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Evaluating Heterogeneity in Meta-Analyses: A Review

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Abstract
Meta-analysis, as a fundamental aspect of evidence-based practice, synthesizes findings from multiple studies to draw comprehensive conclusions. A critical element of this synthesis is heterogeneity - the variability in outcomes, methodologies, and characteristics across studies. This review provides an in-depth exploration of heterogeneity in meta-analyses, highlighting its types, impact, and evolution over time. It emphasizes the significance of methodological rigor in detecting and managing heterogeneity, which is crucial for the credibility and utility of meta-analytic results. We delve into the methods for evaluating heterogeneity, including statistical tests like Cochran's Q test and the I^2 statistic, and visual methods such as forest plots and funnel plots. The paper also discusses strategies for managing identified heterogeneity, such as subgroup analysis, meta-regression, and sensitivity analysis, and the importance of choosing the appropriate statistical model. Advanced developments in heterogeneity evaluation, driven by statistical, technological, and methodological innovations, are also examined. This includes Bayesian approaches, individual participant data (IPD) meta-analysis, and automated tools for literature search and data extraction. The review includes case studies to demonstrate the application of these methods in various research contexts, underscoring the complexity and necessity of continuous advancements in handling heterogeneity. This paper serves as a comprehensive guide for researchers, contributing to the enhancement of meta-analytic practices and the quality of research findings across disciplines.

Keywords: Meta-Analysis, Heterogeneity, Statistical Methods, Research Synthesis, Methodological Rigor

1. Introduction

1.1 Heterogeneity: Definition and Significance

Meta-analysis, a cornerstone of evidence-based practice, amalgamates findings from multiple studies to arrive at comprehensive conclusions. Central to this process is the concept of heterogeneity - the variability or differences in study outcomes, methodologies, and characteristics. Heterogeneity is not merely a statistical nuance; it fundamentally impacts the interpretation and validity of meta-analytic results (Rokhshad et al., 2023). Understanding and appropriately addressing this heterogeneity is vital for ensuring that meta-analyses provide accurate and meaningful insights into the research questions they aim to answer.

1.2 Challenges Posed by Heterogeneity

The presence of heterogeneity in meta-analyses presents unique challenges. It can stem from various sources, such as differences in study populations, interventions, outcomes measured, or study designs. When unacknowledged or improperly managed, heterogeneity can lead to misleading conclusions, either overstating the consistency of findings across studies or obscuring meaningful patterns and relationships. The challenge for researchers lies in identifying the extent of heterogeneity, understanding its sources, and determining how to integrate diverse study results into a coherent and reliable conclusion.

1.3 Purpose and Scope of the Review

This review aims to elucidate the concept of heterogeneity in meta-analyses, its implications, and the methodologies for its evaluation and management. By delving into statistical tests and measures designed to detect and quantify heterogeneity, we provide a comprehensive overview of the current best practices in the field. Additionally, we aim to bridge the gap between statistical heterogeneity and its practical implications, offering insights into how researchers can interpret and address variability in meta-analysis to enhance the reliability and applicability of their findings.

In doing so, this review serves as a vital resource for researchers engaged in conducting meta-analyses, contributing to the refinement of methods and the advancement of knowledge in various scientific disciplines. It underscores the nuanced understanding required to navigate the complexities of combining disparate studies and highlights the continuous evolution of methodologies in this ever-expanding field.

1.4 Background and Evolution of Heterogeneity in Meta-Analyses

The concept of heterogeneity has evolved significantly since the inception of meta-analytic techniques. Initially, the focus was predominantly on quantifying and mitigating statistical variance among study results. However, as the field of meta-analysis has matured, there is an increasing recognition of the multifaceted nature of heterogeneity. It encompasses not just statistical discrepancies, but also clinical and methodological diversity. This broader understanding acknowledges that heterogeneity is an inherent and sometimes valuable aspect of meta-analysis, reflecting the real-world diversity of populations, settings, and interventions.

1.5 The Importance of Methodological Rigor

The credibility of a meta-analysis largely hinges on how well it addresses heterogeneity. Methodological rigor in detecting and managing heterogeneity not only strengthens the validity of the findings but also enhances the utility of the meta-analysis for informing policy, practice, and future research. Given the expanding role of meta-analyses in guiding decision-making in various fields, including healthcare, education, and public policy, the need for robust methodologies in evaluating heterogeneity has never been more critical.

1.6 Objectives and Structure of the Review

This review aims to provide a thorough exploration of the methodologies used to evaluate heterogeneity in meta-analyses. We will discuss statistical tests such as Cochran's Q test and the I^2 statistic, delve into visual methods like forest plots, and consider advanced techniques like meta-regression. Furthermore, we will examine the challenges and debates surrounding the interpretation of these methods, offering insights into both their strengths and limitations.

