8	17	−0.18	0.06	−0.29	−0.07			
Effect size type							2.21	2.94	0.12
Continuous	36	80	−0.20	0.05	−0.29	−0.11			
Dichotomous	9	16	−0.05	0.08	−0.20	0.11			
Percent males	44	96	0.03	0.03	−0.03	0.10	0.96	1.20	0.49
Percent nonwhite	44	96	−0.11	0.12	−0.34	0.12	−0.94	19.66	0.36

df degrees of freedom

Source: "A Systematic Review and Meta-Analysis of Interventions to Decrease Cyberbullying Perpetration and Victimization," by J. R. Polanin et al., 2022, *Prevention Science*, 23, p. 439-454 (https://doi.org/10.1007/s11121-021-01259-y).

Limitations of RVE

- Poor performance with small samples or with moderators with unbalanced distributions
- Imprecise estimation of heterogeneity parameters if working model is misspecified
- Just because the model can handle dependent effects does not mean it is appropriate to include them all in the same model

Network Meta-Analysis

Network Meta-Analysis (NMA)

- Traditional meta-analysis approaches are useful for examining pairwise contrasts (e.g., Program vs. Control; Program A vs. B)
- But often interested in the **comparative effectiveness** of multiple programs (e.g., Programs A vs. B vs. C vs. D)
- NMA simultaneously compares 3+ interventions in a single analysis; useful for assessing comparative effects and **rankings** of programs (Caldwell et al., 2005; Dias et al., 2013)

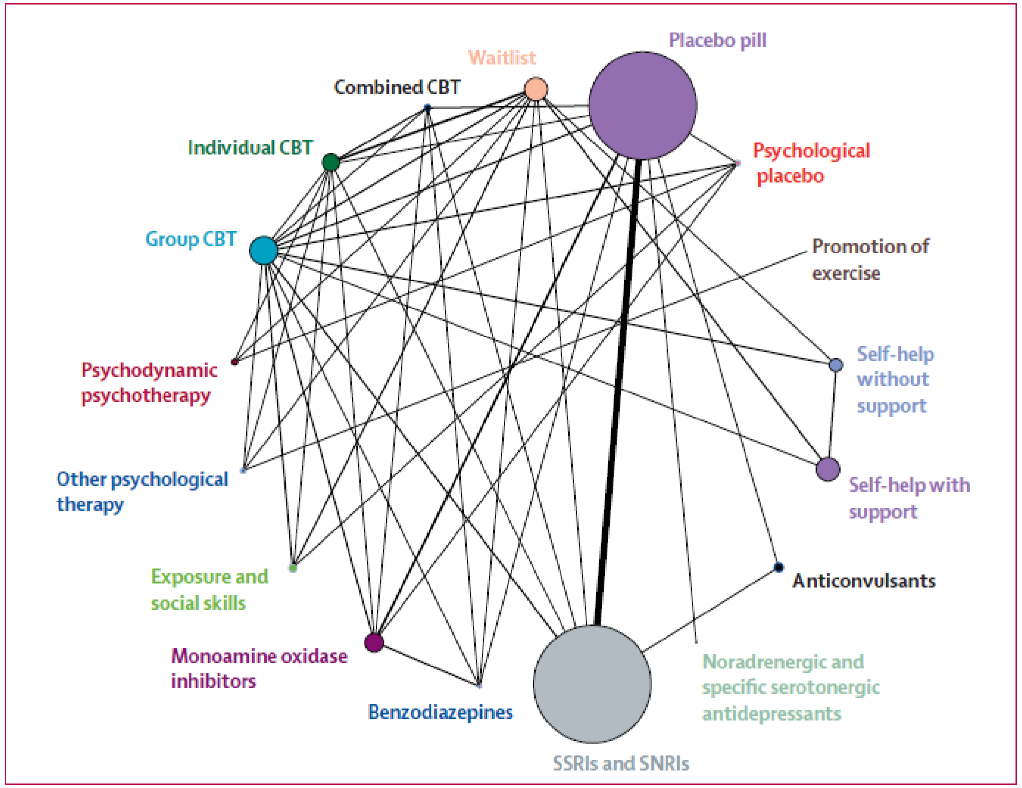
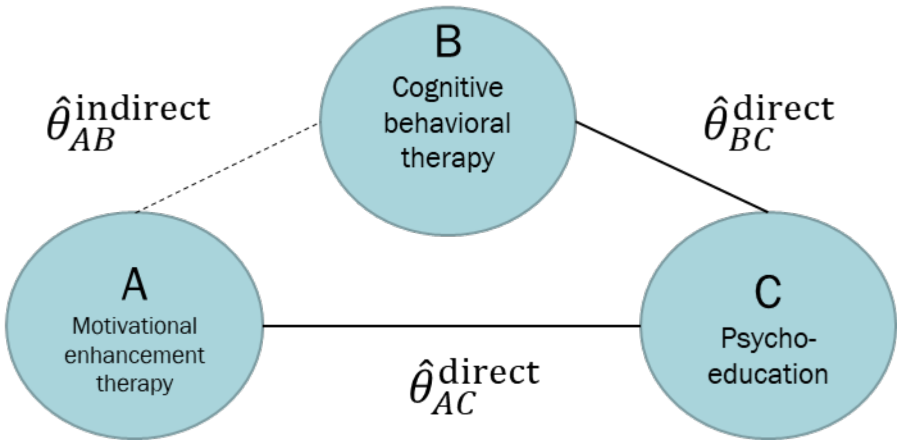


