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Bridging Statistical Rigor and Clinical Usability: The CORMeta App for Meta-Analysis of Correlated Outcomes

Klinik Uygulamalarda CORMeta Meta-Analiz Uygulaması

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ABSTRACT

Background: In clinical research, multiple outcomes are often measured within the same cohort, leading to statistical dependencies that violate assumptions of traditional meta-analytic methods. While advanced models can accommodate such correlations, they typically require programming expertise, limiting accessibility for many physician-researchers.

Objective: We present a user-friendly, interactive Shiny web application designed to perform meta-analyses of correlated outcomes, with particular relevance for cohort-based clinical datasets.

Methods: The application implements a modified multivariate meta-analytic framework that accounts for the correlation structure of outcomes within cohorts. Users can upload their data, define correlation matrices, and filter observations by any variable (e.g., age, domain, exposure) without writing code. The application provides graphical output (forest plots) along with estimates of overall effect size, heterogeneity (τ^2), and p-values.

Results: A demonstration dataset on prenatal alcohol exposure and neurodevelopmental outcomes is simulated to illustrate the application's functionality. The application automatically generates correlation matrices where needed, adjusts for intra-cohort dependencies, and produces interpretable results suitable for clinical research reports.

Conclusion: This open-access application bridges the gap between complex statistical modeling and clinical usability. It enables physicians to conduct robust meta-analyses of correlated outcomes with ease, supporting evidence-based practice and local research initiatives. The tool is particularly valuable in multi-domain or multi-cohort studies where outcome correlation is non-negligible.

Availability: The CORMeta app is freely available at https://fasdprojectapp.shinyapps.io/CORMetaApp/ . Users can upload their own summary datasets or explore the app using a preloaded sample dataset (example_data.csv), which is included with the source code. The complete app and codebase are available at https://github.com/takkaya/Meta-Analysis-of-Correlated-Outcomes-Made-Easy-Introducing-CORMeta-for-Clinicians.git

Keywords: meta-analysis, correlated outcomes, Shiny app, clinical research, multivariate models

ÖZET

Arka Plan: Klinik araştırmalarda, aynı kohort içinde birden fazla sonuç ölçütü değerlendirilmekte olup bu durum, geleneksel meta-analiz yöntemlerinin varsayımlarını ihlal eden istatistiksel bağımlılıklara yol açmaktadır. Bu tür korelasyonları dikkate alabilen gelişmiş modeller mevcut olmakla birlikte, bu modellerin kullanımı genellikle programlama bilgisi gerektirdiğinden, birçok hekim araştırmacı için erişilebilir değildir.

Amaç: Kohort tabanlı klinik veri setleriyle ilişkili korele sonuçlar üzerinde meta-analiz yapabilmeyi kolaylaştırmak amacıyla, kullanıcı dostu ve etkileşimli bir Shiny web uygulaması sunmaktayız.

Yöntemler: Bu uygulama, kohort içi sonuçların korelasyon yapısını dikkate alan, uyarlanmış bir çok değişkenli meta-analiz çerçevesini uygulamaktadır. Kullanıcılar veri yükleyebilir, korelasyon matrislerini tanımlayabilir ve herhangi bir değişkene (örneğin yaş, alan, maruziyet) göre gözlemleri filtreleyebilir; tüm bunlar kod yazmadan gerçekleştirilebilmektedir. Uygulama, grafiksel çıktılar (orman grafikleri) ile birlikte genel etki büyüklüğü, heterojenite (τ^2) ve p-değerleri gibi sonuçları sunmaktadır.

Bulgular: Uygulamanın işlevselliğini göstermek amacıyla, doğum öncesi alkol maruziyeti ve nörogelişimsel sonuçlara ilişkin simüle edilmiş bir veri seti kullanılmıştır. Uygulama, gerekli durumlarda korelasyon matrislerini otomatik olarak oluşturur, kohort içi bağımlılıkları dikkate alır ve klinik araştırma raporlarına uygun, yorumlanabilir sonuçlar üretir.