The subsequent sections of this review are structured to offer a comprehensive understanding of heterogeneity in meta-analyses. We begin with a detailed background of heterogeneity, followed by an exploration of the various methods for its evaluation. We then discuss strategies for addressing heterogeneity, including statistical models and sensitivity analyses. Case studies are presented to illustrate these concepts in practice, followed by a discussion

of recent advances and ongoing challenges in the field. The review concludes with a summary of key findings and recommendations for future research.

In sum, this review endeavors to provide a holistic view of heterogeneity in meta-analyses, equipping researchers with the knowledge and tools to navigate this complex but crucial aspect of research synthesis. Through this exploration, we aim to contribute to the enhancement of meta-analytic practices, ultimately improving the quality and impact of research findings across various disciplines.

2. Background

In the realm of meta-analysis, heterogeneity stands as a pivotal concept, encompassing the variability or differences observed across individual studies. This variability manifests in various forms: clinical, methodological, and statistical heterogeneity (Smela et al., 2023). Clinical heterogeneity arises from differences in participant characteristics, interventions, or outcomes, reflecting the diverse nature of research settings and populations. Methodological heterogeneity, on the other hand, stems from variations in study design, measurement tools, and risk of bias, critically influencing the meta-analysis's validity. Finally, statistical heterogeneity refers to the degree of variation in effect sizes reported in different studies that extends beyond chance, a quantifiable aspect crucial for assessing the consistency of study findings.

The impact of heterogeneity on meta-analysis outcomes is profound. It can significantly influence the results and conclusions, potentially leading to an overestimation or underestimation of the true effect size. High levels of heterogeneity might indicate that pooling data from the studies is inappropriate, necessitating a cautious interpretation of the meta-analysis results. However, heterogeneity is not solely a challenge to be mitigated; it can also offer valuable insights into the variability of effects in different contexts or subgroups, reflecting real-world diversity and aiding in the application of findings.

Historically, the treatment and perception of heterogeneity in meta-analyses have undergone a significant evolution. Initially regarded as a nuisance, heterogeneity is now acknowledged as an integral and informative component of meta-analysis. This shift is supported by methodological advancements that have improved the detection and quantification of heterogeneity, enabling a more nuanced interpretation and understanding of its implications. There are several good examples of assessing the heterogeneity, e.g., (Alhasan et al., 2023; Bhattacharjee & Khan, 2023; Chen et al., 2023; Cormier et al., 2023; Dong et al., 2023; Huang et al., 2023; Li et al., 2023; Mokhtari-Ardekani, 2023; Pereira et al., 2023; Rahmani, Fayyazishishavan, et al., 2023; Salazar de Pablo et al., 2023; Varhlunchungi et al., 2023; Zhang et al., 2023).

Heterogeneity also plays a critical role in guiding meta-analytic decision-making. The presence and extent of heterogeneity influence the choice of statistical models, such as fixed-effect or random-effects models, and shape the interpretation of results and formulation of conclusions. It is also integral to conducting meaningful subgroup analyses and meta-regression, which can explore the sources of variability and provide tailored insights for specific populations or contexts (Soleimani et al., 2023).

In essence, heterogeneity in meta-analysis is a multifaceted and dynamic element, the understanding of which is essential for ensuring the reliability and relevance of meta-analytic findings. The appropriate evaluation and interpretation of heterogeneity are key to advancing the field and enhancing the impact of research synthesis.

2. Methods for Evaluating Heterogeneity

The evaluation of heterogeneity in meta-analysis involves several statistical methods and measures, each offering unique insights into the degree and implications of variability among studies. Understanding and correctly applying these methods is crucial for a valid interpretation of meta-analytic results.

2.1 Statistical Tests for Detecting Heterogeneity

1. Cochran's Q Test: This is a widely used statistical test for detecting heterogeneity. The test is based on the principle that, under the null hypothesis of no heterogeneity, the weighted sum of squared deviations of individual study estimates from the overall estimate follows a chi-square distribution. The formula for Cochran's Q is:

$$Q = \sum_{i=1}^{k} w_i (x_i - \bar{x})^2 \quad (1)$$

where $x_i$is the effect estimate from the i-th study, w_i is the weight given to the i-th study (usually the inverse of the variance), and $\bar{x}$ is the weighted mean of the effect estimates.

2. Significance of Q: A significant Q (p-value < 0.10 is often used due to low power of the test) suggests the presence of heterogeneity. However, it's important to note that the test has limitations, particularly in terms of its power to detect heterogeneity in meta-analyses with a small number of studies or with studies of varying sizes.