Figure 2: Network diagram representing direct comparisons among classes
The width of lines represents the number of trials in which each direct comparison is made. The size of each circle represents the number of people who received each treatment. CBT=cognitive–behavioural therapy. SNRI=serotonin–norepinephrine reuptake inhibitor. SSRI=selective serotonin-reuptake inhibitor.

Source: "Psychological and Pharmacological Interventions for Social Anxiety Disorder in Adults: A Systematic Review and Network Meta-Analysis," by E. Mayo-Wilson et al., 2014, *The Lancet*, 1(5), p. 368-376 (https://doi.org/10.1016/S2215-0366(14)70329-3).

Direct, Indirect, and Combined Evidence

- NMA can be used to combine direct (observed) and indirect (unobserved) evidence to estimate mixed/combined (direct + indirect) evidence
- Validity of NMA requires transitivity for every indirect comparison, and coherence for every loop of evidence within the network



$$\hat{\theta}_{AB}^{\text{indirect}} = \hat{\theta}_{AC}^{\text{direct}} - \hat{\theta}_{BC}^{\text{direct}}$$

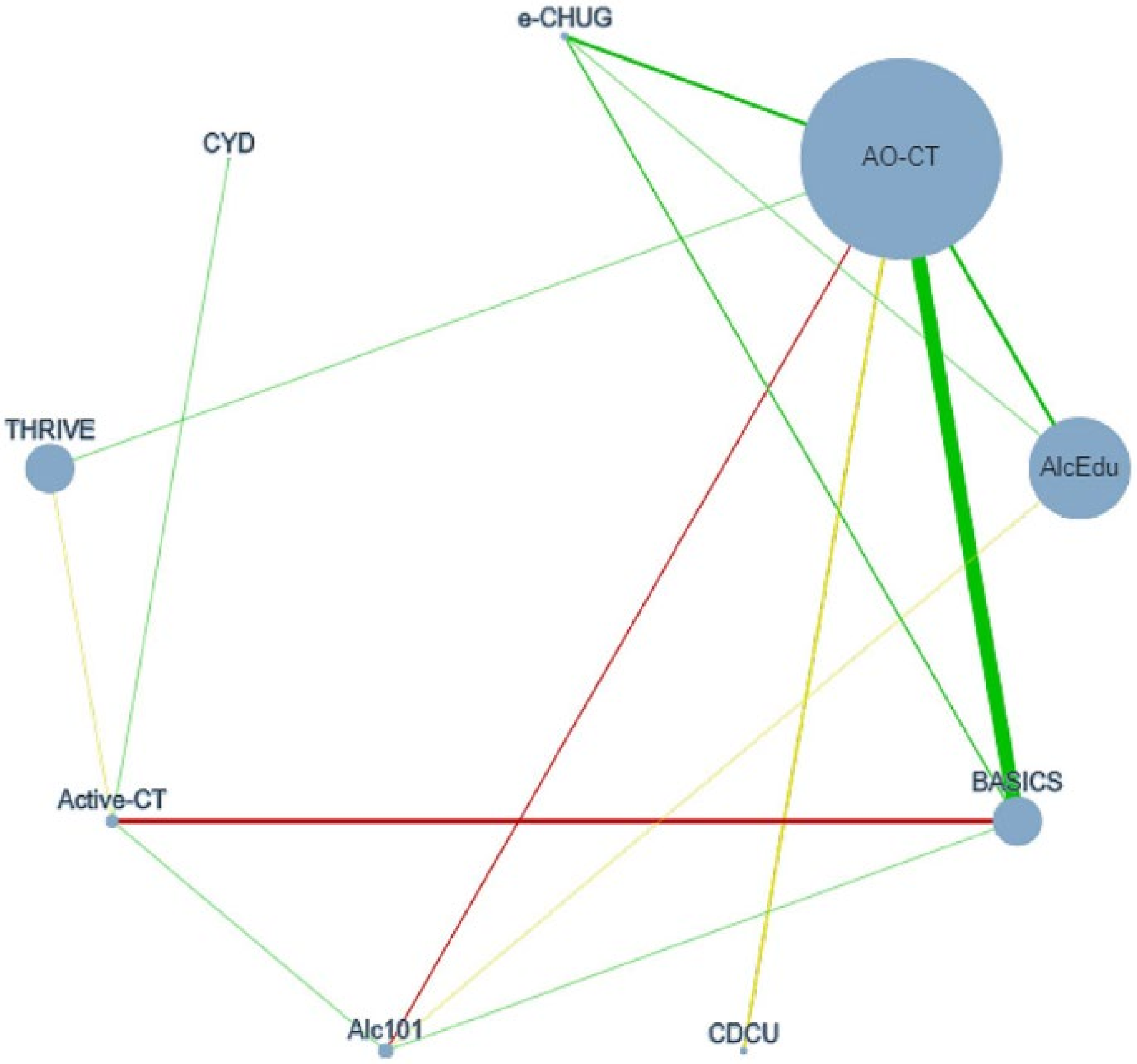
$$\hat{\theta}_{AB}^{\text{mixed}} = \frac{\dfrac{\hat{\theta}_{AB}^{\text{direct}}}{Var(\hat{\theta}_{AB}^{\text{direct}})} + \dfrac{\hat{\theta}_{AB}^{\text{indirect}}}{Var(\hat{\theta}_{AB}^{\text{indirect}})}}{\dfrac{1}{Var(\hat{\theta}_{AB}^{\text{direct}})} + \dfrac{1}{Var(\hat{\theta}_{AB}^{\text{indirect}})}}$$