Sonuç: Bu açık erişimli uygulama, karmaşık istatistiksel modelleme ile klinik uygulanabilirlik arasındaki boşluğu kapatmaktadır. Hekimlerin, korele sonuçlar üzerinde sağlam meta-analizler yapabilmesini kolaylaştırarak kanıta dayalı uygulamaları ve yerel araştırma girişimlerini desteklemektedir. Araç, özellikle çok alanlı veya çok kohortlu çalışmalarda, sonuçlar arasındaki korelasyonun göz ardı edilemeyecek düzeyde olduğu durumlarda büyük değer taşımaktadır.

Anahtar kelimeler: Meta-analiz, korele sonuçlar, Shiny uygulaması, klinik araştırma, çok değişkenli modeller

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Introduction

Meta-analysis plays an important role in synthesizing evidence across studies, particularly in clinical research where multiple outcomes are often reported within the same cohort. In such settings, traditional univariate meta-analytic approaches may be inappropriate [1], as they typically assume that outcomes are statistically independent. This assumption is frequently violated when correlated outcomes—such as neurodevelopmental domains or imaging markers—are measured within the same study population. Ignoring these dependencies can lead to biased estimates and underestimated uncertainty [2].

To address this issue, advanced multivariate meta-analytic methods have been developed. These methods explicitly account for the correlation structure among outcomes. One such method is multivariate meta-analysis, which allows for the simultaneous synthesis of multiple outcomes across studies, estimating multiple pooled effects while preserving their interrelationships. Another technique, the three-level meta-analytic model [3], accommodates dependencies by modeling the nested structure of effect sizes, where non-independence arises from clustering rather than repeated measurements on the same individuals.

An additional strategy is the two-stage meta-analysis using summary measures, which incorporates robust variance estimation (RVE) [4]. RVE adjusts the standard errors of pooled effects or meta-regression coefficients without needing to model the dependence structure explicitly. Instead, it approximates the correlation between outcomes to estimate between-study variance and derive near-optimal weights.

Building upon these advances, Akkaya Hocagil et al. (2022) proposed a novel hierarchical meta-analysis tailored for cases where each cohort provides multiple, potentially correlated endpoints [5]. They applied this method to data from six longitudinal cohorts that used various cognitive assessments to measure child neurodevelopment. Their model assumes that all endpoints reflect effects of exposure on a shared underlying construct. A major advantage of this approach is its ability to integrate multiple outcomes within cohorts and evaluate whether consistent patterns emerge across cohorts.

Despite these methodological developments, adoption of these methods in clinical setting has been limited due to the requirement of statistical and programming expertise to run such models. Consequently, many clinician-researchers rely on simpler, less suitable methods that may compromise the validity of their results.

To bridge this gap between methodological rigor and clinical usability, we developed a user-friendly, interactive Shiny web application, CORMeta. The application is designed specifically for conducting meta-analyses of correlated outcomes and tailored for researchers working with cohort-based datasets where multiple outcomes are measured per study. The application enables users to upload their own data, define correlation structures, and customize the analysis through an intuitive graphical interface without requiring any programming skills. It provides comprehensive outputs, including forest plots, pooled effect estimates, heterogeneity statistics, and confidence intervals.

In this paper, we introduce the methodological framework underpinning the application, demonstrate its use with a simulated dataset that mimics a real-world dataset on prenatal alcohol exposure and neurodevelopment, and discuss its potential to improve evidence-based practice in clinical settings where accounting for outcome correlation is essential.

Statistical Framework

Multivariate Meta-Analysis of Correlated Outcomes

In many clinical studies, multiple outcomes are reported within the same patient cohort. When these outcomes are synthesized across studies, conventional univariate meta-analytic methods may not be appropriate, as they assume independence among effect sizes. This assumption is violated when outcomes are measured on the same participants, leading to correlated effect estimates and underestimation of standard errors.