2.2 Measures of Heterogeneity

1. I^2 Statistic: The I^2 statistic quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. It is calculated as:

$$I^2 = \frac{Q-(k-1)}{Q} \times 100\% \quad (2)$$

where Q is Cochran's Q and k is the number of studies. I^2 values of 25%, 50%, and 75% are typically considered to represent low, moderate, and high heterogeneity, respectively (Taşçı et al., 2023).

2. Tau^2 (Tau Squared): This is an estimate of the between-study variance in a random-effects meta-analysis. It gives an idea of the absolute amount of variability between studies. There is no direct formula for Tau^2; it is usually estimated using iterative statistical methods (Sharma et al., 2023).

2.3 Visual Methods

1. Forest Plots: These plots visually represent the results of individual studies and the overall meta-analysis estimate. The degree of heterogeneity can be visually assessed by observing the spread and overlap of the confidence intervals of the individual studies.
2. Funnel Plots: Used primarily for assessing publication bias, funnel plots can also provide insights into heterogeneity. Asymmetry in the plot may suggest heterogeneity, although this interpretation should be made cautiously.

Each of these methods contributes to a comprehensive understanding of heterogeneity in meta-analyses. While statistical tests and measures provide quantifiable evidence of variability, visual methods offer an intuitive understanding of the spread and impact of this variability. It's crucial for researchers to use a combination of these methods to fully grasp the extent and implications of heterogeneity in their meta-analytic work.

3. Addressing Heterogeneity in Meta-Analyses

Successfully addressing heterogeneity is a critical step in ensuring the reliability and validity of meta-analytic results (Ji et al., 2023). Once heterogeneity has been identified and quantified, researchers must employ various strategies to manage and interpret it appropriately.

3.1 Strategies for Managing Identified Heterogeneity

1. Subgroup Analysis: This involves breaking down the overall set of studies into smaller, more homogenous groups based on shared characteristics (Oliva Morgado Ferreira et al., 2023). By comparing these subgroups, researchers can explore potential sources of heterogeneity, such as differences in study populations, interventions, or outcomes. Subgroup analysis helps in understanding whether and how the effect size varies across different categories.
2. Meta-Regression: Meta-regression extends the idea of subgroup analysis by examining the impact of continuous or categorical study-level variables on the effect size. It allows for a more nuanced exploration

of how and why results vary across studies, providing insights into potential moderators of the effect.

3. Sensitivity Analysis: This method involves repeating the meta-analysis while varying certain methodological decisions, like inclusion/exclusion criteria, effect measure, or statistical model. Sensitivity analyses can reveal the robustness of the overall findings to these changes and help identify if specific studies or methodological choices are driving the heterogeneity.

3.2 Choosing the Appropriate Statistical Model

1. Fixed-Effect vs. Random-Effects Models: The choice of model is pivotal in the context of heterogeneity.
    - Fixed-Effect Model: Assumes that all studies estimate the same underlying effect and that observed differences are due to sampling error. This model is appropriate when studies are sufficiently homogenous.
    - Random-Effects Model: Assumes that study effect sizes follow a distribution, considering both within-study and between-study variability. This model is more suitable in the presence of heterogeneity, as it allows for variability between studies.
2. Interpreting Results from Different Models: Understanding the implications of model choice on the results is crucial. A random-effects model, while it provides a more generalizable estimate, may also introduce more uncertainty into the meta-analysis results.

3.3 Limitations and Challenges

Addressing heterogeneity in meta-analysis is not without its challenges (Zhao et al., 2023). Subgroup analyses and meta-regression require sufficient data and can be limited by the availability and quality of reported variables. Overinterpretation of subgroup differences can lead to spurious conclusions (Oliva Morgado Ferreira et al., 2023). Similarly, sensitivity analyses are only as informative as the range of variations tested . The choice of model also comes with trade-offs in terms of interpretability and applicability of results.

3.4 Best Practices

To address heterogeneity effectively, researchers should:

- Clearly justify the choice of statistical model based on the level of heterogeneity.
- Use subgroup analyses and meta-regression to explore potential sources of heterogeneity, while being cautious of overinterpretation.
- Conduct sensitivity analyses to assess the robustness of the results.
- Interpret the findings in the context of identified heterogeneity, acknowledging limitations and implications for generalizability.

In summary, addressing heterogeneity is an integral part of conducting a meta-analysis. Through careful consideration of the sources of heterogeneity and the application of appropriate statistical methods and models, researchers can provide more accurate and meaningful interpretations of the combined study results.

4. Advances and Innovations

The field of heterogeneity evaluation in meta-analyses has witnessed significant advancements and innovations, particularly in recent years (Varhlunchungi et al., 2023). These developments not only enhance our understanding of heterogeneity but also improve the accuracy and efficiency of meta-analytic practices.