NMA Model Estimation

- Straightforward estimation if all included studies are 2-arm trials, but calculating indirect estimates becomes more complex when synthesizing evidence from multi-arm trials
- Several models have been proposed to conduct Bayesian or frequentist NMA (Efthimiou et al., 2016)
  - Bayesian hierarchical model
  - Multivariate meta-analysis model
  - Frequentist graph theoretical model
- Software packages/macros available in R (`BUGSnet, gemtc, pcnetmeta, netmeta, viscomp`), SAS (`BGLIMM, PROC GLIMMIX`), Stata (`mvmeta, network, network graphs`).
  - See https://methods.cochrane.org/cmi/network-meta-analysis-toolkit for additional software and materials
  - See https://crsu.shinyapps.io/MetaInsight/ for a Shiny app for visualizations

Brief Alcohol Intervention Example (Seitidis et al., 2022)

Fig. 1 Network plot showing the network's geometry. The plot has been constructed via CINeMA web application. The node sizes indicate the numbers of participants randomized to each intervention while the thickness of the edges indicates the number of studies comparing the different intervention/comparator groups. The edge color indicates the majority of studies' risk of bias determination in the corresponding treatment comparison. Green, yellow, and red indicate low, unclear, and high risk of bias, respectively



Source: "Network Meta-Analysis Techniques for Synthesizing Prevention Science Evidence," by G. Seitidis et al., 2022, *Prevention Science*, 23, p. 415-424 (https://doi.org/10.1007/s11121-021-01289-6).

Brief Alcohol Intervention Example (Seitidis et al., 2022)

