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Invited Review Article

Recent Research Trends in Meta-analysis

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SUMMARY

The use of meta-analysis (MA), which is placed on top of the evidence hierarchy, in studies has been increasing exponentially. MA has three effect size families. Using the category of effect size families, this paper introduces the important points in the MA process and highlights the recent research trends in this field, such as network MA, meta-analytic structural equation modeling, and diagnostic test accuracy MA. Several reporting standards were established for primary studies and MA. The critical assessment reviews demonstrated that the current quality of nursing MA reporting was low. The problematic areas of the current nursing MA include study search, study selection, risk of bias, publication bias, and additional analysis based on quality assessment. Directions for future research are also presented in this paper.

Introduction

The use of meta-analysis in studies has been increasing exponentially since the end of the 1970s. The rapid development of meta-analysis (MA) is also related to the increasing use of evidence-based practice approaches. To date, people are overwhelmed by the flood of information available, but these data vary in terms of directionality and quantity. For example, different studies show contradictory and varying effects of vitamin C on human health. Furthermore, most nurses and nursing researchers are not aware of every research finding. Therefore, MA is a valid method of finding evidences so that clinicians and researchers can have a theoretical basis in solving health-related issues.

MA refers to the statistical analysis of the synthesis of the quantitative studies' result. Additionally, MA is different from narrative review, vote counting, and other research review methods because it provides information on the directionality and magnitude of research findings. Effect size is the key concept in MA and an essential part of quantitative research reporting and other quantitative hypothesis testing [1]. Moreover, effect size is a quantitative index of research findings and is considered to be the dependent variable in the MA process, in contrast to the study characteristic, which is the independent variable.

The effect size is composed of three families, namely, d, r, and odds ratio (OR), and is related to research design in the primary studies. In the experimental design, d- and OR families are adequate indices for hypothesis testing and result interpretation, whereas correlation is a good index for the measure of association and relationship between variables. The nursing research MA can be categorized into three groups based on the effect size and research design (intervention, measure-of-association, and diagnostic test accuracy meta-analyses [DTA MA]) and into two groups based on the research characteristics (intervention and measure-of-association meta-analyses). Evans and Pearson explained the challenges encountered in nursing systematic review (SR) and MA [2]. The nursing MA mainly focuses on the effectiveness of intervention. However, appropriateness and feasibility are also important issues in health intervention. Randomized controlled trials (RCTs) only provide a portion of important evidences; therefore, nursing MA should answer other vital questions to gather all valid and relevant evidences together. The aforementioned three categories can be used to adequately examine the research trends in nursing MA. This paper will introduce the recent research trends and important issues on nursing MA based on these categories, as shown in Table 1.

Intervention effect MA: Direct comparison MA vs. network MA

Among the effect size families, intervention effect MA is the most closely related to mean difference and dichotomous outcome effect sizes. Thus, the Cochrane intervention handbook mainly deals with OR, risk ratio, and risk difference of the RCT research designs, in addition to the mean difference, without considering the measure-of-association studies. In 1976, Glass coined the term

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Table 1 *Effect Size Family and Meta-analysis Development Trends.*

Category	Effect size	Study design	Recent development
Intervention meta-analysis	D family	Unmatched groups, post-data only One group, pre–post Unmatched group, pre–post	Indirect comparison, MTC, network meta-analysis (transitivity, consistency)
	OR family	Unmatched groups, prospective Matched groups, prospective Unmatched groups, retrospective	
Measure-of-association meta-analysis	R	Correlation, regression, path analysis, SEM, HLM	Meta-analytic PA, CFA, SEM, HLM
Diagnostic test accuracy meta-analysis	Sensitivity Specificity	Test accuracy research	Bivariate and HSROC approach

MA to refer to the synthesis of the results of psychotherapy studies. The mean difference and OR between the experimental and control groups are the two families of effect size. The standardized mean difference (SMD) is used to represent the continuous variables, whereas the OR is utilized to indicate the dichotomous and categorical research results.