4.1 Recent Developments in Evaluating Heterogeneity

1. Advanced Statistical Techniques: New statistical methods have been developed to better detect and quantify heterogeneity. For instance, Bayesian meta-analysis approaches provide a framework for incorporating prior knowledge and uncertainty into the analysis, offering a more nuanced assessment of heterogeneity.

2. Improved Measures of Heterogeneity: Researchers are increasingly recognizing the limitations of traditional measures like I^2 and Q tests. In response, enhanced measures that provide a more detailed understanding of heterogeneity are being developed. These include the incorporation of prediction intervals, which offer a range within which the true effect size of a new study is expected to lie, acknowledging the variability across studies.
3. Meta-Analysis of Individual Participant Data (IPD): IPD meta-analysis, where raw data from each study are analyzed, rather than summarized results, has gained traction. This approach allows for a more thorough investigation of heterogeneity, especially in terms of patient-level characteristics and responses.

4.2 Technological Advancements and Software Tools

1. Automation in Literature Search and Data Extraction: Advances in AI and machine learning have led to the development of tools that can automate the often laborious processes of literature search and data extraction, reducing the time and potential biases inherent in manual methods.
2. Sophisticated Meta-Analysis Software: New software and updates to existing platforms have made complex statistical analyses more accessible to researchers. Tools like RevMan, Stata, and R packages (e.g., 'metafor') offer advanced functionalities for heterogeneity assessment, including graphical representations, sensitivity analyses, and subgroup analyses.
3. Interactive and Dynamic Reporting: There's a growing trend towards interactive meta-analysis reports, where readers can manipulate parameters to see how conclusions might change under different assumptions. This dynamic approach offers a deeper understanding of the impact of heterogeneity on meta-analysis results.

4.3 Future Directions in Heterogeneity Analysis

1. Integration of Diverse Data Types: As research becomes more interdisciplinary, meta-analyses will increasingly need to integrate heterogeneous data types, including qualitative data, big data, and real-world evidence. Developing methods to handle this diversity while accurately assessing heterogeneity is a key future challenge.
2. Personalized Medicine and Heterogeneity: In the era of personalized medicine, understanding heterogeneity is crucial for tailoring treatments to individual patient characteristics. Future research might focus on how meta-analyses can contribute to personalized healthcare by dissecting heterogeneity at a granular level.
3. Enhancing Transparency and Reproducibility: There is a growing emphasis on transparency and reproducibility in research. Future advancements in heterogeneity evaluation will likely include standardized reporting practices and open-source tools, enhancing the reliability and credibility of meta-analytic findings.
4. Cross-Disciplinary Methodologies: As different fields grapple with heterogeneity in their meta-analyses, cross-disciplinary methodological exchanges are expected to grow. Innovations in one field could inform and enhance heterogeneity assessment in others.
5. Ethical and Regulatory Considerations: With increasing complexity in meta-analyses, ethical and regulatory considerations, particularly in the context of patient privacy in IPD meta-analyses and the use of AI in data handling, will become more prominent.

In conclusion, the field of heterogeneity evaluation in meta-analyses is rapidly evolving, driven by statistical, technological, and methodological innovations. These advancements promise to enhance the depth, accuracy, and applicability of meta-analytic research, ultimately contributing to more informed decision-making in various scientific and clinical domains.

5. Case Studies: Methods Used in Meta-Analyses and Their Alignment with Advanced Methodologies

This paper discusses various methodologies for assessing and addressing heterogeneity in meta-analyses. To contextualize these methods, we can examine how they were applied in four different meta-analytic studies.

1. Study: "Barriers and facilitators of childhood obesity prevention policies: A systematic review and meta-synthesis" (Taghizadeh et al., 2022)

- Methods Used: The study employed a systematic review approach to synthesize barriers and facilitators of childhood obesity prevention policies, incorporating both qualitative and quantitative analyses.
- Alignment with Advanced Methodologies:
    - Heterogeneity Evaluation: Given the diverse nature of the policies and settings, the study likely faced clinical and methodological heterogeneity, aligning with the importance of recognizing different heterogeneity types as discussed in the review paper.
    - Subgroup Analysis and Meta-Regression: The focus on individual, sociocultural, and structural levels suggests a form of subgroup analysis, exploring how different factors influence policy implementation.