To address this issue, we implement a multivariate meta-analytic (MVMA) framework that explicitly models the correlation between multiple outcomes measured within the same study. This approach allows for the simultaneous estimation of multiple effect sizes while accounting for their interdependencies, improving the accuracy and interpretability of pooled estimates.

While traditional multivariate meta-analysis estimates separate pooled effects for each outcome, our framework simplifies to a univariate structure when only one outcome is available per study but retains valid heterogeneity and standard error estimation by incorporating user-specified outcome correlations. This enables flexible modeling of both single and multiple correlated endpoints within cohorts.

The general form of the multivariate model [6] is:

$\hat{\theta}_i \sim N(\theta_i, V_i)$, $\theta_i \sim N(\mu, \Sigma)$

Where:

- $\hat{\theta}_i$ is the vector of observed effect sizes from study i
- V_i is the corresponding within-study variance-covariance matrix
- μ is the overall vector of true effect sizes
- Σ is the between-study variance-covariance matrix capturing heterogeneity and outcome correlations

2.2. Modeling Within-Cohort Correlation Structure

To correctly estimate V_i, the within-study variance-covariance matrix must reflect the correlations between outcomes within each cohort. In our application, users can either:

- Upload a custom correlation matrix that reflects outcome dependencies (e.g., based on domain knowledge, pilot data, or previous validation studies), or
- Allow the application to automatically generate a pooled or cohort-aware dummy correlation matrix from cohorts reporting more than one outcome, under the assumption of a shared correlation structure.

If users do not have access to an empirically derived correlation matrix, they may choose to generate a dummy matrix using a predefined or manually selected value of ρ (residual correlation). This approach is particularly useful when exact correlations are unknown but can be reasonably approximated based on outcome type and measurement context. Suggested default values, informed by prior literature [7,8], include:

- Surrogate endpoints: ρ=0.1users must ensure that stratification does not lead to overfitting
- Psychological test scores: ρ=0.5
- Longitudinal repeated measures: ρ=0.8
- Independent outcomes: ρ=0

This flexibility ensures that outcome dependency is explicitly incorporated into the meta-analytic model, thereby avoiding biased estimates and inflated precision that arise from ignoring within-cohort correlations. However, when only one outcome is provided per study and users select the “Independent” correlation option (ρ = 0), the residual correlation matrix becomes the identity matrix, and the analysis simplifies to a standard univariate meta-analysis [9]. In this scenario, the model behavior is equivalent to conventional random-effects meta-analysis methods (e.g., **rma.uni()** from the **metafor** package [10]), and results (effect size, standard error, τ^2) are interpreted as in traditional meta-analyses.

2.3. Estimation of Effect Sizes and Heterogeneity

Parameter estimation is performed using Restricted Maximum Likelihood (REML), which is robust for estimating between-study variance components in multivariate models. REML jointly estimates the pooled effect sizes (μ) and the between-study covariance matrix (Σ), which includes both heterogeneity (e.g., τ^2) and cross-outcome correlations. To derive study-specific and overall estimates, we employ Best Linear Unbiased Predictions (BLUPs), which improve precision by borrowing strength across correlated outcomes and cohorts. The primary heterogeneity measure reported is τ^2, representing the variance of the true effect sizes across studies, adjusted for outcome correlation.