The research designs in experimental studies can be categorized into three groups based on the mean difference: unmatched-group post-data-only, unmatched-group pre–post data (standardized mean change difference effect size), and one-group pre–post data and matched-group designs. The unmatched-group post-data-only design is similar to the independent t-test. On the contrary, the one-group pre–post data design is closely related to the dependent t-test, whereas the unmatched-group pre–post data design is associated with the mean change difference effect size [3]. If a researcher uses the mean difference effect size, then one effect size as a main measure of MA should be chosen because synthesizing different research designs into one MA has its own pros and cons.

Researchers can choose one of the study designs for the problem formulation stages or inclusion criteria. Borenstein et al. suggest that the synthesis of different research designs has no technical barriers [4]. Therefore, three different research designs can be synthesized together in nursing research MA [5]. Furthermore, no technical barriers might be in the synthesis of dependent and independent t-test results together, but some arguments in the educational settings might be present. Hedges' g is applicable only in the correction of small sample bias, and a meta-analyst can use Hedges' g, instead of Cohen's d, in the three mean difference study designs.

Some information could be missing, such as correlation, in the one-group pre–post data and unmatched-group pre–post data effect size calculation. The problem is that almost every study will not report the correlation between pretest and posttest measures, because it is not considered to be a reporting value in regular studies. However, meta-analysts cannot calculate effect size without this information, which has to be imputed in some way [6].

The OR families are the most widely used study designs in the medical research areas. For dichotomous outcome, researchers can choose one of the OR, risk ratio, and risk difference based on the index stability and substantive meaning. OR and risk difference are the most frequently used and substantive indexes, respectively, in medical research. Similar to the mean difference, the OR families are composed of three research designs: unmatched group, prospective (controlled trials, cohort studies); matched groups, prospective (crossover trials, pre–post data designs); and unmatched group, retrospective (case–control studies). Researchers can choose one study design for the inclusion criteria or three studies simultaneously to analyze three research designs together. Generally, RCTs and non-RCTs are usually analyzed separately in medical research. However, researchers can synthesize these studies together to determine side effects or answer other important research questions. Medical researchers are increasingly paying attention to network MA because the use of direct comparison has several limitations, such as insufficient availability of direct comparison research and discrepancies in the comparison of more than three interventions together. Nowadays, MA and network MA are on top of the evidence hierarchy [7]. Network MA requires special assumption and analysis methods, such as heterogeneity, transitivity, and consistencies. Furthermore, it is also applicable to social science research fields [8]. Additionally, network MA can be used to provide valuable information to patients, practitioners, and decision makers.

Measure-of-association MA: Correlation MA vs. meta-analytic structural equation modeling (SEM) approach

Measures of association are utilized in the studies of psychological issue and relationship between health clinicians and patients. The correlation in the measure-of-association analysis is highly similar to SMD in the intervention effect MA. Additionally, covariance has similar concepts to unstandardized mean difference. A correlation is considered to be a standardized covariance, and is defined as a direct measure of relationship between two variables. Furthermore, correlation can also be extended to simple and multiple regression, path and confirmatory factor analyses, and structural equation and hierarchical linear modeling. Therefore, primary studies using these methods are directly related to measure-of-association meta-analyses. Fisher's z-transformation is used, instead of correlation, when conducting measure-of-association MA. This method is very similar to log OR in dichotomous outcomes because of the data distributional assumption. The signs of the correlation coefficients are another factor that should be considered by researchers when synthesizing correlations between two constructs. Some researchers synthesize positive and negative relationships separately, whereas others synthesize these relationships together through careful consideration of the direction of relationships between variables [9,10]. Additionally, researchers should also consider the unidimensionality of the main outcome variable when conducting measure-of-association MA. For example, if a researcher wants to analyze the relationship between depression and other psychological variables as the main outcome variable, then only depression should be used as the main dependent variable, and depression and anxiety should not be synthesized as dependent variables together because of the presence of variabilities between them. If a researcher uses these two constructs simultaneously, then we cannot explicitly distinguish the relationship between depression and the other variable. The most important factor to consider when performing measure-of-association MA is the theoretical model. The measure-of-association MA is different from RCT and intervention effect studies. Researchers want to explain the relationship of variables based on theoretical or research model. Without a theoretical model, categorizing related variables and explaining the result of relationship adequately would be very difficult, similar to

