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A Statistical Method for Synthesizing Mediation Analyses Using the Product of Coefficient Approach Across Multiple Trials

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Abstract

Mediation analysis often requires larger sample sizes than main effect analysis to achieve the same statistical power. Combining results across similar trials may be the only practical option for increasing statistical power for mediation analysis in some situations. In this paper, we propose a method to estimate: 1) marginal means for mediation path a , the relation of the independent variable to the mediator; 2) marginal means for path b , the relation of the mediator to the outcome, across multiple trials; and 3) the between-trial level variance-covariance matrix based on a bivariate normal distribution. We present the statistical theory and an R computer program to combine regression coefficients from multiple trials to estimate a combined mediated effect and confidence interval under a random effects model. Values of coefficients a and b , along with their standard errors from each trial are the input for the method. This marginal likelihood based approach with Monte Carlo confidence intervals provides more accurate inference than the standard meta-analytic approach. We discuss computational issues, apply the method to two real-data examples and make recommendations for the use of the method in different settings.

Keywords

Mediation; Multiple trials; Data Synthesis; Restricted maximum likelihood; R

1 Introduction

Mediation analysis seeks to describe how predictors affect outcomes through an intermediate variable. It can be used to test etiologic theory as well as to test how an intervention functions in practice. A large literature now exists describing methodological and statistical approaches for investigating mediation in a single research study (MacKinnon, 2008). There is much less guidance for combining mediation analysis results across several research studies, although there is some early work on this topic (Becker and Schram, 1994; Harris

and Rosenthal, 1985; Shadish, 1996). There are also several computer programs available to compute point and confidence intervals for mediated effects with individual level data from a single study (Arbuckle, 1995; Muthén and Muthén, 2010; Preacher and Hayes, 2008), and when two summary regression coefficients — the so-called a and b coefficients and their standard errors — are available (Tofighi and MacKinnon, 2011).

The classic linear mediator model that relates an independent variable X to a dependent variable Y through a mediator variable M is shown in Figure 1 and defined through mediating regression Equations 1 and 2 below. The relation of X to M reflects a test of action theory as shown in the first equation. The relation of M to Y , conditional on X in the second equation is a test of what is called conceptual theory.

$$M = i_2 + aX + e_2 \quad (1)$$

$$Y = i_1 + c'X + bM + e_1 \quad (2)$$

The parameters i_1 and i_2 , are intercepts; the conditional effects of X and M on Y are the regression effects c' and b respectively; the regression coefficient of X on M is a , and e_1 and e_2 are residuals. These two equations can be combined in Equation 3 to show the total effect of X on Y .

$$Y = i_1 + bi_2 + (c' + ab)X + e_1 + be_2 = i_3 + cX + e_3 \quad (3)$$

where $c = c' + ab$. Thus the total effect c is the sum of direct effect c' and the mediated effect ab . In classic mediation analysis, this product of the two regression coefficients, $\hat{a}\hat{b}$, is the estimated mediated effect. The main computational issue for a single study is that the distribution of this product is not asymptotically normal, so integration or bootstrapping is needed for accurate confidence interval estimation (Horowitz, 2001; MacKinnon et al., 2004). Assumptions of the statistical model include no confounding, reliable measures, and a correctly specified model (MacKinnon, 2008).

Recently, there has been more attention paid to assessing mediation by combining data across multiple randomized trials. Single trials are almost always powered to examine main effects, and mediation analyses often require larger sample sizes than main effect analyses to achieve the same statistical power (Fritz and MacKinnon, 2007). Thus, combining the findings across similar trials may be a practical option for increasing the statistical power needed for mediation analyses. The methodology for combining mediation relations across trials is called mediation synthesis. If the individual-level data are available from each trial, regression estimates of a and b can be obtained through two-level mixed effects modeling. This method that includes individual-level data from each trial is a type of integrative data analysis (Curran and Hussong, 2009; Brown et al., 2013).

However in many instances individual-level data are not available for all trials. When this is the case, the analyst needs to combine summary statistics from trials reporting the results of mediation analysis with comparable statistics derived from trials where individual-level data are available. We refer to this as “parallel analysis” (Brown et al., 2013).

This paper presents statistical theory that can be used in parallel analysis to combine regression coefficients from multiple trials to estimate a combined mediated effect and a Monte Carlo confidence interval under a random effects model. Values of a and b , along with their standard errors from each trial are the input data for this parallel analysis method. This proposed method can help synthesize mediation results across multiple trials. We describe computational details of the method and apply the method to two example datasets.