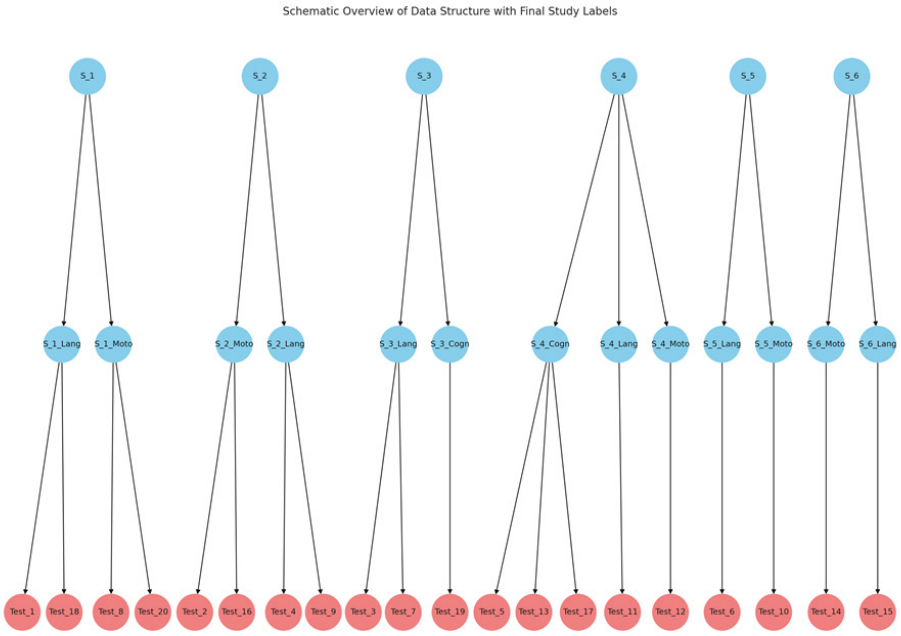


Figure 1. Schematic representation of the multilevel data structure used in CORMeta

Application Architecture and Design

Overview of the Shiny App Framework

The CORMeta application was developed using the Shiny web framework for R, which facilitates the creation of interactive, browser-based tools. Shiny allows reactive programming and dynamic UI rendering, enabling users to upload data, adjust parameters, and view real-time outputs without requiring any programming expertise. This architecture was chosen to maximize accessibility for clinician-researchers who may not have experience with statistical software or coding. The app runs entirely in the browser, either via a hosted web server or locally, and does not require users to install R or other dependencies.

Backend Libraries Used

The core analytical engine of the application builds upon the widely used metafor package in R, which offers flexible modeling of complex random-effects structures, REML estimation, and forest plot visualization. To accommodate correlated outcomes within cohorts, we extended metafor's functionality by incorporating methodology described in Akkaya Hocagil et al. (2022), enabling hierarchical multivariate meta-analysis with user-specified correlation structures [5].

Additional libraries such as 'shinyWidgets', 'DT', and 'ggplot2' are used for enhancing user interface components, data tables, and graphics respectively. These packages enable seamless interaction and customization, even for users unfamiliar with R.

User Workflow and Application Guidance

Clinical studies frequently assess multiple outcomes within the same group of participants. For example, in studies of child neurodevelopment, researchers may evaluate several domains such as language, motor skills, and cognitive function each assessed using multiple standardized tests. These outcomes are inherently correlated, as they are measured on the same individuals and often reflect overlapping constructs.

CORMeta is specifically designed to handle this type of complex, multilevel data structure. The tool assumes and accommodates the following hierarchy:

1. Study Level (e.g., S_1 to S_6): Each study or cohort includes participants assessed under a common study protocol.
2. Domain Level (e.g., Language, Motor, Cognitive): Within each study, outcomes are organized into broader conceptual domains.
3. Test Level (e.g., $Test_1$ to $Test_{20}$): Each doma-

Table 1. Structure of the Summary Dataset Used in the CORMeta application

cohort_new	domain	dependent	age	beta_alcohol	se_beta
Study_1	Language	Test_1	7	-0.011	0.163
Study_1	Language	Test_18	5	0.747	0.144
Study_1	Motor	Test_20	6	0.121	0.271
Study_1	Motor	Test_8	7	0.892	0.284
Study_2	Language	Test_4	5	-1.507	0.199
Study_2	Language	Test_9	5	-0.204	0.299
Study_2	Motor	Test_16	5	-0.318	0.202
Study_2	Motor	Test_2	6	-0.991	0.278
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.	.	.	.	.	.
.	.	.	.	.	.
.	.	.	.	.	.
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in contains specific outcome measures or tests (e.g., vocabulary comprehension for language, reaction time for motor skills).

