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SUPPLEMENTARY MATERIAL **OPEN ACCESS**

Synthesis Methods for Meta-Analysis: A Scoping Review

Rabeya Illyas Noon[1,2], Michelle M. Hospital[1,2,3] and Nan Hu[1,2,*]

[1]*Department of Biostatistics, Robert Stempel College of Public Health & Social Work, Florida International University, Florida, United States of America*
[2]*Research Centers in Minority Institutions (RCMI), Florida International University, Florida, United States of America*
[3]*Community-Based Research Institute (CBRI), Florida International University, Florida, United States of America*

*Address correspondence to this author at the Department of Biostatistics, Robert Stempel College of Public Health & Social Work, Florida International University, Florida and Research Centers in Minority Institutions (RCMI), Florida International University, Florida, United States of America; E-mail: nhu@fiu.edu

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PRISMA 2009 Checklist

Section/topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page No 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page No 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page No 2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page No 2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (*e.g.*, Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (*e.g.*, PICOS, length of follow-up) and report characteristics (*e.g.*, years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page No 2

Section/topic	#	Checklist Item	Reported on Page #
Information sources	7	Describe all information sources (*e.g.*, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page No 2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	NA
Study selection	9	State the process for selecting studies (*i.e.*, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page No 2
Data collection process	10	Describe method of data extraction from reports (*e.g.*, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	NA
Data items	11	List and define all variables for which data were sought (*e.g.*, PICOS, funding sources) and any assumptions and simplifications made.	NA
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (*e.g.*, risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (*e.g.*, I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (*e.g.*, publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (*e.g.*, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page No.2-3 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (*e.g.*, study size, PICOS, follow-up period) and provide the citations.	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (*e.g.*, sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (*e.g.*, healthcare providers, users, and policy makers).	Page No. 4
Limitations	25	Discuss limitations at study and outcome level (*e.g.*, risk of bias), and at review-level (*e.g.*, incomplete retrieval of identified research, reporting bias).	Page No. 4
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page No. 4
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (*e.g.*, supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
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Table S1. Overview of available methods for methodological synthesis analysis.

S.No.	Year	Author	Title	Source	Goal	Design and Setting	Method	Conclusion	Findings (quantified)/Summary
01	2005	Samsa, Hu, Root	Combining Information from Multiple Data Sources to Create Multivariable Risk Models	Journal of Biomedicine and Biotechnology	To develop a method for combining univariate risk estimates from different studies into a multivariable risk model	Simulation-based study using synthetic data and epidemiological examples	Univariable synthesis method using regression coefficients, standard deviations, and correlations from multiple datasets	The method is robust for predicting outcomes but less so for estimating regression coefficients.	Predicted values from synthesized models closely match those from gold-standard datasets
02	2009	Xiao-Hua Zhou, Nan Hu, Guizhou Hu, and Martin Root	Synthesis analysis of regression models with a continuous outcome	Stat Med	To propose a new synthesis method for multivariate regression with a continuous outcome that improves on the existing SHR method by eliminating the normality assumption, reducing bias, and allowing for variance estimation.	The paper describes the new method, reports a simulation study comparing it to the existing SHR method, and illustrates its use with a real-life example from the 1999-2000 National Health and Nutritional Examination Survey.	The new method involves estimating synthesized parameters by solving a system of linear equations derived from conditional expectations. It also provides a method for variance estimation using the delta method. Inputs include univariate relations of each predictor (X) with the outcome (Y) and two-way correlations between Xs.	The proposed new synthesis method improves on the existing SHR method by eliminating the normality assumption, reducing bias, and allowing for variance estimation of parameters for continuous outcomes.	Simulation studies showed the new method generally had better mean bias and MSE for regression parameters than the SHR method, especially with skewed distributions. For predicted values, correlations were similar, but the new method had smaller mean bias and MSE. The real-world example showed the new method produced coefficient estimates comparable to the gold standard.
03	2010	Bagos, Liakopoulos	A Multipoint Method for Meta-Analysis of Genetic Association Studies	Genetic Epidemiology	To develop a multivariate meta-analysis method for genetic association studies using multiple linked polymorphisms	Meta-analysis of published genetic studies using summary data and linkage disequilibrium (LD) estimates	Extension of multivariate meta-analysis incorporating LD to compute within-study covariances	The method improves power and accuracy, especially when studies report overlapping polymorphisms.	Allows borrowing strength across studies and identifies causal variants more effectively

(Table S1) contd.....