2 Theory

2.1 Notation

We derive the restricted maximum likelihood estimator, standard error estimate, and confidence interval of a common mediator across multiple trials using the product of coefficients approach that links a baseline factor (e.g., an intervention condition) to an outcome through a mediating variable. This derivation allows for heterogeneity in both coefficients across trials where the coefficients along with their standard errors are estimated from each trial independently, i.e., the parallel data analysis approach. The set-up is as follows: For each of K trials, let a_i be the i^{th} trial’s estimated regression coefficient of the mediator on intervention condition, and b_i the i^{th} trial’s estimated regression coefficient of the outcome on the mediator, adjusted for intervention condition. Let Ψ_i and Φ_i be their respective asymptotic variance estimates, $i = 1, \dots, K$. The two regression coefficients are known to be asymptotically uncorrelated (MacKinnon, 2008), so in large samples the regression coefficients’ distributions have approximately independent normal distributions,

$$a_i | \alpha_i \sim N(\alpha_i, \Psi_i) \quad (4)$$

$$b_i | \beta_i \sim N(\beta_i, \Phi_i), i=1, \dots, K$$

conditional on trial level means α_i and β_i . These in turn are independently distributed across trials as

$$\begin{pmatrix} \alpha_i \\ \beta_i \end{pmatrix} \sim N(\mu, \Sigma) \quad (5)$$

where $\mu = \begin{pmatrix} \mu_\alpha \\ \mu_\beta \end{pmatrix}$ is the vector of marginal means, and $\Sigma = \begin{pmatrix} \sigma_{11} & \sigma_{12} \\ \sigma_{21} & \sigma_{22} \end{pmatrix}$ is the unknown trial-level variance-covariance matrix.

Defining K dimensional random vectors $\mathbf{a} = (a_1 \dots a_K)'$ and $\mathbf{b} = (b_1 \dots b_K)'$, and combining Equations 4 and 5, we have

$$\begin{pmatrix} \mathbf{a} \\ \mathbf{b} \end{pmatrix} | \mu \sim N(\mu * \mathbf{1}, \Delta + \Sigma \otimes \mathbf{I}_K) \quad (6)$$

where $*$ is the outer product of two vectors and $\otimes$ is the outer product of two matrices; $\Delta = \text{diag}(\Psi_1, \Phi_1, \dots, \Psi_K, \Phi_K)$, and $\mathbf{I}_K$ is the $k \times k$ dimensional identity matrix.

2.2 Likelihood and Restricted Log Likelihood

Define $\mathbf{Y}_i = \begin{pmatrix} a_i \\ b_i \end{pmatrix}$ and $\mathbf{V}_i = \text{diag}(\Psi_i, \Phi_i) + \Sigma$, $i = 1, \dots, K$. Then the log likelihood obtained from Equation 6 is (up to a constant)

$$\log L(\mu, \Sigma) = -\frac{1}{2} \sum_{i=1}^K ((\mathbf{Y}_i - \mu)' \mathbf{V}_i^{-1} (\mathbf{Y}_i - \mu) + \log |\mathbf{V}_i|) \quad (7)$$

For more than one trial, we maximize the restricted likelihood (REML),

$$R\log L(\mu, \Sigma) = -\frac{1}{2} \sum_{i=1}^K ((\mathbf{Y}_i - \mu)' \mathbf{V}_i^{-1} (\mathbf{Y}_i - \mu) + \frac{K-1}{K} \log |\mathbf{V}_i|). \quad (8)$$

Maximum Likelihood Estimates for μ

The restricted likelihood equations are obtained by setting the derivatives equal to zero. We work directly with vector differentials (for μ) and matrix differentials (for Σ), so that

$$dR\log L = \sum_{i=1}^K d(\mu)' \mathbf{V}_i^{-1} (\mathbf{Y}_i - \mu) - \frac{1}{2} (\mathbf{Y}_i - \mu)' d(\mathbf{V}_i^{-1}) (\mathbf{Y}_i - \mu) - \frac{K-1}{2K} d(\log |\mathbf{V}_i|) \quad (9)$$

The likelihood equations for μ are formed by setting the differential with respect to these two parameters equal to zero, namely, for μ these equations are

$$0 = \sum_{i=1}^K \mathbf{V}_i^{-1} (\mathbf{Y}_i - \mu) \text{ or } \mu = \left(\sum_{i=1}^K \mathbf{V}_i^{-1} \right)^{-1} \sum_{i=1}^K \mathbf{V}_i^{-1} \mathbf{Y}_i, \quad (10)$$

that is, the ML solution for μ is average of the observed parameter estimates weighted inversely to their marginal variance-covariance matrix.