conducting SEM research. In the SEM research, the theoretical model is the basis of the research model, which is one of the many equivalent and alternative models. Without a theoretical model, SEM researchers cannot conduct, interpret, and discuss the research results theoretically and logically. This rationale is also applicable for measure-of-association MA. Therefore, researchers and reviewers should focus on the dependent variable in the measure-of-association MA. In contrast, the independent variable is more important than the dependent variable in the intervention effect MA. As randomization is the key concept in the intervention MA, so is the theoretical model in the measure-of-association MA. Becker proposed a model-based MA [11], Viswesvaran established a meta-analytic path model, and Cheung developed meta-analytic SEM [12,13]. Behavioral and psychological researchers are increasingly paying attention to meta-analytic SEM approach because the use of correlation has several limitations, such as insufficient availability of indirect relationship research and discrepancies in the association of more than three variables together.

Diagnostic test accuracy (DTA) meta-analysis

DTA MA is another developing field of MA. Table 2 presents the difference between intervention MA and DTA MA. In terms of problem formulation, population, intervention, comparison, and outcome (PICO) and patient, presentation, prior tests, index test, comparator test, purpose, target condition, and reference standard (PPP IC PTR) are the key items in intervention MA and DTA MA, respectively. Intervention MA mainly searches for RCT and uses filters, such as Medical Subject Heading terms, but DTA MA does not use filters and has various study designs. These MA have two effect sizes: specificity and sensitivity. The threshold effect is crucial because sensitivity and specificity depend on cutoff scores. The random effect model approach is not an option but a basic approach in DTA MA because of the threshold effect. Furthermore, in DTA MA, the use of the Moses–Littenberg analysis approach in RevMan has some limitations when dealing with the threshold effect well, so bivariate and hierarchical summary receiver operating characteristic (HSROC) approaches using Stata or R software program are recommended.

DTA MA is not only applicable to medical research areas, similar to network MA, but also to social science research fields. For example, Kilgus et al. conducted a curriculum-based measurement DTA MA to measure the test accuracy between oral reading and high-stake testing in a reading achievement test [14]. The Cochrane Handbook for Diagnostic Test Accuracy Review is currently being developed. Additionally, RevMan 5 has an analysis function for DTA MA, in addition to that for intervention MA. However, RevMan 5 has some limitations when conducting more advanced approaches for DTA MA, such as bivariate and HSROC, which require other software, for example, STATA or R program.

Table 2 *Comparison between Intervention MA and DTA MA.*

Category	Intervention MA	DTA MA
Problem formulation	PICO	PPP IC PTR
Searching	Filters may be used Searches for RCTs and CCTs	No filters, Various study designs
Risk of bias	Few key items (blinding, randomization, follow-up)	Quality: many items, variation also important
Effect size	Risk ratio Odds ratio Risk difference Single outcome	Odds ratio, depending on the cutoff scores (threshold effect) Pairs of outcome (sensitivity vs. specificity)
Analysis	Fixed or random Subgroup analysis Meta-regression	Always random, threshold effect Moses–Littenberg analysis Bivariate and HSROC approaches

Abbreviations: CCTs, controlled clinical trials; HSROC, hierarchical summary receiver operating characteristic; MA, meta-analysis; RCTs, randomized clinical trials; PICO, population, intervention, comparison, and outcome; PPP IC PTR, patient, presentation, prior tests, index test, comparator test, purpose, target condition, and reference standard.

Reporting standard and evaluation of nursing MA qualities

Compared with the social science research fields, primary studies and MA have numerous reporting standards in the medical research. The reason for which may be attributed to the main research design. In medical research, randomization is the most important factor in the experimental research design. Thus, internal validity is the main issue, and primary study should report well the process of the experiment. However, randomization is not easy to perform in social science research areas, so these fields mainly use theoretical model and relationship research. For example, Zeng et al. surveyed the methodological quality assessment tools for primary clinical studies, SR, and MA [15].