S.No.	Year	Author	Title	Source	Goal	Design and Setting	Method	Conclusion	Findings (quantified)/Summary
04	2012	Bagos	On the Covariance of Two Correlated Log-Odds Ratios	Statistics in Medicine	To derive a general method for calculating the covariance of two correlated log-odds ratios using summary data	Theoretical framework with applications to epidemiological and genetic studies	Theoretical framework with applications to epidemiological and genetic studies	The method is simple, general, and applicable to various study designs using only published data	Enables accurate pooling of correlated estimates in meta-analysis without access to raw data
05	2014	Elisa Sheng, Xiao Hua Zhou, Hua Chen, Guizhou Hu, and Ashlee Duncan	A new synthesis analysis method for building logistic regression prediction models	Statistics in Medicine	To propose a new synthesis analysis method specific to binary outcomes (logistic regression) that can estimate coefficients of a comprehensive multivariate model and is theoretically justified.	The paper proposes a method based on the relationship between incomplete and complete logistic regression coefficients under the assumption of multivariate normality of the underlying data. It includes a simulation study comparing the new method to Hu and Root's method and a real population dataset example (NHANES 2007).	**Three-Step Method:** 1. Estimate subpopulation means (μ0,μ1) using coefficients from incomplete univariate logistic models and a risk factor dataset. 2. Estimate the common covariance matrix (Σ) using the risk factor dataset's covariance matrix and estimated subpopulation means. 3. Estimate complete logit model coefficients by plugging estimates into Efron's (1975) formulas, assuming underlying multivariate normality of predictors conditional on outcome.	The proposed synthesis analysis method for logistic regression is statistically justified under multivariate normality and can estimate multivariate model coefficients, unlike Hu and Root's method. While Hu and Root's method showed better predictive performance in simulations with non-normal data, the new method's ability to provide coefficient estimates is an advantage.	Simulation studies showed the Hu and Root method performed comparably or better than the new method in terms of predicted probabilities across normal, lognormal, and uniform distributions. The new method's performance improved with increased sample size, especially for normally distributed data. In the real data example, the new method's synthesized coefficients were generally closer to the multivariate model coefficients than univariate coefficients.

Table S2. Overview of available statistical applications for synthesis analysis.