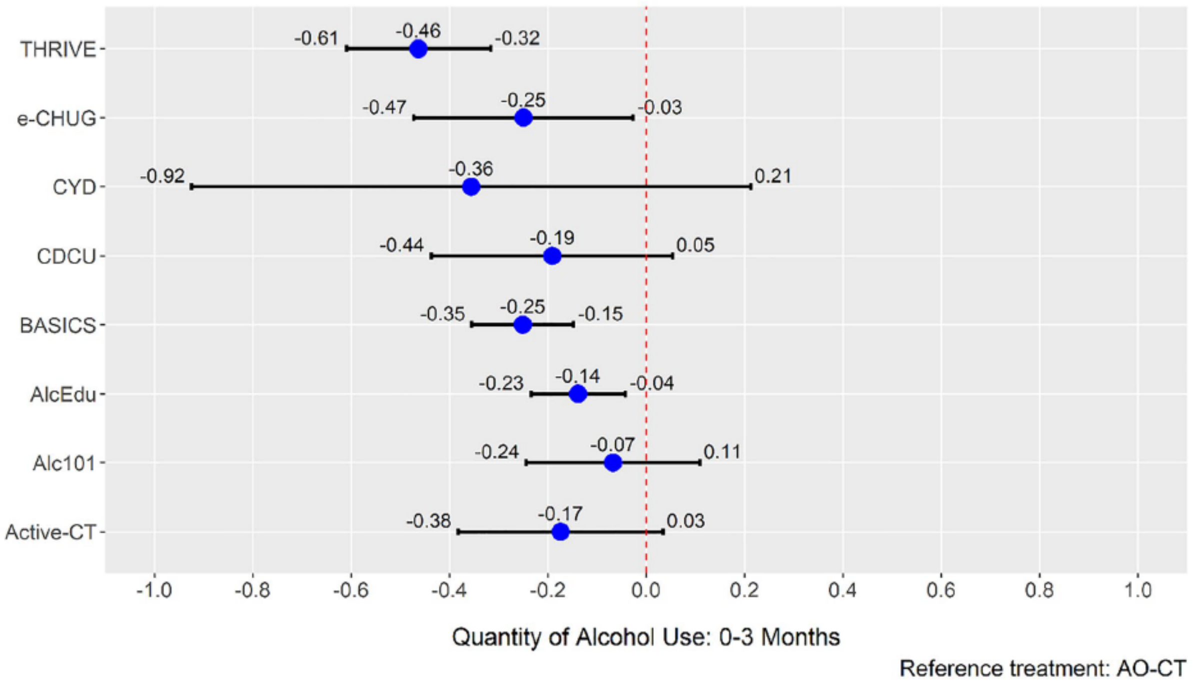


Fig. 2 Forest plot of the effectiveness on quantity of alcohol use with AO-CT as a reference treatment for each named intervention. A negative effect size indicates a reduction in alcohol use in that treatment group compared to the reference treatment, AO-CT

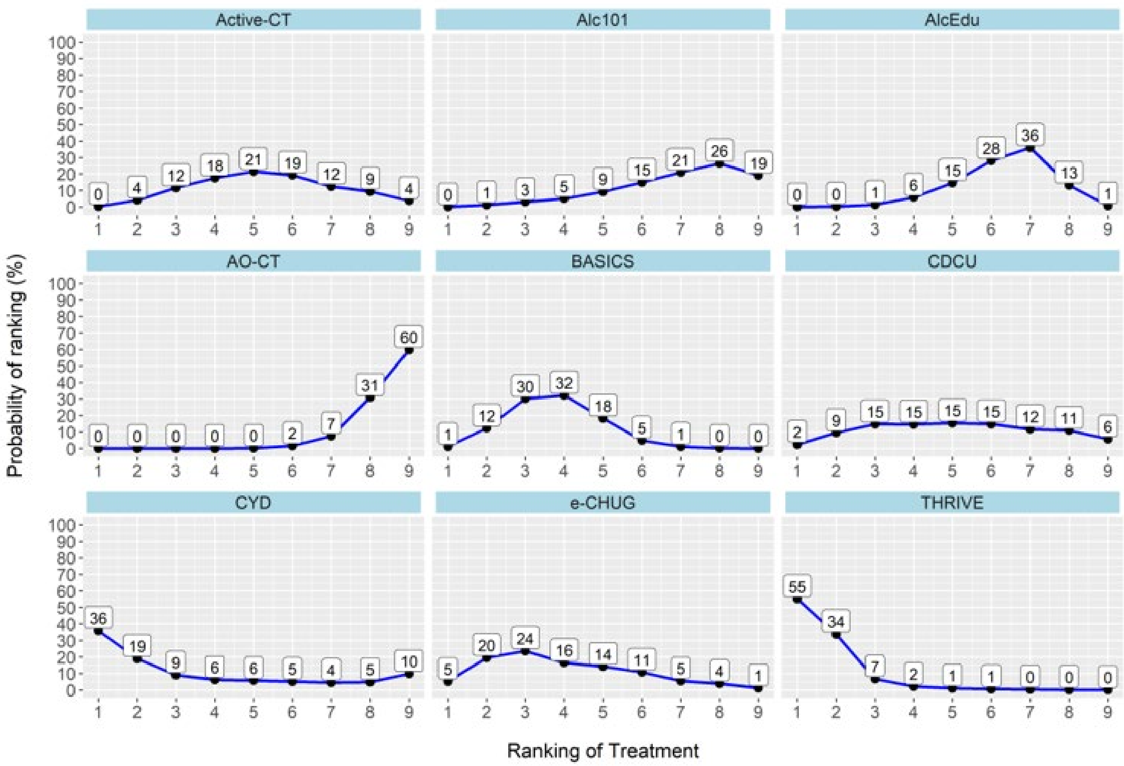


Fig. S2 Rankograms. The probability of each treatment to achieve each rank is presented.