Maximum Likelihood Estimates for Σ

We manipulated the matrix differentials (for Σ) to obtain the derivative of the log likelihood function with respect to Σ . We finally obtain:

$$dR\log L = \sum_{i=1}^K \frac{1}{2} \text{tr} \left[\{(\mathbf{Y}_i - \mu)(\mathbf{Y}_i - \mu)' \mathbf{V}_i^{-1} - \frac{K-1}{K} I_2\} d(\mathbf{V}_i) \mathbf{V}_i^{-1} \right] \quad (11)$$

For details of the proof see Appendix.

2.3 Cholesky Transformation to Ensure Positive Definiteness

Our maximization of $R\log L$ restricts Σ to be positive definite, so we have transformed the unknown parameters $\theta = (\mu', \sigma_{11}, \sigma_{12}, \sigma_{22})'$ into the following set $\theta^* = (\mu', \omega_1, \omega_2, \omega_3)$ based on a Cholesky decomposition so there are no range restrictions; i.e.

$$\omega_1 = \log \sigma_{11} \quad (12)$$

$$\omega_2 = \sigma_{12} / \sqrt{\sigma_{11}}$$

$$\omega_3 = \log \sigma_{22.1} = \log(\sigma_{22} - \sigma_{12}^2 / \sigma_{11})$$

The derivative of this transformation is

$$\frac{\partial \sigma}{\partial \omega'} = \begin{pmatrix} e^{w_1} & 0 & 0 & 0 & 0 \\ \frac{1}{2} w_2 e^{w_1/2} & e^{w_1/2} & 0 & 0 & 0 \\ 0 & 2w_2 & e^{w_3} & 0 & 0 \end{pmatrix} \quad (13)$$

and can be used to premultiply the likelihood equations.

2.4 Estimation of a Common Mediated Effect and its Standard Error

Finally, the ML estimate of the mediated effect, $\delta = \mu_a \times \mu_b$, is the product of the estimates for μ , that is, $\hat{\delta} = \hat{\mu}_a \hat{\mu}_b$. The estimated asymptotic variance for this estimate is based on the inverse of the information matrix for θ , namely,

$$\widehat{\text{Var}}(\hat{\delta}) = (\hat{\mu}_b, \hat{\mu}_a, 0, 0, 0) \mathcal{J}^{-1}(\hat{\mu}_b, \hat{\mu}_a, 0, 0, 0)' \quad (14)$$

and its standard error

$$\text{se}(\hat{\delta}) = \sqrt{\widehat{\text{Var}}(\hat{\delta})}. \quad (15)$$

2.5 Confidence Intervals for the Mediated Effect

It is well known that the asymptotic distribution of the product of two normal random variables is not normally distributed (Springer, 1979), so we apply the Monte Carlo method to obtain $1 - \alpha$ confidence intervals. Again $\delta = \mu_a \times \mu_b$ is the parameter of interest, $\hat{\delta}$ is the estimate and se is the sample estimate of standard error of $\hat{\delta}$. The complete set of parameters $\theta = (\mu, \Sigma)$, where $\mu = (\mu_a, \mu_b)$, and $\Sigma = (se(\mu_a), se(\mu_b))$. We seek lower and upper bounds $L(\hat{\delta})$ and $U(\hat{\delta})$ depending on the data such that

$$\Pr(\delta < L(\hat{\delta})) = \Pr(\delta > U(\hat{\delta})) = \alpha/2 \quad (16)$$

where the data are generated from θ .

The general setup is as follows.

Step 1: we define $F_{\hat{\delta}}()$ to be the true distribution of the pivotal quantity $(\hat{\delta}B - \hat{\delta})/seB$ when sampled under θ . $\hat{\delta}B$ are the bootstrapped estimates of $\hat{\delta}$ and seB are the Sobel standard error estimates based on the bootstrap samples. The Monte Carlo procedure estimates $F_{\hat{\delta}}$ by generating the empirical distribution of $F_{\hat{\delta}}$ obtained by repeated sampling using the estimated value of θ to generate samples under Equations 4 and 5.