S.No.	Year	Author	Title	Source	Goal	Design and Setting	Method	Conclusion	Findings (quantified)/Summary
01	2011	Jackson, Riley, White	Multivariate meta-analysis: Potential and promise	Statistics in Medicine	To evaluate the benefits and limitations of multivariate meta-analysis compared to univariate methods	Review and application across four example datasets	Multivariate random effects model with REML, ML, and method of moments estimation	Multivariate meta-analysis can improve precision and handle correlated outcomes but requires careful application	Offers better statistical properties and borrowing strength, but demands more assumptions and data completeness
02	2013	Liansheng Larry Tang, Michael Caudy, and Faye Taxman	A Statistical Method for Synthesizing Meta-Analyses	Computational and Mathematical Methods in Medicine	To introduce a method to synthesize meta-analytic results when multiple meta-analyses use the same type of summary effect estimates and propose a two-step frequentist procedure for when different types of effect sizes are used.	The paper introduces methods for synthesizing meta-analyses with the same or different types of summary statistics (standardized mean differences, odds ratios, correlation coefficients) using fixed-effects and random-effects models. It illustrates the methods with two examples.	**Same Effect Size:** Weighted average of summary effect sizes, with weights being the inverse of variances. **Different Effect Sizes (Two-Step):** 1. Convert statistics (log-transformed OR, correlation coefficient) to a common metric (sample mean difference). 2. Combine using a weighted average in a REM or FEM. The method aims to yield the same overall effect size as meta-analyzing all individual studies.	The proposed methods offer two ways to synthesize multiple meta-analyses, providing the same overall effect size as a full meta-analysis of all individual studies when effect sizes are the same, and a robust approach when effect sizes differ. The technique is useful when multiple meta-analyses on the same topic exist, especially with conflicting results or for updating prior syntheses.	**Fixed-Effects Model (Same Effect Size):** Synthesizing meta-analyses is equivalent to meta-analyzing all individual studies. **Random-Effects Model (Same Effect Size):** Synthesizing meta-analyses can yield slightly different results from combining all individual studies due to different estimates of between-study variance (τ^2). **Different Effect Sizes:** The proposed two-step procedure allows for combining meta-analyses with different effect size metrics. Illustrated with examples showing the method's utility.
03	2014	Hu, Root, Duncan	Adding multiple risk factors improves Framingham coronary heart disease risk scores	Vascular Health and Risk management	To improve CHD risk prediction beyond the Framingham Risk Score (FRS) by integrating additional risk factors	Comparative analysis using NHANES III and ARIC cohort data	Synthesis analysis combining FRS with six additional risk factors	NEW-CHD model outperforms FRSv1 and FRSv2 in discrimination, calibration, and reclassification	NEW-CHD model significantly improves CHD risk prediction, comparable to adding HDL to FRS

(Table S2) contd.....

S.No.	Year	Author	Title	Source	Goal	Design and Setting	Method	Conclusion	Findings (quantified)/Summary
04	2017	Zhou, Wang, Duncan, Hu, Zheng	Statistical evaluation of adding multiple risk factors improves Framingham stroke risk score	BMC Medical Research Methodology	To enhance stroke risk prediction by integrating additional risk factors into the Framingham Stroke Risk Score (FSRS)	Validation using ARIC cohort data	Synthesis analysis combining FSRS with seven literature-derived risk factors	NEW-STROKE model outperforms FSRS in discrimination, calibration, and reclassification	All seven added risk factors significantly contribute to stroke risk prediction
05	2005	Guizhou Hu, Martin M. Root	Building prediction models for coronary heart disease by synthesizing multiple longitudinal research findings	European Journal of Cardiovascular Prevention and Rehabilitation	To introduce and validate a new method called Synthesis Analysis — a multivariate meta-analytic technique — for developing comprehensive disease prediction models, particularly for coronary heart disease (CHD), by combining data from multiple longitudinal studies.	Design: Development and validation of statistical prediction models. Setting: Secondary analysis using public datasets and literature-based risk factor associations. Empirical models developed using: Framingham Heart Study NHANES I Epidemiologic Follow-up Study Cross-sectional correlations derived from: NHANES III	Uses univariate regression coefficients from various longitudinal studies. Uses correlation matrices from cross-sectional data. Builds logistic regression models step-by-step, adding risk factors iteratively. Two analyses were conducted: Comparison within one dataset (Framingham): Synthesis *vs.* logistic regression. Model validation across datasets: Base model (from Framingham) *vs.* synthesized model (applied to NHANES I).	It allows for integration of emerging risk factors into existing models, thus improving predictive power. Though slightly approximate compared to full regression, it offers greater flexibility and external validity.	When using the same data and variables, Synthesis Analysis approximated logistic regression with only minor loss in AUC (about 0.001). When additional risk factors (*e.g.*, diabetes, smoking, BMI, albumin, leukocyte count) were added using literature, the synthesized model: Significantly improved predictive power over the base model ($\chi^2 = 43.8$, $p < 0.00001$). AUC improved from 0.802 to 0.812 (not statistically significant but directionally better). Sensitivity increased from 55% to 58% ($p = 0.005$), with specificity unchanged at 82%. The model is robust, even when input risk factor estimates slightly differ from the test population