Source: "Network Meta-Analysis Techniques for Synthesizing Prevention Science Evidence," by G. Seitidis et al., 2022, *Prevention Science*, 23, p. 415-424 (https://doi.org/10.1007/s11121-021-01289-6).

Component Network Meta-Analysis (CNMA)

- Extends standard NMA models to address questions about the comparative effects of different program components/elements (Rücker et al., 2020; Welton et al., 2009)
  - Additive main effects: assumes the effect of a multi-component intervention is the sum of the effects of its components
  - Two-way interaction: allows interactions between components (synergistic or antagonistic)

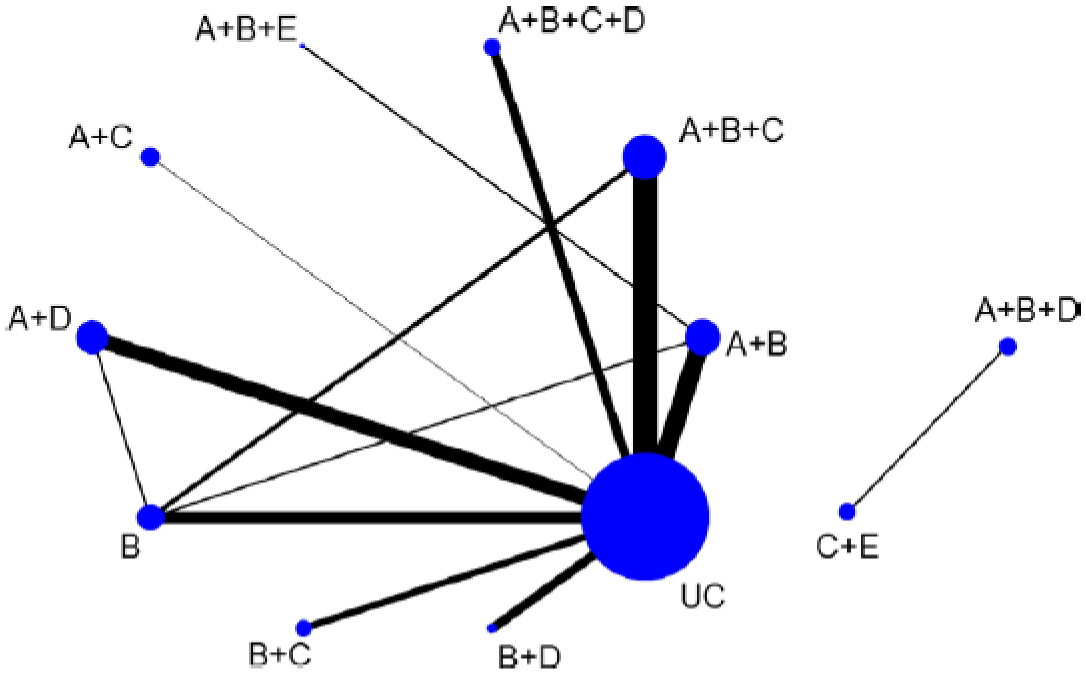


Figure 1 Network plot of multicomponent interventions comprising five components (A, B, C, D, E) and UC. The size of the nodes and the thickness of the edges are proportional to the number of studies included and the number of participants randomised to an intervention, respectively. UC, usual care.

Source: "Component network meta-analysis in a nutshell," by S. Tsokani et al., 2022, *BMJ Evidence-Based Medicine*, Online First 27 July 2022 (http://dx.doi.org/10.1136/bmjebm-2021-111906).