4. Correlation Structure: Outcome measures within the same domain and study are typically correlated, as they are administered to the same participants and assess related aspects of development. CORMeta explicitly models this correlation structure, leading to more accurate effect estimates and confidence intervals.

To operationalize this hierarchical data structure within the CORMeta application (Figure 1), users follow a structured workflow that mirrors the organization of their dataset. The interface is designed to guide users through each step of the analysis process—beginning with uploading properly formatted data and continuing through model specification, correlation handling, and result interpretation. Below, we outline the key steps for preparing and analyzing your data using the application.

Step 1: Upload Summary Data

Users begin by uploading a .csv file containing study-level summary data (Table 1). The dataset must include the following columns:

- Effect Size Estimates: A column containing regression coefficients or other effect size estimates (e.g., beta_alcohol).
- Standard Errors: A corresponding column with the standard errors of the effect sizes (e.g., se_beta).
- Study Identifier: A column indicating the study or cohort from which each estimate originates (e.g., cohort_new).
- Outcome Label: A column specifying the outcome measure or domain being assessed (e.g., domain or dependent_label_new).

Each row represents a single outcome measured within a study cohort. The dataset includes the study identifier (cohort_new), outcome domain (e.g., language, motor, cognitive), specific test name (de-

pendent), participant age at assessment, estimated effect size (beta_alcohol) for prenatal alcohol exposure, and its associated standard error (se_beta). Multiple outcomes from different domains are often reported within the same cohort, reflecting the hierarchical structure of the data. Once the file is uploaded, the application automatically detects all column names for use in subsequent steps.

Step 2: Specify Column Names

Using the dropdown menus, users select the appropriate column names corresponding to:

- Effect size (Select Effect Size Column)
- Standard error (Select Standard Error Column)
- Study/Cohort ID (Select Study ID Column)

These menus are dynamically populated based on the uploaded dataset, reducing the risk of typos and promoting flexibility across datasets with varying column names.

Step 3: Upload or Generate Correlation Matrix

If available, users can upload a pre-computed residual correlation matrix (e.g., derived from model residuals). Alternatively, the user can generate a study-aware dummy correlation matrix using a predefined or manually selected value of ρ (residual correlation), based on common scenarios [7,8] such as:

- Surrogate endpoints (ρ = 0.1)
- Psychological test scores (ρ = 0.5)
- Longitudinal repeated measures (ρ = 0.8)
- Independent outcomes (ρ = 0)

After selecting an appropriate correlation profile, clicking the "Generate Dummy Correlation Matrix" button creates a block-diagonal matrix that assumes constant residual correlations within each cohort and independence between cohorts. This matrix can be previewed and downloaded for verification or further refinement. The flexibility to specify or simulate within-study correlations ensures that the meta-analytic model appropriately accounts for outcome dependency, avoiding biases and overconfident inferences that arise when correlations are ignored.

Step 4: Optional Subgroup Analysis

Users may optionally perform subgroup analyses by selecting a variable from the *Subgroup Analysis By* dropdown menu. Based on the chosen variable type, the application dynamically displays appropriate filtering controls—such as a range slider for continuous variables or a checkbox selector for categorical variables—allowing users to restrict the analysis to a specific subset of the data.