RCT and nonrandomized studies are the main categories in primary research, as shown in Table 3. Consolidated Standards of Reporting Trial statement and risk of bias tool is used for RCTs, whereas Strengthening the Reporting of Observational Studies in Epidemiology statement and Newcastle–Ottawa scale is utilized for observational studies. On the contrary, the reporting standard for primary diagnostic accuracy study is the Standards for Reporting Diagnostic Accuracy statement. Network MA usually deal with RCT studies, so its reporting standard is similar to that for RCT primary studies. Some meta-analysis reporting standards (MARS) were established based on the research designs in the early 1990s [16]. The reporting standards for RCT MA are Assessing the Methodological Quality of Systematic Reviews (AMSTAR) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [17,18], whereas those for the MA of observational studies includes Meta-Analysis of Observational Studies in Epidemiology (MOOSE). The MARS for medical research were developed starting in the 1990s. In 2008, the American Psychological Association (APA) MARS was established based on previous medical reporting standards [1]. Network MA was developed for multiple and indirect RCT intervention MA, and the PRISMA statement has only been recently utilized for network MA [19]. The primary diagnostic studies can be evaluated to include DTA MA using Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-1 or QUADAS-2. Moreover, DTA MA should be conducted and reported

Table 3 *Reporting Standard for Primary Study and Meta-analysis.*

Category	Primary study	Meta-analysis
RCT	CONSORT statement Risk of bias	AMSTAR 2007, PRISMA 2009
Observational studies	STROBE statement Newcastle–Ottawa scale	MOOSE 2000, APA 2008
Diagnostic meta-analysis	STARD statement QUADAS 1/QUADAS 2	DTA reporting standard (under development) BMC guideline
Network meta-analysis		PRISMA extension 2015

Abbreviations: AMSTAR, Assessing the Methodological Quality of Systematic Reviews; BMC, BioMed Central; CONSORT, Consolidated Standards of Reporting Trial; DTA, diagnostic test accuracy; MOOSE, Meta-Analysis of Observational Studies in Epidemiology; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; STARD, Standards for Reporting Diagnostic Accuracy; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; QUADAS, Quality Assessment of Diagnostic Accuracy Studies.

Table 4 *Critical Evaluation of the Quality of Nursing MA.*

Author (yr)	Country	Major/no. of journal	Standard/no. of paper	Median/mean	Overall evaluation
Tam et al. (2017)	Asia, Europe, America	Nursing/107 journals in 2014	PRISMA/37 SR, 37 MA	Median rate: 64.9% (17.6–92.3), 73.0% (59.5–94.6) 27 items	Low adherence of SRs in nursing journals to PRISMA
Yang et al. (2017)	China	TCMN/	PRISMA and AMSTAR/73 SR, 2005–2015	PRISMA mean: 63.2% AMSTAR mean: 45.9%	Study search, study selection, risk of bias, publication bias
Jin et al. (2016)	China	TCMN/20 MA or SR	AMSTAR and GRADE	4.5–8	Risk of bias, inconsistency
Song et al. (2015)	Korea	Cancer, pain management	AMSTAR/17 SR or MA	Mean: 5.47	Characteristics of included studies, publication bias, quality assessment
Jin et al. (2014)	China	Nursing/63 SR or MA	PRISMA and AMSTAR	PRISMA mean:75% AMSTAR mean: 63.6%	Literature search, heterogeneity issue, publication bias
Kim & Kim (2013)	Korea	Nursing/42 SR or MA	AMSTAR	Mean: 5.61	Publication bias, quality, synthesis
Seo & Kim (2012)	Korea	Nursing intervention/1950–2010	AMSTAR/22 SR or MA	Median: 5 (2–11) Mean: 4.7 (3.8–5.7)	Literature search, publication bias, risk of bias

Abbreviations: AMSTAR, Assessing the Methodological Quality of Systematic Reviews; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MA, meta-analysis; SRs, systematic reviews; TCMN, Traditional Chinese Medicine Nursing.

in accordance with the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy and didactic guidelines [20].