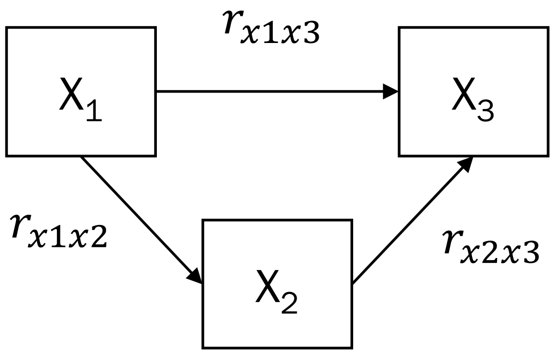
Limitations of (C)NMA

- Combining direct & indirect evidence can yield increased precision, but requires strong assumptions about transitivity (exchangeability) and coherence (consistency)
- Sparse networks may yield imprecise estimates of relative intervention effects
- Indirect evidence is observational
- Heterogeneity within the comparisons in the network can yield substantively meaningless summary effects

Meta-Analytic Structural Equation Modeling

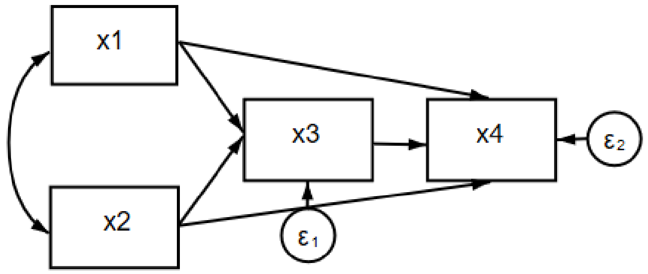
Testing Hypothesized Multivariate Models

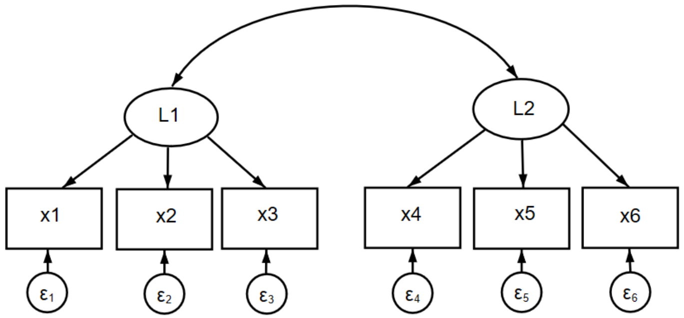
- Traditional univariate meta-analysis approaches can be used to synthesize correlation coefficients between pairs of variables (e.g., $r_{x1x2}, r_{x1x3}, r_{x2x3}$)
- But meta-analyzing these effects (coefficients) one at a time is limited (Cheung & Hong, 2017) and does not
  - Permit testing a hypothetical model
  - Allow for specification of models with latent variables
  - Account for the presence of other (potentially correlated) variables
  - Allow estimation of indirect effects



Meta-Analytic Structural Equation Modeling (MASEM)

- Combines meta-analysis and SEM approaches to fit and test hypothesized multivariate models using effect size data obtained from multiple research studies (Cheung, 2015)
  - Allows evaluation of the unique effects of multiple simultaneous predictors
  - Permits testing new theories or pathways that may not have been tested directly in any primary studies
  - Commonly used to evaluate path models, but can also be used for models with latent variables
- Software packages/macros available in R (`metaSEM`)
  - See also https://sjak.shinyapps.io/webMASEM/ for a Shiny app





Two-Stage Structural Equation Modeling (TSSEM)

Method involves two stages of estimation (Cheung & Chan, 2005)

1. Estimate pooled (meta-analytic) correlation matrix that combines the correlation matrices from multiple research studies
   - Inverse-variance weighted multivariate meta-analysis using ML estimation
2. Fit a structural equation model (e.g., path model, factor analytic model) to the pooled correlation matrix and its asymptotic sampling covariance matrix
   - WLS estimation to fit structural equation models
   - Produces likelihood ratio statistics and goodness-of-fit statistics to evaluate model fit
   - Permits testing of equality constraints, indirect effects
   - Only allows examination of one categorical moderator at a time

One-Stage Meta-Analytic Structural Equation Modeling (OSMASEM)

- Fits the structural equation model directly on the data from primary studies, treating studies as ‘participants’ (Jak & Cheung, 2020)
  - Inverse-variance weighted multivariate meta-analysis using ML estimation + SEM
  - Correlations and heterogeneity modelled as the mean and covariance structures in SEM
  - Imposes a model implied correlation structure on the average correlation matrix across studies
- Allows all parameters in the SEM to be modeled by multiple moderators at any level of measurement

Dysfunctional Attitudes and Depression Review (Valentine et al., 2022)