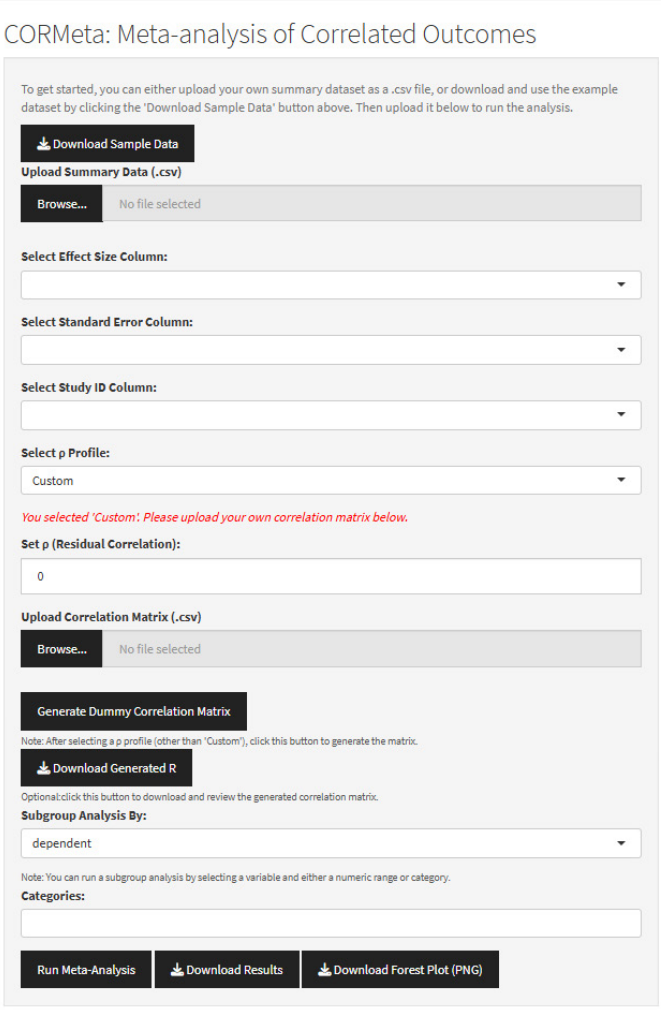


Figure 2. Screenshot of the CORMeta user interface during Step 2.

Users assign column roles using dropdown menus that are automatically populated based on the uploaded dataset. This design minimizes user error and allows flexibility in handling datasets with diverse naming conventions.

Step 5: Run Meta-Analysis

After defining the inputs, the user initiates the me-

ta-analysis by clicking Run Meta-Analysis. The app executes the modified multivariate meta-analytic model, accounting for the correlation structure and study identifiers as described in Section 3.

Step 6: Review and Download Results

Upon completion, the application displays:

- A forest plot summarizing the pooled effect
- A data table of the included studies and parameters
- A printed summary of key statistics, including:
- Pooled estimate ($\hat{\mu}$)
- Standard error (SE)
- Between-study variance (τ^2)
- P-value

Results can be exported as an Excel workbook containing both the input data and the statistical summary using the Download Results button. Users can also download the forest plot as png file.

Demonstration: Case Example

Description of Demonstration Dataset

To demonstrate the functionality of the application, we generated a simulated dataset that mimics real-world cohort studies examining the association between prenatal alcohol exposure and neurodevelopmental outcomes in children. The simulated data reflect the typical structure of such studies, including:

Multiple correlated neurodevelopmental outcomes (e.g., cognitive, motor, language),

Binary exposure variable (prenatal alcohol exposure: exposed vs. unexposed),

Several cohorts contributing data, each with unique sample sizes and measurement variability,

A shared latent structure where all outcomes reflect an underlying neurodevelopmental construct influenced by exposure.

Analytical Setup

Users selected three neurodevelopmental outcomes—cognitive, motor, language domains—for analysis. For each cohort, effect estimates and associated standard errors were derived from regression models examining the association between prenatal alcohol exposure and each outcome given all potential confounders. These estimates reflect adjusted regression coefficients (e.g., from linear models), accounting for relevant covariates within each study. Because multiple outcomes were measured on the same individuals within each cohort, the estimates are likely correlated. To account for this within-study correlation structure, users can specify or upload a correlation matrix, enabling multivariate meta-analysis that appropriately pools effects across outcomes and cohorts.