Step 2: then Defining a critical value L_{crit} and U_{crit} to satisfy

$$\Pr((\hat{\delta}B - \hat{\delta})/seB > L_{crit}) = \alpha/2, \quad (17)$$

and

$$\Pr((\hat{\delta}B - \hat{\delta})/seB > U_{crit}) = 1 - \alpha/2, \quad (18)$$

which are satisfied when $L_{crit} = F_{\hat{\delta}}^{-1}(\alpha/2)$ and $U_{crit} = F_{\hat{\delta}}^{-1}(1 - \alpha/2)$. Thus we have $(\hat{\delta}B - \hat{\delta})/seB$ lies within $[F_{\hat{\delta}}^{-1}(\alpha/2), F_{\hat{\delta}}^{-1}(1 - \alpha/2)]$.

Step 3: replacing $(\hat{\delta}B - \hat{\delta})/seB$ with $(\hat{\delta} - \delta)/se$, it shows $(\hat{\delta} - \delta)/se$ lies within $[F_{\hat{\delta}}^{-1}(\alpha/2), F_{\hat{\delta}}^{-1}(1 - \alpha/2)]$.

Thus, we have

$$U(\delta) = \hat{\delta} - se F_{\hat{\delta}}^{-1}(\alpha/2), \quad (19)$$

and similarly

$$L(\delta) = \hat{\delta} - se F_{\hat{\delta}}^{-1}(1 - \alpha/2). \quad (20)$$

3 Examples

Here we provide two examples. The first is a direct application of this method applied to eight trials, all of which have the same intervention, hypothesized mediator, and outcome. The second example illustrates the use of this mediational synthesis method to examine variation in mediational effects as a function of baseline characteristics, the so-called moderated mediation model (MacKinnon, 2008).

3.1 Human memory trials

Data from a study of human memory demonstrate how the proposed method can be used to estimate the mediation effect across multiple trials with real data from a study described in MacKinnon et al. (2014). The study was based on the mediating variable theory that processing of words with imagery improves recall of words. Young adult participants were randomized to one of two conditions in which they were either: 1) instructed to use imagery to remember a list of words; or 2) instructed to repeat the words as they heard them. After recalling as many words as they could from a list of 20 words, participants indicated the extent to which they formed images of the words. The beneficial effects of imagery on word recall should lead to a substantial mediated effect of the manipulation to imagery to memory performance. So this was a case where the mediation process is assumed known whereby a manipulation to increase imagery (X) increases imagery (M) which increases word recall (Y). Eight memory studies were conducted to investigate the mediation relation using the same procedure (data from MacKinnon et al., 2014). Table 1 reports the data for each of the eight studies. Columns 2 to 6 give the reported a path coefficient, its standard error, b path coefficient, its standard error, and sample size for each study. The small sample sizes and varying path coefficient estimates of individual trials provided inconclusive mediation results within each trial; the mediation effect for trials 1, 3, 4, 6 and 8 was statistically significant but was not statistically significant for trials 2, 5 and 7. In order to examine the overall mediation effect, a synthesis of mediation results from the eight trials was conducted with the proposed method.

3.2 Familias Unidas trials

A second illustrative example combined data from three randomized clinical trials of the Familias Unidas intervention (Prado and Pantin, 2011) to examine the mechanisms or mediators by which this intervention operates to reduce youth internalizing symptoms (depression and anxiety symptoms). While this family-focused intervention was designed to prevent and reduce substance use and HIV risk behavior among Hispanic adolescents, analyses had also found that the intervention also inadvertently reduced internalizing symptoms among certain youth (Perrino et al., 2015; Prado and Pantin, 2011). Understanding how this intervention influenced youth internalizing symptoms was important to inform future intervention efforts. Again, the relatively small sample sizes of individual trials and small regression coefficient estimates provided insufficient statistical power to permit robust mediation analyses within each trial (none of the mediation effects for each of the single trials was significant). By synthesizing mediation results from these three trials, the overall mediation effect can be examined with increased statistical power. Thus, results from three randomized clinical trials of Familias Unidas were combined and used to

demonstrate variation in mediation effects as a function of baseline characteristics across multiple trials. These three trials were used to assess the extent to which the effect of Familias Unidas on youth internalizing symptoms was mediated through improvements in parent-adolescent communication, the hypothesized mediator by which this intervention works to improve internalizing symptoms. In a previous publication (Perrino et al., 2014), we reported a significant mediation effect when parent-adolescent communication at baseline was low, and no significant mediation effect when baseline parent-adolescent communication was high. In this paper, we analyze these same data at two different levels of baseline parent-adolescent communication, “low/medium” and “high”, and provide confidence bounds for each of these two levels. Table 2 gives the coefficients for each of the three trials at each baseline level. Columns 3 to 7 give the reported a path coefficient, its standard error, b path coefficient, its standard error, and sample size for each analysis.