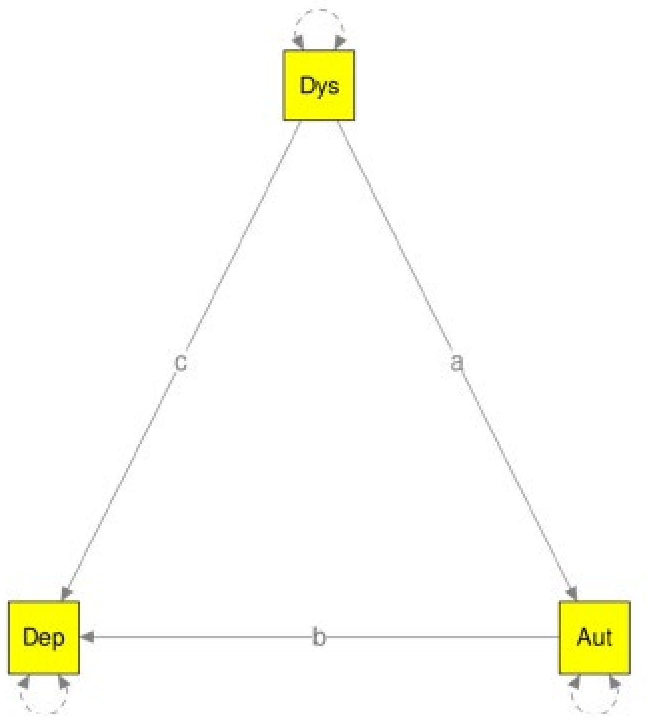


Fig 1 Proposed mediation model. Dys, dysfunctional attitudes; Aut, automatic thoughts; Dep, depression. Path c represents the hypothesized direct effect of dysfunctional attitudes on depression. The indirect effect of dysfunctional attitudes on depression via automatic thoughts is represented by the *a*×*b*

Table 3 Weighted descriptive statistics for the correlations of interest

Construct pair	Mean correlation	SE	τ	I^2	*k*	*n*
Dysfunctional attitudes — automatic thoughts	0.4701	.0269	.0721	53%	19	3,718
Depression — dysfunctional attitudes	0.4026	.0135	.0978	71%	90	18,550
Depression — automatic thoughts	0.6719	.0240	.0605	49%	52	11,980

SE standard error, τ estimated standard deviation of the true effect sizes, I^2 proportion of variability in true effect size that appears to be attributable to between-study differences, *k* number of correlations in the meta-analytic database, *n* total number of participants represented in the meta-analysis

Table 4 Moderating effects on the path coefficients and their standard errors

	Path *a* (dysfunctional attitudes → automatic thoughts)	Path *b* (automatic thoughts → depression)	Path *c* (dysfunctional attitudes → depression)
General samples	0.4831 (0.0166)	0.5911 (0.0428)	0.1312 (0.0303)
Clinical samples	0.2847 (0.0257)	0.5604 (0.0640)	0.1513 (0.0391)
Mixed samples	0.5163 (0.0328)	0.6805 (0.0627)	0.0923 (0.0572)

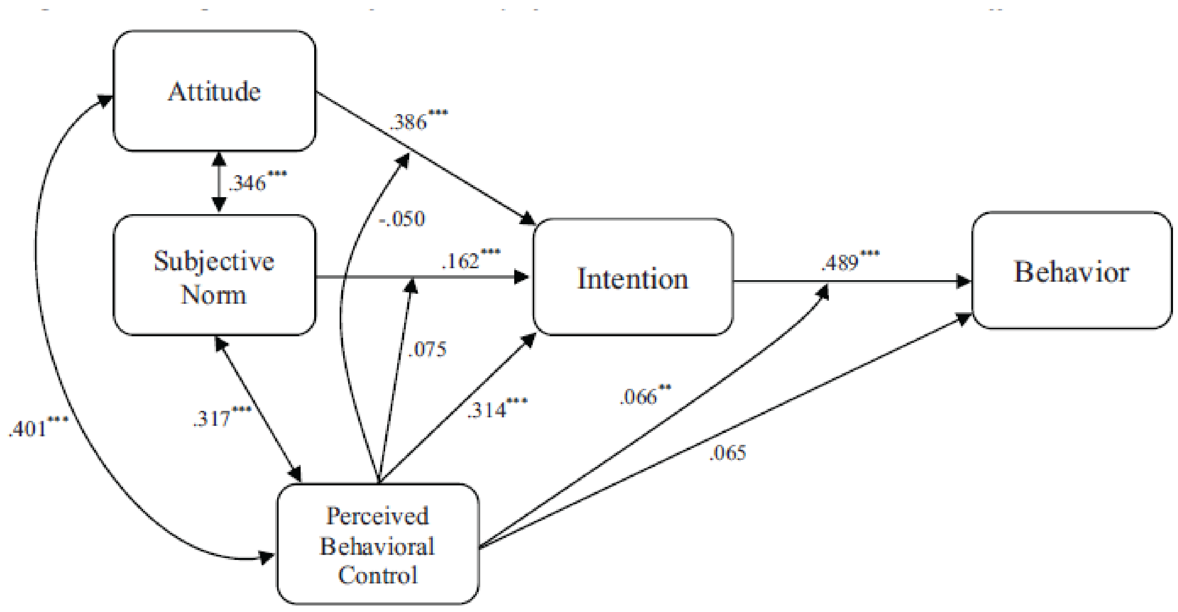
Values in parentheses are standard errors