2. Study: "Diagnostic Accuracy of Ottawa Knee Rule for Diagnosis of Fracture in Patients with Knee Trauma; a Systematic Review and Meta-analysis" (Kazemi et al., 2023)

- Methods Used: This study, following PRISMA-DTA guidelines, conducted a systematic search across multiple databases and used QUADAS-2 for quality assessment. The heterogeneity was evaluated using the I^2 statistic, and DerSimonian-Laird pooling method was employed for statistical analysis.
- Alignment with Advanced Methodologies:
    - Heterogeneity Evaluation: The use of I^2 and DerSimonian-Laird method aligns with the methodologies discussed in the review paper for assessing and addressing statistical heterogeneity.

3. Study: "The Association Between Screen Use and Central Obesity Among Children and Adolescents: A Systematic Review and Meta-Analysis" (Ghasemirad et al., 2023)

- Methods Used: Adhering to PRISMA guidelines, the study involved a comprehensive database search and quality assessment using the AHRQ checklist. Statistical analysis included heterogeneity assessment with Cochran's Q and I-squared tests, subgrouping, meta-regression analysis, and publication bias evaluation.
- Alignment with Advanced Methodologies:
    - Heterogeneity and Meta-Regression: The use of Cochran's Q, I^2, and meta-regression for exploring heterogeneity sources is in line with the advanced methodologies discussed in the review paper.

4. Study: " Diagnostic Accuracy of Ultrasonography for Detection of Intussusception in Children; a Systematic Review and Meta-Analysis" (Rahmani, Amani-Beni, et al., 2023)

- Methods Used: Following PRISMA-DTA guidelines, this study utilized a systematic database search and QUADAS-2 for quality assessment. Statistical analysis included I^2 and Cochran-Q tests for heterogeneity, and both DerSimonian-Laird and Mantel-Haenszel models were used depending on the heterogeneity levels. Publication bias was assessed using funnel plot, Egger's test, and Begg's test.
- Alignment with Advanced Methodologies:
    - Heterogeneity Assessment and Model Choice: The approach to heterogeneity assessment and the flexible use of statistical models depending on heterogeneity levels align well with the methodologies discussed in the review paper.

5. Study: "Effects of Biofeedback on Biomechanical Factors Associated with Chronic Ankle Instability" (Mousavi et al., 2023)

- Methods Used: This systematic review and meta-analysis, aiming to assess the impact of biofeedback on biomechanical parameters in individuals with chronic ankle instability (CAI), searched four databases including PubMed, Web of Science, Scopus, and Embase. The Downs and Black appraisal scale was used for quality assessment. The study focused on outcomes such as kinetics and kinematics, with data extraction carried out by two independent authors. The analysis included a range of biomechanical outcomes from various studies.

- Alignment with Advanced Methodologies:
    - Comprehensive Search and Quality Assessment: The thorough database search and use of a recognized quality assessment tool aligns with best practices in conducting systematic reviews and meta-analysis as discussed in the review paper.
    - Subgroup Analysis and Data Synthesis: The focus on specific biomechanical outcomes, such as center of pressure (COP) and lateral plantar pressure, and the distinction between auditory and visual biofeedback effects, reflects a detailed approach to subgroup analysis. This is important for understanding the nuances of heterogeneity in meta-analysis, as highlighted in the review paper.
    - Clinical and Methodological Heterogeneity: Given the variability in intervention types (auditory vs. visual biofeedback), participant characteristics, and biomechanical outcomes measured, the study likely encountered both clinical and methodological heterogeneity. This necessitates careful interpretation of the meta-analysis results, a key point emphasized in the review paper on heterogeneity evaluation.
    - Implications for Future Research: The study's conclusion, emphasizing the need for further research and development of user-friendly biofeedback devices, resonates with the review paper's emphasis on continuous methodological advancements and the application of meta-analysis findings in practical settings.

6. Study: "Effects of Prone Positioning on ARDS Outcomes of Trauma and Surgical Patients" (Phoophiboon et al., 2023)

- Methods Used: This systematic review and meta-analysis, conducted to assess the effects of prone positioning on acute respiratory distress syndrome (ARDS) outcomes in trauma and surgical patients, followed the PRISMA 2020 guidelines. The researchers conducted database searches in MEDLINE and EMBASE, supplemented by additional searches of primary literature and review articles. A random-effects model was used for estimating various clinical outcomes, including PF ratio, mortality rate, mechanical ventilator days, and intensive care unit length of stay, using Review Manager 5.4.1 software.
- Alignment with Advanced Methodologies:
    - Comprehensive Search and PRISMA Compliance: The study's adherence to PRISMA 2020 guidelines and thorough database search aligns with the best practices in conducting systematic reviews and meta-analysis as discussed in the review paper on heterogeneity evaluation.
    - Random-Effects Model Usage: The use of a random-effects model for data synthesis is particularly apt for studies like this, where clinical heterogeneity is expected due to varying patient characteristics and treatment protocols. This approach aligns with the recommendation in the review paper to consider heterogeneity when choosing the statistical model.
    - Heterogeneity Assessment: Although not explicitly detailed in the abstract, the use of a random-effects model suggests an acknowledgment of the potential for heterogeneity, which is a critical aspect of meta-analysis discussed in the review paper.
    - Clinical Relevance and Future Research: The study's focus on clinically relevant outcomes (like mortality rate and ventilator days) and the call for prospective multicenter studies reflect an understanding of the practical applications and limitations of meta-analysis findings, a point emphasized in the review paper.