4 Results

We have written an R program to calculate the marginal means μ and the confidence interval for their product (available from the first author or can be down-loaded at <https://drive.google.com/folderview?id=0ByG6JaVgX9soWUtGOTVIRC1sMjQ&usp=sharing>).

The R syntax includes the following: First, we defined the negative log likelihood function ($minusLogL.v$) with respect to μ and Σ as specified in formula 8. The default setting is with the restricted likelihood correction. We also defined a negative log likelihood function that was based on Cholesky decomposition of Σ ($minusLogL.w$). Thus, there are no range restrictions to insure maximization of $RlogL$ restricts Σ to be positive definite.

Second, we employed the R general-purpose optimization function (*optim*), with the “L-BFGS-B” Method (Byrd et al., 1995), to calculate maximum likelihood estimates for μ and Σ (*MLsolution*). Gradients were also provided in the *optim* function as specified in formulas 10 and 11.

Third, we write out estimates of μ and Σ , their variance-covariance matrix, negative log likelihood value, and derivatives with respect to μ and Σ .

Finally, we used the R *mvnrm* function to parametrically generate repeated sets of sample values of μ_α and μ_β under bivariate normal distribution. The Σ , variance-covariance matrix for μ was estimated by solving the Hessian matrix estimated from the *MLsolution* function. The confidence interval is then calculated as specified in formulas 19 and 20.

4.1 Calculations for the Memory Study Example

In our first example involving the memory tests, because Σ was not strictly positive definite, we used a Cholesky transformation. In cases of positive definite Σ , readers can use functions without the Cholesky transformation.

The restricted maximum likelihood estimates for μ are $\begin{pmatrix} \mu_\alpha=3.98 \\ \mu_\beta=0.53 \end{pmatrix}$. In the memory study example, the point estimate of mediation effect across multitrials was $\mu_\alpha \times \mu_\beta$, which is 3.98

$\times 0.53 = 2.11$, or an effect of the manipulation through imagery of about 2 words. This result is consistent with the theory that increasing imagery increases word recall.

Then we used the R *mvrnorm* function to parametrically generate 2000 repeated sets of

sample values of μ_α and μ_β under bivariate normal distribution with $\mu = \begin{pmatrix} \mu_\alpha = 3.98 \\ \mu_\beta = 0.53 \end{pmatrix}$, and $\Sigma = \begin{pmatrix} 0.138 & -0.01 \\ -0.01 & 0.07 \end{pmatrix}$.

The confidence interval was then calculated as specified in formula 19 and 20, and was 1.89 to 2.39, for the upper and lower limit, respectively. Again, there was a statistically significant mediated effect of the manipulation on word recall through imagery and a smaller confidence interval when multiple studies are combined. These results provide a quantitative value for the mediated effect of the manipulation on word recall through imagery combined across the eight trials.

4.2 Calculations for the Familias Unidas Example

When parent-adolescent communication at baseline was low, the results showed that estimation with the Cholesky Transformation converged. In this example, the Maximum

Likelihood estimates for μ was $\begin{pmatrix} \mu_\alpha = -3.73 \\ \mu_\beta = -0.045 \end{pmatrix}$ and Σ was $\begin{pmatrix} 0.649 & -0.0 \\ -0.0 & 0.0006 \end{pmatrix}$.

Thus, the point estimate of the mediation effect across three trials, $\mu_\alpha \times \mu_\beta$, was 0.168. The confidence interval was then calculated as specified in formula 19 and 20, and was equal to 0.008 to 0.37. This synthesized mediation analysis found that the Familias Unidas intervention had a significant effect in reducing internalizing symptoms among youth who had low/medium parent-adolescent communication level by improving parent-adolescent communication.

When parent-adolescent communication at baseline was high, estimation with the Cholesky Transformation converged. In this example, the Maximum Likelihood estimates for μ was $\begin{pmatrix} \mu_\alpha = 0.23 \\ \mu_\beta = -0.14 \end{pmatrix}$ and Σ was $\begin{pmatrix} 1.068 & -0.031 \\ -0.031 & 0.008 \end{pmatrix}$. Thus, the point estimate of the mediation effect across three trials, $\mu_\alpha \times \mu_\beta$, was -0.032 . The confidence interval was then calculated as specified in formula 19 and 20, resulting in a range of -0.33 to 0.203 . This synthesized mediation analysis found that the Familias Unidas intervention did not have a statistically significant effect in reducing internalizing symptoms among youth who had high parent-adolescent communication at baseline.