Source: “A Primer on Meta-Analytic Structural Equation Modeling: The Case of Depression,” by J.C. Valentine et al., 2022, *Prevention Science*, 23, p. 346-365 (https://doi.org/10.1007/s11121-021-01298-5).

Theory of Planned Behavior Review (Hagger et al., 2022)

Figure 1

Diagrammatic Representation of the Theory of Planned Behavior With Interaction Effects



Note. Coefficients are standardized parameter estimates.
* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 2

Standardized Path Coefficients for Direct and Indirect Effects and Correlations for the Meta-Analytic Structural Equation Models of the Theory of Planned Behavior With Interaction Effects

Effect	β	Wald CI_{95} LL	Wald CI_{95} UL
Direct effects			
Intention→Behavior	0.489***	0.384	0.594
Attitude→Intention	0.386***	0.319	0.452
Subjective Norm→Intention	0.162***	0.100	0.225
PBC→Intention	0.314***	0.240	0.388
PBC→Behavior	0.065	−0.054	0.184
Interaction effects			
Attitude × PBC→Intention	−0.050	−0.148	0.047
Subjective Norm × PBC→Intention	0.075	−0.015	0.164
Intention × PBC→Behavior	0.066**	0.025	0.107
Indirect effects			
Attitude→Intention→Behavior	0.189***	0.141	0.237
Subjective Norm→Intention→Behavior	0.079***	0.045	0.113
PBC→Intention→Behavior	0.154***	0.099	0.209
Correlations			
Attitude↔Subjective norm	0.346***	0.302	0.391
Attitude↔PBC	0.401***	0.359	0.444
Attitude↔Attitude × PBC	−0.274***	−0.345	−0.204
Attitude↔Subjective norm × PBC	−0.075***	−0.115	−0.036
Attitude↔Intention × PBC	−0.170***	−0.225	−0.115
Subjective norm↔PBC	0.317***	0.269	0.364
Subjective norm↔Attitude × PBC	−0.076***	−0.116	−0.036
Subjective norm↔Subjective Norm × PBC	−0.178***	−0.251	−0.104
Subjective norm↔Intention × PBC	−0.090***	−0.130	−0.051
PBC↔Attitude × PBC	−0.226***	−0.289	−0.162
PBC↔Subjective Norm × PBC	−0.187***	−0.254	−0.120
PBC↔Intention × PBC	−0.343***	−0.405	−0.281
Attitude × PBC↔Subjective Norm × PBC	0.558***	0.426	0.689
Attitude × PBC↔Intention × PBC	0.931***	0.775	1.087
Subjective norm × PBC↔Intention × PBC	0.631***	0.503	0.760

Note. β = standardized path coefficient; Wald CI_{95} = Wald 95% confidence interval of path coefficient; LL = lower limit of CI_{95}; UL = upper limit of CI_{95}; CI_{95} = conventional 95% confidence interval; β_{diff} = difference in standardized path coefficient; PBC = perceived behavioral control.
* $p < .05$. ** $p < .01$. *** $p < .001$.

Source: "Perceived Behavioral Control Moderating Effects in the Theory of Planned Behavior: A Meta-Analysis," by M. S. Hagger et al., 2022, *Health Psychology*, 41, p. 346-365 (https://doi.org/10.1037/hea0001153).

Limitations of MASEM

- Poor performance with small sample sizes
- Missing correlations assumed to be MAR or MCAR
- With TSSEM, the pooled correlation matrix may not provide a realistic reflection of the actual correlation matrix in any given study
- With OSMASEM, do not quantify the heterogeneity of the SEM parameters (only the heterogeneity of the correlation coefficients)

Summary

- Rigorous meta-analyses can play an important role in evidence-based decision-making in prevention
- Recent innovations in meta-analytic methods can help address the types of complex questions facing the field
  - Complex data structures
  - Comparative effectiveness questions
  - Theories of change and causal pathways

Questions?

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