These case studies, when compared with the methodologies discussed in this paper, offer practical insights into the application of heterogeneity evaluation techniques in diverse research contexts. They highlight the relevance and complexity of dealing with heterogeneity in meta-analyses and underscore the need for continuous methodological advancements to handle this multifaceted aspect effectively.

6. Conclusion

Meta-analysis, an integral component of evidence-based research, has evolved considerably, particularly in its approach to handling heterogeneity. This review has comprehensively explored the multifaceted nature of

heterogeneity in meta-analysis, addressing its types, methods for evaluation, and strategies for management, as well as the advancements and challenges in this field.

Understanding and appropriately managing heterogeneity are paramount for the reliability and validity of meta-analytic results. Heterogeneity can stem from a variety of sources, and its presence significantly impacts meta-analysis outcomes. High levels of heterogeneity necessitate cautious interpretation of results and may indicate that pooling data from the studies is inappropriate. However, heterogeneity also offers valuable insights into the variability of effects in different contexts, reflecting the diversity of research settings and populations.

Advanced statistical techniques have been developed for a more nuanced assessment of heterogeneity, including Bayesian meta-analysis approaches and improved measures of heterogeneity. The meta-analysis of individual participant data has emerged as a powerful tool, allowing for a more thorough investigation of heterogeneity, especially in terms of patient-level characteristics.

Technological advancements and software tools have revolutionized the meta-analytic process. Automation in literature search and data extraction, sophisticated software for heterogeneity assessment, and interactive and dynamic reporting of meta-analysis results have made complex analyses more accessible and transparent.

Looking ahead, the field faces several challenges and opportunities. As research becomes more interdisciplinary, meta-analyses must adapt to integrate diverse data types, including qualitative data and big data. The era of personalized medicine underscores the importance of understanding heterogeneity for tailoring treatments to individual patient characteristics. Future research in this field should focus on developing methods to handle the diversity of data while accurately assessing heterogeneity.

The case studies presented in this review demonstrate the practical application of heterogeneity evaluation techniques in various research contexts. They underscore the importance of rigorous methodology, careful consideration of heterogeneity, and the practical implications of meta-analysis findings.

In conclusion, the field of heterogeneity evaluation in meta-analyses is rapidly evolving, driven by statistical, technological, and methodological innovations. These advancements promise to enhance the depth, accuracy, and applicability of meta-analytic research, ultimately contributing to more informed decision-making in various scientific and clinical domains. As researchers and practitioners continue to grapple with the complexities of combining disparate studies, the insights provided in this review will be invaluable for navigating the challenges and harnessing the full potential of meta-analytic research.

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References

Alhasan, A. S., Daqqaq, T. S., Alhasan, M. S., Ghunaim, H. A., & Aboualkheir, M. (2023). Complication Rates and Risk of Recurrence After Percutaneous Radiofrequency Ablation and Microwave Ablation for the Treatment of Liver Tumors: a Meta-analysis. *Acad Radiol*. https://doi.org/10.1016/j.acra.2023.11.005

Bhattacharjee, P., & Khan, Z. (2023). Sacubitril/Valsartan in the Treatment of Heart Failure With Reduced Ejection Fraction Focusing on the Impact on the Quality of Life: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Cureus*, *15*(11), e48674. https://doi.org/10.7759/cureus.48674

Chen, S., Xu, X., Gong, H., Chen, R., Guan, L., Yan, X., Zhou, L., Yang, Y., Wang, J., Zhou, J., Zou, C., & Huang, P. (2023). Global epidemiological features and impact of osteosarcopenia: A comprehensive meta-analysis and systematic review. *J Cachexia Sarcopenia Muscle*. https://doi.org/10.1002/jcsm.13392

Cormier, P., Meylan, C., Agar-Newman, D., Geneau, D., Epp-Stobbe, A., Lenetsky, S., & Klimstra, M. (2023). A Systematic Review and Meta-Analysis of Wearable Satellite System Technology for Linear Sprint Profiling: Technological Innovations and Practical Applications. *J Strength Cond Res*. https://doi.org/10.1519/jsc.0000000000004689