5 Does combining studies increase statistical power for mediation?

Studies have shown that individual trials are often underpowered to detect mediation effects (Fritz and MacKinnon, 2007). To examine whether combining mediation findings across multiple studies does lead to higher statistical power, even in the presence of trial heterogeneity, we conducted a simulation study of our method in the case of trial

heterogeneity. The sample size was set to 200. The a path coefficient was set to 0.385 and the b path coefficient was set to 0.195 for 80% power to detect a significant a path and b path. The simulation results found that although we had 80% power to detect a significant a path and b path, the power to detect a significant product of a and b was only about 70%. We then computed power for testing the product of these coefficients using 2, 3 and 5 trials under four different levels of heterogeneity, with intraclass correlations ICC = 0, 0.01, 0.05 and 0.1, i.e., none, negligible, moderate, and high. For all cases we assumed the second level correlation between a and b was zero. The simulation results are given in Table 3. As seen in Table 3, when synthesizing mediation analyses results with the proposed method, there was about 95% power to detect a significant mediation effect with three trials that were powered at 80% to detect a significant a path and b path. With five trials, the power was 100%. However, the power with two trials was problematic because with only two trials, the estimated trial-level variance-covariance matrix has only one degree of freedom and is therefore not well estimated.

6 Discussion

Pooling results across multiple trials provides a way to assess the overall strength of mediation across trials, thereby increasing statistical power. In this paper, we presented the statistical theory and applications for synthesizing findings about mediation across multiple trials. This method estimates marginal means for the mediation path coefficients a and b across multiple trials, as well as the between-trial variance-covariance matrix, based on a bivariate normal distribution. The product of μ_a and μ_b and its 95% confidence interval are then calculated. These values include information from all available research studies. It is worth noting that this program also allows researchers to evaluate mediation effects in clustered data, such as studies conducted in multiple schools and classrooms, where mediation effects are estimated for each cluster. A related routine has been recently included in the Mplus program (Muthén and Muthén, 2010) that could also be used to combine information across trials.

We compared the results for the memory studies to traditional meta-analysis results using the product of a and b paths and their standard errors as input. We treated each product as the summary measure, averaged them with weights inversely proportional to the standard error of $a * b$ squared, and then used normal-based methods to form a confidence interval for this weighted product of coefficients. The test of heterogeneity of mediation effect found there was no significant difference of the mediation effect across studies ($Q = 2.06$, $df = 7$, $p = 0.957$). Fixed-effects meta-analysis showed that the mean mediation effect was 1.91 with a 95% confidence interval from 1.36 to 2.47. These meta-analysis results were slightly different and had a much wider confidence interval than our results (2.11, 95% confidence interval from 1.89 to 2.40). Our method of synthesizing the mediation effect is different from meta-analysis because: 1) we specify the within trial level distribution of the a path and b path as independent normal distributions with mean equal to α_j and β_j , and at between-trial level, we specify α_j and β_j as having a bivariate normal distribution with mean equal to μ and an unknown trial-level variance-covariance matrix, Σ ; and 2) we use a Monte Carlo method to obtain the confidence interval instead of using the asymptotic normal distribution method. We do not generally recommend the use of standard meta-analytic programs, either

under fixed or random effects, as a way of synthesizing mediational findings across studies. The statistical approach that we have developed here more accurately handles the non-normality of the product, and even the fixed-effect analysis shown here provides far wider confidence intervals than our method, which does take into account heterogeneity across studies. If random effects meta-analysis were used, the confidence interval would necessarily be even larger.

We recommend that efficient methods for combining mediational findings across studies should be used as alternatives to standard meta-analyses, even with relatively small numbers of studies. As we mentioned earlier, with only two studies the trial level variance-covariance matrix is not well estimated; however, even in this case it still produces a valid total variance estimate.

The proposed method will be useful in synthesis projects where individual level data are difficult or impossible to obtain. Unfortunately, there are many instances where individual studies do not report their mediation results, and therefore these summary statistics are not readily obtained from the published literature. Also, even if a mediated effect estimate is reported, our method requires knowledge of the individual values of paths and their standard errors for the calculation of the overall mediated effect and confidence interval. In this situation, we have proposed elsewhere (Brown et al., 2013) a solution that is politically and logistically simpler to carry out than obtaining individual-level data where data analyses are carried out by the team that collected and is responsible for the data. A synthesis for mediation would specify that researchers on each trial produce their own a and b coefficients and standard errors, controlling for specified variables and/or restricted to specified subsets of participants.