As previously mentioned, MA is on top of the evidence hierarchy, but the critical evaluations of previous MA commonly indicated that their quality was very low. Most clinicians and nurses are so busy, so they cannot follow the findings of every study. Therefore, the results of MA are a good source of theoretical basis in the implementation evidence-based practice (EBP). Table 4 shows several reviews related to the critical evaluation of the quality of nursing MA. Seven studies were directly related to the quality evaluation of nursing MA, which mainly used PRISMA and AMSTAR as reporting standards [21–27]. Four authors were from China, and three authors were from Korea.

The evaluation results revealed that most nursing MA have almost similar quality levels, ranging from low to moderate. For healthcare intervention decision making, the reporting standards should be followed more carefully to achieve high-quality nursing MA. Four studies only used AMSTAR, one study only utilized PRISMA, and two studies combined PRISMA and AMSTAR as reporting standards. PRISMA and AMSTAR are composed of 27 and 11 items, respectively. The critical evaluation of AMSTAR showed that the mean or median score is 4–6 points, and that of PRISMA revealed that the mean or median rate of accordance was 56.5%–75%. These weak points were mainly related to study search, study selection, quality assessment or risk of bias, publication bias, and additional analysis. Although these studies are not entire population of the critical evaluations for nursing MA, they can satisfactorily show the big picture of the present research status. These evaluations are directly related to intervention MA, so AMSTAR and PRISMA are utilized as reporting standards. As stated by Evans and Pearson, RCT cannot cover all important healthcare issues without observational, correlational, and test accuracy studies [2].

Directions for future research

Several issues need to be studied further for better implementation of EBP.

First, intervention MA usually utilized direct comparison, but several possible interventions should be considered in healthcare decision-making. Network MA includes indirect and mixed comparisons and is the new approach for intervention MA. Therefore, nursing intervention MA can be extended to network MA.

Second, measure-of-association MA is another important field of nursing MA. Similar to intervention MA, the present measure-of-association MA is mainly used to evaluate direct relationship, such as correlation, between two constructs. However, several relationships need to be considered in the clinical setting, such as those among patient, nurse, doctors, and other healthcare decision makers. Indirect relationship should be considered, as well. The meta-analytic path model, confirmatory factor analysis, and meta-analytic SEM can be applied to nursing research fields.

Third, intervention and measure-of-association MA are currently the focus of nursing MA issues. The use of DTA MA in medical research areas is increasing. In the social science research fields, DTA MA has already been applied in educational testing. Thus, it can possibly be utilized in solving nursing educational measurement issues or conducting other test accuracy studies in nursing research.

Fourth, the critical evaluation of nursing intervention MA is mainly based on AMSTAR and PRISMA, and RCT cannot encompass every important nursing research issue. Hence, critical evaluations based on MOOSE or APA can provide better implications for the improvement of nursing MA. For example, the APA MARS has several detailed statistical methodology issues, such as effect size metric, weighting, dependency, random effect model, heterogeneity, outlier, and power of MA. Sutton and Higgins emphasized that the recent developments in MA include heterogeneity, random effect model, meta-regression, statistical power, and multiple outcomes [28]. However, in the previous nursing meta-analysis quality evaluation, we cannot confirm these statistical issues because ARMSTA and PRISMA do not have specific categories.

In the future, APA or MOOSE can be used to evaluate other MA designs in nursing research. AMSTAR is frequently utilized in the evaluation of RCT MA, but Burda et al. emphasized the limitations of AMSTAR and suggested some modifications for the improvement of its usability, reliability, and validity [29]. Higgins et al. also reported that the existing tools do not pay enough attention to statistical and interpretational issues; thus, the development of new quality assessment tool is necessary [30]. Further research will provide more insights and better evidences for healthcare decision making than the present studies.

Conflict of interest

The author does not have any conflict of interest to declare.

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