Dong, Y., Shi, J., Wang, S., Liu, Y., Yu, S., & Zhao, L. (2023). The efficacy of immunosuppressive drugs induction therapy for lupus nephritis: a systematic review and network meta-analysis. *Ren Fail*, *45*(2), 2290365. https://doi.org/10.1080/0886022x.2023.2290365

Ghasemirad, M., Ketabi, L., Fayyazishishavan, E., Hojati, A., Maleki, Z. H., Gerami, M. H., Moradzadeh, M., Fernandez, J. H. O., & Akhavan-Sigari, R. (2023). The association between screen use and central obesity among children and adolescents: a systematic review and meta-analysis. *J Health Popul Nutr*, *42*(1), 51. https://doi.org/10.1186/s41043-023-00391-5

Huang, X., Dannya, E., Liu, X., Yu, Y., Tian, P., & Li, Z. (2023). Effect of sodium-glucose cotransporter-2 inhibitors on myocardial infarction incidence: A systematic review and meta-analysis of randomized controlled trials and cohort studies. *Diabetes Obes Metab*. https://doi.org/10.1111/dom.15405

Ji, H., Yang, Y., Lu, Y., Kong, X., Yang, G., Liu, J., Yang, Y., Wang, X., & Ma, X. (2023). Prevalence of dry eye during the COVID-19 pandemic: A systematic review and meta-analysis. *PLoS One*, *18*(12), e0288523. https://doi.org/10.1371/journal.pone.0288523

Kazemi, S. M., Khorram, R., Fayyazishishavan, E., Amani-Beni, R., Haririan, Y., Hosseini Khameneh, S. M., Rahmani, E., Minaei Noshahr, R., Sarikhani, M., Rahimi, R., Saeidi, S., Saeidi, D., & Farrokhi, M. (2023). Diagnostic Accuracy of Ottawa Knee Rule for Diagnosis of Fracture in Patients with Knee Trauma; a Systematic Review and Meta-analysis. *Arch Acad Emerg Med*, *11*(1), e30. https://doi.org/10.22037/aaem.v11i1.1934

Li, L., Zhong, H., Shao, Y., Hua, Y., Zhou, X., & Luo, D. (2023). Association between the homeostasis model assessment of insulin resistance and coronary artery calcification: a meta-analysis of observational studies. *Front Endocrinol (Lausanne)*, *14*, 1271857. https://doi.org/10.3389/fendo.2023.1271857

Mokhtari-Ardekani, A., Fayyazishishavan, E., Akhavanfar, R. Abbasalizad-Farhangi, M. (2023). Circulating Advanced Oxidation Protein Products (AOPPs) increases the risk of metabolic syndrome among adults: A systematic review and meta-analysis. *International Journal of Diabetes in Developing Countries*. https://doi.org/https://doi.org/10.1007/s13410-023-01178-4

Mousavi, S. H., Khorramroo, F., Minoonejad, H., & Zwerver, J. (2023). Effects of biofeedback on biomechanical factors associated with chronic ankle instability: a systematic review with meta-analysis. *BMC Sports Sci Med Rehabil*, *15*(1), 168. https://doi.org/10.1186/s13102-023-00780-7

Oliva Morgado Ferreira, R., Trevisan, T., Pasqualotto, E., Chavez, M. P., Marques, B. F., Lamounier, R. N., & van de Sande-Lee, S. (2023). Continuous glucose monitoring systems in non-insulin-treated people with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Technol Ther*. https://doi.org/10.1089/dia.2023.0390

Pereira, M., Castro, C. T., Magno, L., Oliveira, T. A., Gomes, F. S., Neves, F. M. F., Nascimento, P., & Dourado, I. (2023). Adverse effects of daily oral pre-exposure prophylaxis in men who have sex with men and transgender women: a systematic review and meta-analysis. *Cad Saude Publica*, *39Suppl 1*(Suppl 1), e00089522. https://doi.org/10.1590/0102-311xen089522

Phoophiboon, V., Owattanapanich, N., Owattanapanich, W., & Schellenberg, M. (2023). Effects of prone positioning on ARDS outcomes of trauma and surgical patients: a systematic review and meta-analysis. *BMC Pulm Med*, *23*(1), 504. https://doi.org/10.1186/s12890-023-02805-w

Rahmani, E., Amani-Beni, R., Hekmatnia, Y., Fakhre Yaseri, A., Ahadiat, S. A., Talebi Boroujeni, P., Kiani, M., Tavakoli, R., Shafagh, S. G., Shirazinia, M., Garousi, S., Mottahedi, M., Arzaghi, M., Pourbagher Benam, S., Rigi, A., Salmani, A., Abdollahi, Z., Karimzade Rokni, F., Nikbakht, T., . . . Farrokhi, M. (2023). Diagnostic Accuracy of Ultrasonography for Detection of Intussusception in Children; a Systematic Review and Meta-Analysis. *Arch Acad Emerg Med*, *11*(1), e24. https://doi.org/10.22037/aaem.v11i1.1914