Mediational synthesis improves understanding of how intervention impact occurs by combining findings from randomized trials. The recent trend at the National Institutes of Mental Health towards demonstrating significant impact of an intervention on hypothesized mediators before conducting a large-scale trial (Insel and Gogtay, 2014) emphasizes the importance of identifying mediational pathways as a scientific stepping stone.

In addition to supporting the development of scientific, generalizable knowledge about the effect of interventions, mediational analysis is an important tool for implementation research. A critical scientific challenge is understanding the relationship between fidelity of program delivery and the outcome on the target population. There is often too little variation in program fidelity in efficacy studies to evaluate mediational processes, and most effectiveness trials are underpowered for such mediational analyses. Methodology to synthesize studies is important because basic understanding of how fidelity affects outcomes will likely require combining data from implementation studies, including those randomizing geographical areas such as counties or other large delivery systems to different implementation strategies (Brown et al., 2014).

Synthesis analyses that combine data across multiple trials and examine mediation effects are expected to become more common in prevention and treatment research. The statistical theory set forth in this manuscript can facilitate this research. In an example of these

synthesis analyses (Perrino et al., 2014), the authors combined and analyzed individual-level, longitudinal data from 721 adolescents across three randomized clinical trials of Familias Unidas, a prevention program for youth. Using integrative data analysis (IDA) methods applied to trials, this synthesis study examined whether baseline levels of parent-adolescent communication moderated the effects of the intervention on internalizing symptoms (i.e., symptoms of depression or anxiety), and whether there were any moderated mediation effects. Findings from this synthesized mediation analyses confirmed that parent-adolescent communication changes mediated the intervention's effects on youth internalizing symptoms, with stronger effects for youth with poorer baseline communication levels. That parent-adolescent communication is an important mediator suggests that intervention-targeted improvements in parent-adolescent communication are an “active ingredient” of the intervention and a mechanism by which adolescent internalizing symptoms are reduced (Perrino et al., 2014).

Future extensions to this work include methods to incorporate missing data for path a and path b , and methods to include an interaction term of X and M jointly affecting Y in Equation 2. Our approach also assumes that measures of M and Y are continuous, there is no confounding of mediation relations, and the ordering of the causal mediation effect is correct. It will be helpful to extend the method to studies where the primary outcome or mediator is categorical and to develop methods that model the influence of potential confounding variables in multi-trial mediation analysis.

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Appendix

Restricted Maximum Likelihood Estimates for Σ

The differential $d(\mathbf{V}_i^{-1})$ of this symmetric matrix can be expressed in terms of the the differential of the matrix itself by noting that by the chain rule,

$$d(\mathbf{V}_i^{-1}\mathbf{V}_i) = d(\mathbf{V}_i^{-1})\mathbf{V}_i + \mathbf{V}_i^{-1}d(\mathbf{V}_i) \quad (21)$$

and using $d(\mathbf{V}_i^{-1}\mathbf{V}_i) = d(\mathbf{I}_K) = 0$, we have

$$d(\mathbf{V}_i^{-1}) = -(\mathbf{V}_i^{-1})d\mathbf{V}_i\mathbf{V}_i^{-1} \quad (22)$$

To find the differential $d\log|\mathbf{V}_i|$ we note that a determinant of any positive definite symmetric matrix Ψ can be related to an integral for a multivariate normal distribution.

$$1 = \int e^{-\frac{1}{2} \mathbf{u}' \Psi^{-1} \mathbf{u}} / (2\pi)^{K/2} |\Psi|^{-\frac{1}{2}} d\mathbf{u} \quad (23)$$

Thus

$$|\Psi| = J^2(\Psi) \quad (24)$$

where the definite multivariate integral

$$J(\Psi) = \int e^{-\frac{1}{2} \mathbf{u}' \Psi^{-1} \mathbf{u}} / (2\pi)^{K/2} d\mathbf{u} \quad (25)$$

Differentiating the logarithm on each side of Equation 24,

$$d \log |\Psi| = |\Psi|^{-1} d|\Psi| = |\Psi|^{-1} d(J^2(\Psi)) = 2|\Psi|^{-1} J(\Psi) d(J(\Psi)) = 2|\Psi|^{-\frac{1}{2}} d(J(|\Psi|)) \quad (26)$$