Interpretation of Output

The application generated pooled effect size estimates for each outcome, along with 95% confidence intervals and τ^2 heterogeneity statistics. The forest plot provided a clear visual summary of the effect sizes, illustrating both individual study estimates and the overall pooled estimate for each outcome. The results revealed moderate negative associations between prenatal alcohol exposure and all three outcomes, with the largest effect observed in expressive language. Heterogeneity was moderate across outcomes, indicating variation in effect sizes that was partially explained by cohort-level differences.

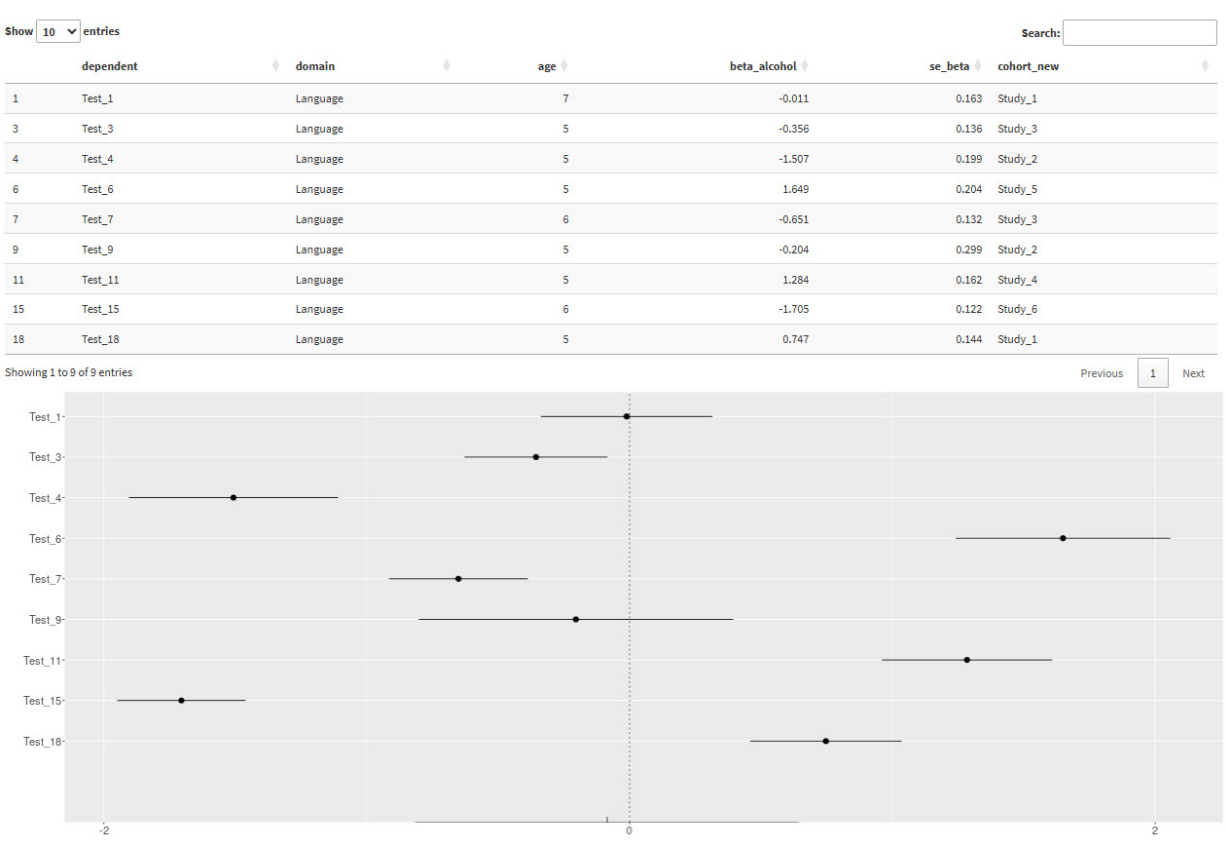
Example Forest Plot and Heterogeneity Results

Each dot represents the estimated regression coefficient for the association between prenatal alcohol exposure and a specific neurodevelopmental test (e.g., Test_1, Test_3, Test_4, etc.). Horizontal lines denote the 95% confidence intervals, while the vertical dashed line at zero represents the **null** hypothesis of no effect.