Rahmani, E., Fayyazishishavan, E., Afzalian, A., Varshochi, S., Amani-Beni, R., Ahadiat, S. A., Moshtaghi, Z., Shafagh, S. G., Khorram, R., Asadollahzade, E., Atbaei, R., Kahrizi, M. S., Rahbari, A., Baharlouie, N., Mostanbet, F., Amirabadiquchani, B., Kiani, M., Memarizadeh, M., Keshtkar Rajabi, S., . . . Farrokhi, M. (2023). Point-Of-Care Ultrasonography for Identification of Skin and Soft Tissue Abscess in Adult and Pediatric Patients; a Systematic Review and Meta-Analysis. *Arch Acad Emerg Med*, *11*(1), e49. https://doi.org/10.22037/aaem.v11i1.2021

Rokhshad, R., Salehi, S. N., Yavari, A., Shobeiri, P., Esmaeili, M., Manila, N., Motamedian, S. R., & Mohammad-Rahimi, H. (2023). Deep learning for diagnosis of head and neck cancers through radiographic data: a systematic review and meta-analysis. *Oral Radiol*. https://doi.org/10.1007/s11282-023-00715-5

Salazar de Pablo, G., Aymerich, C., Guinart, D., Catalan, A., Alameda, L., Trotta, G., Armendariz, A., Martinez Baringo, E., Soler-Vidal, J., Rubio, J. M., Garrido-Torres, N., Gómez-Vallejo, S., Kane, J. M., Howes, O., Fusar-Poli, P., & Correll, C. U. (2023). What is the duration of untreated psychosis worldwide? - A meta-

analysis of pooled mean and median time and regional trends and other correlates across 369 studies. *Psychol Med*, 1-11. https://doi.org/10.1017/s0033291723003458

Sharma, M., Papisetty, S., Dhawan, S., Ahluwalia, M. S., Venteicher, A. S., & Chen, C. C. (2023). Comparison of Stereotactic Radiosurgery (SRS) and Hypo-fractionated Radiosurgery (hSRS) for Vestibular Schwannomas: A Meta-Analysis of available literature. *World Neurosurg*. https://doi.org/10.1016/j.wneu.2023.12.029

Smela, B., Toumi, M., Swierk, K., Gawlik, K., Clay, E., & Boyer, L. (2023). Systematic literature reviews over the years. *J Mark Access Health Policy*, *11*(1), 2244305. https://doi.org/10.1080/20016689.2023.2244305

Soleimani, E., Ardekani, A. M., Fayyazishishavan, E., & Farhangi, M. A. (2023). The interactive relationship of dietary choline and betaine with physical activity on circulating creatine kinase (CK), metabolic and glycemic markers, and anthropometric characteristics in physically active young individuals. *BMC Endocr Disord*, *23*(1), 158. https://doi.org/10.1186/s12902-023-01413-3

Taghizadeh, S., Hashemi, M. G., Zarnag, R. K., Fayyazishishavan, E., Gholami, M., Farhangi, M. A., & Gojani, L. J. (2022). Barriers and facilitators of childhood obesity prevention policies: A systematic review and meta-synthesis. *Front Pediatr*, *10*, 1054133. https://doi.org/10.3389/fped.2022.1054133

Taşçı, Ö., Özer, N., & Çoğaltay, N. (2023). The Effect of Virtual Reality Application on Pain During Wound Care Dressing Change: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Pain Manag Nurs*. https://doi.org/10.1016/j.pmn.2023.11.008

Varhlunchungi, V., Kalaivani, M., Hemraj, C., Gupta, S., Malhotra, S., & Tandon, N. (2023). Metabolic Syndrome Among Adolescents Aged 10-19 Years in India: A Systematic Review and Meta-Analysis. *Cureus*, *15*(11), e48636. https://doi.org/10.7759/cureus.48636

Zhang, H., Li, X., Sun, W., Zhang, R., & Cai, W. (2023). Comparison of complications and indwelling time of midline catheter at different tip locations: A systematic review and meta-analysis. *J Vasc Access*, 11297298231199776. https://doi.org/10.1177/11297298231199776

Zhao, H., Wang, L., Fang, C., Li, C., & Zhang, L. (2023). Factors influencing the diagnostic and prognostic values of circulating tumor cells in breast cancer: a meta-analysis of 8,935 patients. *Front Oncol*, *13*, 1272788. https://doi.org/10.3389/fonc.2023.1272788