Differentiating the integral can be done by bringing the differential inside the integrand of Equation and using the chain rule, so

$$\begin{aligned} d \log |\Psi| &= 2|\Psi|^{-\frac{1}{2}} d(J(|\Psi|)) \\ &= 2|\Psi|^{-\frac{1}{2}} \int d(e^{-\frac{1}{2} \mathbf{u}' \Psi^{-1} \mathbf{u}}) / (2\pi)^{K/2} d\mathbf{u} \\ &= 2|\Psi|^{-\frac{1}{2}} \int d(-\frac{1}{2} \mathbf{u}' \Psi^{-1} \mathbf{u}) e^{-\frac{1}{2} \mathbf{u}' \Psi^{-1} \mathbf{u}} / (2\pi)^{K/2} d\mathbf{u} \\ &= -|\Psi|^{-\frac{1}{2}} \int \text{tr}[\mathbf{u} \mathbf{u}' d(\Psi^{-1})] e^{-\frac{1}{2} \mathbf{u}' \Psi^{-1} \mathbf{u}} / (2\pi)^{K/2} d\mathbf{u} \\ &= -|\Psi|^{-\frac{1}{2}} \text{tr}[E(\mathbf{U} \mathbf{U}') d(\Psi^{-1})] |\Psi|^{\frac{1}{2}} \end{aligned} \quad (27)$$

$$= -\text{tr}[\Psi d(\Psi^{-1})] \quad (28)$$

$$d \log |\Psi| = \text{tr}[d(\Psi) \Psi^{-1}] \quad (29)$$

Equation 27 comes from the Definition of the expectation of the random matrix $\mathbf{U} \mathbf{U}'$, and this expectation evaluates to the variance-covariance matrix for a multivariate normal distribution as in Equation 28. The final equation in this series comes from Equation 22. Substituting Equation 22 and 29 into Equation 9 we finally obtain,

$$\begin{aligned}
dR\log L &= \sum_{i=1}^K \frac{1}{2} \text{tr}[(\mathbf{Y}_i - \mu)(\mathbf{Y}_i - \mu)' \mathbf{V}_i^{-1} d(\mathbf{V}_i) \mathbf{V}_i^{-1}] - \\
&\quad \frac{K-1}{2K} \text{tr}[d(\mathbf{V}_i) \mathbf{V}_i^{-1}] \\
&= \sum_{i=1}^K \frac{1}{2} \text{tr}[\{(\mathbf{Y}_i - \mu)(\mathbf{Y}_i - \mu)' \mathbf{V}_i^{-1} - \frac{K-1}{K} I_2\} d(\mathbf{V}_i) \mathbf{V}_i^{-1}] \quad (30)
\end{aligned}$$

Since $\mathbf{V}_i = \text{diag}(\Psi_i, \Phi_i) + \Sigma$, $i = 1, \dots, K$, we have

$$d\mathbf{V}_i = d\Sigma = \begin{pmatrix} d\sigma_{11} & 0 \\ 0 & 0 \end{pmatrix} + \begin{pmatrix} 0 & d\sigma_{12} \\ d\sigma_{12} & 0 \end{pmatrix} + \begin{pmatrix} 0 & 0 \\ 0 & d\sigma_{22} \end{pmatrix} \quad (31)$$

Substituting this expression into the previous differential results in three scalar equations, one for each component of the variance-covariance matrix.

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Fig. 1.
Mediation model

Table 1

Mediation analysis from eight memory trials

Trial	<i>a</i>	<i>S_a</i>	<i>b</i>	<i>S_b</i>	<i>N</i>	Mediation effect
1	3.7456	.47772	.3890	.15988	77	*
2	5.7483	.60274	.31689	.35127	24	ns
3	2.54526	.84179	.69578	.15348	45	*
4	3.55833	.6894	.61406	.2261	44	*
5	3.9242	.77705	.36685	.19522	43	ns
6	3.2381	.50524	.65524	.12466	79	*
7	5.28333	.79539	.4936	.38804	22	ns
8	3.88333	.76949	.7148	.20622	35	*

Table 2

Mediation analysis from three Familias Unidas trials

Communication level	Trial	<i>a</i>	<i>S_a</i>	<i>b</i>	<i>S_b</i>	<i>N</i>	Mediation effect
Low/Medium	1	-2.517	1.261	-0.003	0.044	110	ns
	2	-4.883	1.510	-0.050	0.031	150	ns
	3	-4.281	1.452	-0.149	0.079	165	ns
High	1	-0.090	1.104	-0.015	0.031	154	ns
	2	-1.873	2.535	-0.120	0.046	63	ns
	3	1.359	1.871	-0.335	0.084	77	ns

Table 3

Power analysis by number of trials and between trial heterogeneity

ICC	1 trial	2 trials	3 trials	5 trials
0	0.7	0.270	0.965	1.000
0.01	–	0.266	0.963	1.000
0.05	–	0.270	0.952	1.000
0.1	–	0.260	0.940	1.000