Most of the CIs span the null value, suggesting that the estimated associations are not statistically significant at the 0.05 level. Notably, no test shows a confidence interval that is clearly separated from zero, indicating limited evidence of a consistent effect of prenatal alcohol exposure across the evaluated outcomes (Figure 3).

The pooled estimate of the effect was:

- Mean estimate **($\hat{\mu}$):** −0.086
- Standard error (SE): 0.364




```
$mu_hat
            [,1]
[1,] -0.08580883

$se
          [,1]
[1,] 0.3648488

$tau2
[1] 1.154688

$pvalue
          [,1]
[1,] 0.8199697
```

Figure 3. Forest plot and summary statistics generated by the CORMeta application.
In Figure 3, the upper panel shows the study-level data table and resulting forest plot for 10 language domain outcomes across multiple cohorts. Each point represents the estimated effect of prenatal alcohol exposure on the respective test, with horizontal lines denoting 95% confidence intervals. The lower panel presents the pooled effect size estimate ($\hat{\mu}$), standard error (SE), between-study variance (τ^2), and p-value derived from the multivariate meta-analytic model.

- Between-study variance **(τ^2):** 1.15
- P-value: 0.820

These findings indicate substantial heterogeneity across outcomes, reflected in the large τ^2 value and variable CI widths. The results highlight the value of using a multivariate meta-analytic approach that accounts for correlations among outcomes and between-study variability. Despite the nonsignificant overall effect, this approach provides more efficient and nuanced insight than a series of univariate models.

Discussion

This paper presents a web-based application, CORMeta, designed to perform multivariate me-

ta-analyses of correlated outcomes, addressing a critical gap in usability for clinician-researchers. While multivariate models are well established in statistical literature, their adoption in clinical research has been limited by accessibility barriers, particularly the requirement for programming expertise and manual data formatting. By integrating these models into a Shiny interface, we allow users to use advanced meta-analytic methods and we promote default values, informed by prior literature methodological rigor in evidence synthesis.

The primary innovation lies in the application's ability to handle outcome correlations that arise when multiple endpoints are measured within the same study population. Failure to account for these correlations can lead to underestimated standard errors, inflated precision, and potentially misleading inferences [11, 12]. Our framework addresses this by allowing users to input custom correlation matrices or apply empirically derived default structures, enabling flexibility while preserving statistical validity.

The demonstration using neurodevelopmental outcomes following prenatal alcohol exposure illustrates how outcome domains with known correlation (e.g., language and cognition) can be simultaneously modeled, yielding pooled estimates that better reflect underlying study heterogeneity. This is especially relevant in pediatrics, neurology, and psychiatry, where multidimensional assessments are standard practice.

Despite its strengths, the application has limitations. It currently supports only continuous outcomes and assumes homogeneity of correlation structures across studies when automatic estimation is used. Additionally, while subgroup analysis is supported, users should be cautious of overfitting or sparsity when performing subgroup analyses. Future updates may incorporate Bayesian estimation, imputation of missing data, and support for binary or time-to-event outcomes to expand functionality.

Conclusion

We developed and validated an open-access, clinician-friendly Shiny application that enables multivariate meta-analyses of correlated outcomes. By removing the need for programming knowledge and providing real-time visualization and customization, the app supports clinician-researchers in conducting more accurate and transparent evidence syntheses. This tool is particularly valuable in multi-domain or multi-cohort studies where statistical dependencies among outcomes are non-negligible. We encourage the research community to adopt, adapt, and contribute to the tool as part of broader efforts to enhance methodological accessibility in clinical research.

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